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Cancer patients can be assured of support by well-trained and qualified oncology pharmacists

Klaus Meier
Editor-in-Chief
EJOP

The European Society of Oncology Pharmacy (ESOP) was founded in 2000 and is acting as a member of the European CanCer Organisation (ECCO). Our members are involved in many different ways in prevention of cancer, therapy and follow-up care, administration of drugs, management of side effects and interactions, clinical research, and the provision of further training and continuing education for pharmacists joining the profession. All these activities are guided by the needs of the patient and embedded in optimum all-round pharmaceutical care and counselling for people with cancer, regardless of the organizational structure in which our members work.

We unreservedly reject unfair and unlawful practices serving purely commercial interests which disregard both the interests of the patient and the professional ethics of the pharmacist. The foundation of our knowledge is based on evidence-based medicine together with our ethical commitment to the principle of patient well-being, and it makes strong input in the improvement of treatment efficiency in oncology patient.

The political challenge here is to improve inter-professional relationships in the health service and draw regularly on the expertise of oncology pharmacists to ensure that patients receive the best possible advice and that the safety of drugs used in therapy meets the highest standards. Cancer outpatients in particular require comprehensive care on a regional basis along with counselling on the use of drugs and possible problems that may arise in conjunction with their medication. The European funding programme to improve adherence in oncology, which is supported by ESOP, is an important milestone in the therapeutic support of patients by pharmacists.

We believe it is essential to improve patient compliance and adherence, drug and therapy security, and personal pharmaceutical care in order to enhance the quality of life for cancer patients. For the sake of the patient, it is crucial to involve multidisciplinary team to work together in the field of oncology and to do it in close contact with the patient. Cancer patients must have the right, wherever they live in this world, to get the best possible healthcare service.

Every day, it is particularly important to us to call ourselves to step up efforts in order to meet our goal.

The European Conference of Oncology Pharmacy (ECOP 3) in Dubrovnik, Croatia, 2016 will offer the next opportunity to exchange and share our experience. Take advantage of the day; meet brothers and sisters in the same spirit.

Quo Vadis regenerative medicine?

Regenerative medicine involves searching for stem cells that can be used safely and efficiently for regeneration of damaged solid organs, e.g. heart, brain or liver. In this review, different strategies that could have potential application in regenerative medicine are presented.

Introduction

By the beginning of the 21st century, mankind had acquired powerful technologies. The development of biology and genetics has begun to explain the mysteries of the creation of organisms and their regeneration, thus leading humanity into the fascinating world of stem cells. Various therapeutic strategies using stem cells have been proposed as alternative treatments for a multitude of diseases that are difficult to treat using standard methods. It is believed that technologies leading to optimization of the clinical use of stem cells in the new developing clinical discipline of regenerative medicine will become the key to increased longevity.

Professor Mariusz Z Ratajczak, MD, PhD

Stem cells and regenerative medicine

A stem cell has been described as a cell that is able to renew itself and to differentiate into daughter cells [1]. This definition, however, is too simplistic, because many types of stem cells differ between themselves according to their proliferative potential and ability to differentiate. The stem cell pool balances the number of somatic cells throughout the organism and is, therefore, responsible for the renewal of somatic cells that are depleted over time as well as regeneration of damaged organs and tissues. Stem cells are heterogeneous, and it is difficult to use one common definition to describe them. A large degree of hierarchy and heterogeneity exists within the pool of stem cells, ranging from the most developmentally primitive to those that are more or less organ or tissue-specific [1].

The goal of regenerative medicine is to use stem cells to treat injured organs and tissues. It is believed that, in the future, transplantation of entire organs will be largely replaced by the transplantation of a suspension of stem cells directed to the given organ, which will perform the task of rebuilding the injured tissues. The rapidly evolving field of regenerative medicine offers hope that stem cells can be used to treat injured organs, such as myocardium after heart infarction, brain after stroke, spinal cord after mechanical injury, damaged liver, extensive skin burns, as well as diabetes and Parkinson's disease.

Pluripotent stem cells isolated from embryos and by genetic induction and transformation of somatic cells

For the purposes of regenerative medicine, the ideal stem cells would be pluripotent stem cells (PSC), which, according to their definition, have a broad potential to differentiate into cells from all three germ layers (mesoderm, ectoderm and endoderm), or multipotent stem cell that differentiate into cells from more than one germ layer. They can be isolated from embryonic tissues [2, 3]. One potential source of PSC can be isolated from surplus embryos stored in *in vitro* fertilization clinics; another can be obtained by carrying out nuclear transfer to oocytes in the process of therapeutic cloning. The use of PSC in clinical medicine has brought hope to the world for the development of new therapeutic methods. At the same time, it has stimulated broad religious and ethical discussions. The ethics of using these cells is controversial, as it touches on the definition of the beginning of human life, which differs between the major religions of the world. An additional interesting strategy for obtaining PSC is genetic modification of adult stem cells, which leads to the generation of somehow transformed induced pluripotent stem cells. The major technical problem with all these cells, however, is that they may grow teratomas after transplantation into recipients, see Table 1. Therefore, the potential application of embryonic stem cells and induced pluripotent stem cells in the clinic is somehow questionable [4].

Stem cells isolated from adult tissues and phenomenon of 'stem cell plasticity'

Stem cells isolated from the adult tissues are the only stem cells currently used in the clinic. Of course, the most important

Table 1: Various potential sources of pluripotent stem cells

	PSC isolated from embryos obtained by		PSC obtained as a result of transformation of somatic cells (induced PSC)
	fertilization and stored in embryo banks	therapeutic cloning	
Risk of developing teratomas	Yes	Yes	Yes
Histocompatibility problems	Yes	No	No/Yes*
Requires ovum donor	Yes	Yes	No
Ethical considerations	Yes	Yes/No**	No

*It has recently been reported that induced pluripotent stem cells may be immunogenic. This possibility needs further study; **This problem is considered differently by the various major religions of the world. A number of religions potentially accept therapeutic cloning, e.g. Buddhism, Islam and Judaism, but unquestionably a majority reject reproductive cloning.
PSC: pluripotent stem cells.

question regarding their use is their potential for multiple tissue differentiation.

Therefore, an alternative possibility is being explored to search for stem cells isolated from postnatal tissues that can be efficiently used in regenerative medicine. A few years ago, it was proposed that adult stem cells, e.g. haematopoietic stem cells, are plastic and may extensively transdifferentiate into cells from different germ layers, but this possibility lacks solid experimental support [1, 5, 6]. As a result, the concept of stem-cell plasticity or transdifferentiation has been challenged [7, 8]. Some positive effects of stem-cell therapies have been explained by alternative mechanisms, such as cell fusion [9] and paracrine effects of stem cells used in treatment as a result of released growth factors, cytokines, chemokines, and microvesicles [10]. Alternatively, it has been proposed that stem cells used for treatment derived from bone marrow, mobilized peripheral blood, or umbilical cord blood, may, from the beginning, contain heterogeneous populations of stem cells, including some rare multipotent or pluripotent stem cells [11-15]. A great deal of effort has been made to unleash the power of these cells, and several preclinical studies in experimental models using these cells are ongoing.

Alternative explanations of stem-cell plasticity

As previously mentioned, several years ago, a theory of 'stem cell plasticity' was developed. This is the ability of tissue-committed stem cells (TCSC) to transdifferentiate into other types of stem cells. According to this theory, TCSC, such as haematopoietic stem cells (HSC) obtained from bone marrow, for example, would be able to dedifferentiate into stem cells typical of other organs, such as myocardium, the central nervous system or liver [6, 7]. On the basis of this theory, great expectations were associated with the potential use of HSC as a source of plastic stem cells. Despite initially promising results [6, 7], however, the direct role of these cells in the regeneration of injured organs by reversing their phenotype has not been proven. Specifically, a series of studies using phenotypically defined and purified subpopulations of HSC have been disappointing, revealing negative results in models of regeneration of myocardium [7] and brain [8]. Several alternative explanations have been proposed to explain these results. First, it is possible that some of the stem-cell plasticity data can be explained by the phenomenon of cell fusion [9]. Specifically, transplanted HSC might undergo fusion (melting) with the cells of injured organs. If so, cells in the injured organs treated with transplanted HSC would be heterokaryons, created as a result of fusion of transplanted HSC with cells belonging to the injured organ. Cell fusion, however, is an extremely rare event that cannot fully account for the extensive positive transdedifferentiation or plasticity data claimed in several reports.

Alternatively, the positive effects observed after stem-cell treatments might be explained by the involvement of stem cell-derived paracrine effects. Stem cells used in treatment are a rich source of growth factors, cytokines, chemokines, and bioactive lipids, which may inhibit apoptosis and promote neovascularization in the damaged tissues. The function and phenotype of cells in the damaged tissues may also be modified by transfer of cell receptors, cytoplasmic proteins, and messenger RNA from surrounding cells by microvesicles, which are spherical structures in which a part of the cell cytoplasm enriched for messenger RNA, microRNA, and functional proteins is encapsulated by cell membrane [10]. Microvesicles released from the surface of cells used to regenerate damaged organs may deliver these cargo molecules to damaged tissues. Evidence has accumulated that microvesicle cargo has positive effects on cell survival and angiogenesis. Thus, paracrine effects associated with microvesicles most likely make the major contribution to the positive results reported in clinical trials using adult stem cells.

We also cannot exclude the possibility that some factors present in the environment of damaged organs induce epigenetic changes in genes that regulate pluripotency of adult cells (involving changes in DNA methylation or acetylation of histones) [1]. This mechanism is obviously involved, for example, in the generation of recently reported stimulus-triggered acquisition pluripotency [15].

Finally, cells used for treatment that are derived, for example, from haematopoietic tissues may from the beginning contain heterogeneous populations of stem cells, including some rare multipotent or pluripotent stem cells that possess a broader differentiation potential.

Potential pluripotent or multipotent stem cells in adult tissues

In support of the presence of early development stem cells in postnatal life, several types of putative pluripotent and multipotent stem cells have been described and isolated, primarily from haematopoietic tissues, which are able to produce cells from more than one germ layer [1]. These cells were isolated by using various strategies, such as *ex vivo* expansion of partially purified immunomagnetic cells or fluorescence activated cell sorting. In most of these cases, the phenotype of the putative pluripotent or multipotent cells with stem cell-like properties was described 'post factum', after phenotyping clones of already differentiated *in vitro*-expanded cells [11-15]. Thus, if early development stem cells endowed with broader differentiation potential reside in adult tissues, they are probably closely related and exist at different levels of tissue specification. Most likely, they represent overlapping populations of early development stem cells. These have been given different names, depending on the isolation strategy used, *ex vivo* expansion protocol, and the markers used for their identification [11-15]. These include multipotent adult stem cells [13], mesenchymal stem cells [1], multipotent adult progenitor cells [12], marrow-isolated adult multilineage inducible cells [14], multipotent progenitor cells [12], spore-like stem cells [15], and, as described by my team, very small embryonic-like stem cells [11].

Overall, the presence of pluripotent or multipotent stem cells in adult tissues can be explained by the possibility that, early during embryogenesis, not all of the earliest development stem cells disappear from the embryo after producing TCSC, but some survive in developing organs as a dormant back-up population of more primitive stem cells [1, 11-15]. These cells could give rise to monopotent TCSC, and thus be involved in tissue or organ rejuvenation and in organ regeneration after organ injury. In support of this notion, evidence has accumulated that adult murine tissues contain, in addition to rapidly proliferating stem cells, a back-up population of more primitive dormant stem cells [1, 11]. An alternative explanation is that some somatic cells may undergo epigenetic changes during stress situations and revert to the pluripotent state. That cells expressing primitive phenotypes are detected during tissue or organ injuries in peripheral blood, and recent observations that somatic cells may be converted into PSC, lend support to this notion.

In conclusion, the quest for PSC or multi-potent stem cells that could be used in the clinic continues. In years to come, we can expect many exciting discoveries.

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A German initiative towards more patient safety in oral anticancer therapy

(please see the full manuscript on pages 34–35)

this endeavour, one of the most important challenges is the nationwide training of pharmaceutical staff in community pharmacies and the provision of adequate tools that support oncology pharmacy practice.

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Do pharmacists need additional education to support patients on oral chemotherapy?

Marika Saar, MSc (ClinPharm); Jana Jaal, PhD; Julienne B Johnson, PhD

Abstract

Introduction/Study objective: The number of patients who receive oral instead of intravenous chemotherapy is increasing steadily. This means challenges both for patients and pharmacists. As oral chemotherapy is dispensed mostly in community pharmacies, pharmacists should provide adequate and appropriate pharmaceutical care for supporting cancer patients. The aim of our project was to identify the need of community pharmacists for a specialized educational programme to support patients receiving oral anticancer medicines.

Method: A mail survey was conducted among community pharmacists in Estonia. A questionnaire was developed to record views of community pharmacists on their confidence at providing oral anticancer therapy services and to find out the need for an educational programme aimed at supporting community pharmacists dispensing oral anticancer drugs.

Results: Ninety-three pharmacists responded to our survey. The average self-assessment provided by these community pharmacists suggested that their knowledge about oral anticancer therapy was quite low. Pharmacists found themselves most knowledgeable about special handling of oral anticancer therapy and drug indications and least knowledgeable about general dosing principles and drug interactions. Overall, 48% of pharmacists indicated that they are not sufficiently confident about oral chemotherapy knowledge to provide service for patients; only 8% were strongly confident about their knowledge.

Discussion/Conclusion: The results of our project clearly indicated limited confidence among Estonian community pharmacists about different aspects of oral anticancer medicines. Pharmacists strongly expressed the need for additional postgraduate educational programmes related to these anticancer medicines.

Keywords: Oral chemotherapy, postgraduate training of pharmacists

Introduction

The global burden of cancer continues to increase largely because of growth of an ageing population. Cancer remains one of the important public health problems in Europe and worldwide [1].

Over the past decade, more and more new oral anticancer agents have been developed that offer cytotoxic or targeted cancer treatment. Although the oral anticancer agents provide additional treatment options, they also pose challenges for patients and healthcare professionals including pharmacists [2-5]. Some of the benefits and problems associated with oral chemotherapy are listed in Table 1.

Several studies have shown that the contribution of pharmacists to management of cancer patients may improve both clinical and economic outcomes [6-8].

Traditionally, anticancer therapy is prescribed, administered and monitored in a hospital setting. Hospital pharmacists are involved in dispensing and preparing anticancer drugs as well as providing pharmaceutical care for cancer patients. Therefore, oncology pharmacy is a well-developed specialty within hospital pharmacy. Additionally, many national and international societies incorporate these oncology pharmacy specialists in preparing guidelines and organizing educational courses for their members [9-11].

Increasing numbers of oral anticancer drugs are prescribed and dispensed through community pharmacies. Moreover, the proportion of oral anticancer medicines is expected to increase further since 25% of all anticancer agents under development are oral formulations [12-13]. Therefore, community pharmacists should be ready to provide patients with proper advice and pharmaceutical care in the field of cancer medication and

Table 1: Advantages and problems associated with oral anticancer drugs

Advantages		Problems
Patient perspective • Autonomy (home-based therapy) • Easy administration, no pain • Less frequent access to the hospital (no transportation cost, lost working time)	**Doctor/nurse/healthcare system perspective** • Less complication related to IV administration (catheter infections, extravasation) • Reduced need of hospitalization • Time saving • No risk for workers exposure • Less cost (salary of medical staff, expenses of medical devices)	• Pharmacologic issues o Possible differences in pharmacokinetics o Variable bioavailability o Interactions o Side effects • Adherence • Medication errors • Problems with administration (swallowing difficulties, vomiting) • Safe handling at home • Availability, reimbursement (especially with new targeted drugs)

treatment. Appropriate training programmes to achieve these aims should be implemented [14].

Most oral chemotherapy will be supplied by community pharmacies in Estonia. However, no special educational programme about oncology or oral anticancer therapy is currently available for community pharmacists in Estonia.

Study objective

The aim of this study was to determine whether community pharmacists need a specialized educational programme to support patients receiving oral anticancer medicines.

Method

The study was carried out among Estonian community pharmacists during March to May 2012. Pharmacists who worked in community pharmacies and dispensed oral anticancer medicines at least once in the previous 12 months were included.

The anonymous questionnaire was developed, validated and distributed to every community pharmacy using the online survey software tool E-formulary (www.eformular.com).

The questionnaire was divided into three parts: (1) general data; (2) self-assessment of knowledge; and (3) need for education.

In the first part, pharmacists were asked the location of their pharmacy and the frequency of dispensing chemotherapy.

In the second part, pharmacists were asked to assess their knowledge about providing information and pharmaceutical care for cancer patients. The questions included drug indications, general administrating principles, drug interactions, adverse effects, and special handling precautions of oral anticancer medicine. A five-point Likert-type scale was used to assess pharmacists' knowledge as follows: (1) no knowledge; (2) insufficient knowledge; (3) basic knowledge; (4) adequate knowledge; and (5) comprehensive knowledge.

In the third part of the questionnaire, community pharmacists were asked which sources of information they used to learn about oncology and oral anticancer drugs.

Finally, any gaps in pharmacists' knowledge of oral anticancer therapy were ascertained and study participants were asked if they had any interest in participating in an educational programme on these topics.

Completed questionnaires were analysed using Microsoft Excel and SPSS software.

The study design was approved by the Research Ethics Committee of the University of Tartu, Estonia.

Results

Four hundred and 69 electronic surveys were sent out to the pharmacies. However, only 93 responses were received (response rate 20%). Most of the pharmacies that responded are located in Harjumaa and Tartumaa where the two biggest cities (Tallinn and Tartu) in Estonia are located and where 38% of the Estonian population live, see Table 2.

Most pharmacists supplied oral chemotherapy less than once a month (46%) or monthly (29%). 11% of responders supplied medication weekly and 14% supplied it every day. The pharmacies dispensing oral chemotherapy were often located in counties that include big cities (Harjumaa and Tartumaa).

In nine questions, pharmacists were asked to assess their knowledge about providing information to patients who are treated with oral anticancer therapy using the five-point Likert-type scale mentioned above.

The average assessment by community pharmacists of their knowledge about oral anticancer therapy was quite low (2.8 on the five-point scale). Pharmacists found themselves most knowledgeable about special handling of oral anticancer therapy (3.5) and drugs indications (2.9) and least knowledgeable about

Table 2: Data about Estonian pharmacies

County	Number of inhabitants*	Number of community pharmacies**	Number of pharmacies that reported dispensing of oral anticancer drugs (% of all responders)
Harjumaa (including Tallinn)	569,977	164	35 (37%)
Tallinn	416,053	119	30 (32%)
Tartumaa (including Tartu)	149,426	69	23 (25%)
Tartu	98,522	41	20 (22%)
Ida-Virumaa	161,997	53	5 (5%)
Pärnumaa	88,827	37	11 (12%)
Lääne-Virumaa	64,608	23	2 (2%)
Viljandimaa	52,098	22	1 (1%)
Võrumaa	37,055	12	1 (1%)
Raplamaa	36,485	16	2 (2%)
Saaremaa	35,581	12	1 (1%)
Jõgevamaa	34,325	12	1 (1%)
Järvamaa	33,817	12	4 (4%)
Valgamaa	33,299	13	3 (3%)
Põlvamaa	30,445	12	1 (1%)
Läänemaa	26,879	10	2 (2%)
Hiiumaa	10,123	6	1 (1%)
Total	**1,363,995**	**469**	**93 (20%)**

*Estonian Population Registry (www.siseministeerium.ee/35796);
**State Agency of Medicine (www.ravimiamet.ee).

Table 3: Self-assessment of pharmacists' knowledge about oral chemotherapy

	Pharmacists' self-assessment according to five-point Likert scale (number of pharmacists)					Average Likert scale (n = 93) (mean ± SD)
	No knowledge	Insufficient knowledge	Basic knowledge	Adequate knowledge	Comprehensive knowledge	
Main indications of oral anticancer drugs	2	33	34	22	2	2.9 ± 0.9
Administration: when to take medication	7	30	39	14	3	2.7 ± 0.9
Administration: how to take medication (with/without food)	8	26	42	11	6	2.8 ± 1.0
Administration: what to do if patient misses the dose	21	30	30	8	4	2.4 ± 1.1
Potential adverse effects	5	27	45	15	1	2.8 ± 0.8
How to react if adverse effects occur	10	29	31	19	4	2.8 ± 1.0
Possible interactions (drug–drug, drug–food)	8	39	37	7	2	2.5 ± 0.8
Which medicines/food supplements should be avoided during treatment	9	37	35	10	2	2.6 ± 0.9
Safe handling of oral anticancer drugs	2	8	45	22	16	3.5 ± 1.0
Average	***8***	***30***	***37***	***14***	***4***	***2.8 ± 0.9***

SD: standard deviation.

general dosing principles (2.6) and interactions (2.5). More detailed answers are shown in Table 3.

We asked about sources used by community pharmacists to get information about oncology and oral anticancer therapy. Easily accessible patient information leaflets (PILs) and summary of product characteristics (SmPC) are the most frequently used information sources, used by 81% and 72% of responders, respectively. Only 18% of pharmacists mentioned educational activities as information sources, see Table 4.

We asked how confident pharmacists were in their oral chemotherapy knowledge to provide service for cancer patients. Overall, 48% of pharmacists indicated that they are not sufficiently confident in their oral chemotherapy knowledge to provide service for patients; 44% of responders felt themselves somewhat confident and only 8% were strongly confident in their knowledge, see Figure 1. However, those pharmacists who dispensed oral anticancer medicines most often were more confident about their knowledge of oral anticancer drugs, see Figure 2.

When pharmacists answered that they were 'not confident' or 'somewhat confident' in their knowledge, they were asked to give more detailed information in order to specify weaknesses and deficiencies in oral chemotherapy knowledge.

Responders felt least confident about drug interactions (33%) and side effects (24%). More than a quarter of pharmacists (26%) declared that they would need more information and training in all aspects of oral chemotherapy, see Table 5.

Finally, pharmacists were asked whether they would need a special training programme about oncology and oral chemotherapy. Almost all responding pharmacists expressed their interest in participating in an additional educational programme, 76 (82%) of responders answered 'Yes, certainly' and 16 (17%) of pharmacists answered 'Maybe'. Only one of the responders (1%) expressed reluctance to participate in a special training programme for pharmacists, see Figure 3.

Discussion

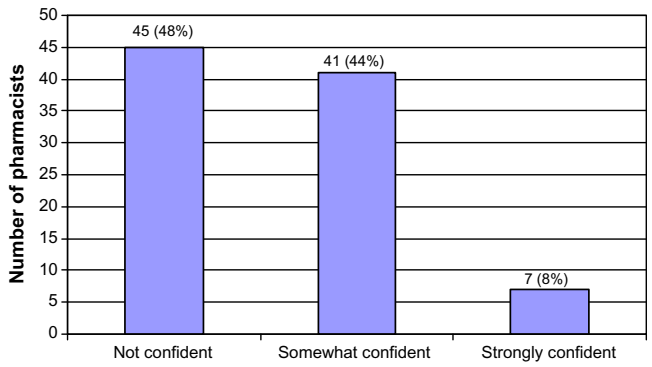
The response rate of pharmacists in our survey was quite low (20%): out of 476 questionnaires that were sent out, only 93 answers were received. Despite the low response rate, our study described a complex situation in Estonia since surveys were sent to all community pharmacies. Currently, there are no other nationwide reports investigating practices concerning oral anticancer drugs.

The highest response rates were obtained from Harjumaa and Tartumaa counties (62%), whereas only 1–12% of replies were returned from other counties. More than half of the answers (54%) came from the two biggest cities in Estonia, Tallinn (Harjumaa County) and Tartu (Tartumaa County). This is not surprising since the country's only cancer centres are located in these cities: two centres in Tallinn—North Estonian Medical Centre, East-Tallinn Central Hospital—and one centre in Tartu—Tartu University Hospital. Presumably most cancer patients get their medicines from pharmacies that are located in close proximity to oncology centres. This is supported by the present study, where the majority of pharmacies (83%) that supplied oral anticancer medicines frequently—daily or weekly—are located in Tallinn and Tartu. The dispensing frequency was much lower in other counties, probably because many small countryside pharmacies do not supply oral anticancer medicines at all.

Table 4: Information sources used by pharmacists

Information sources	Responses (n = 93)
Patient leaflet	75 (81%)
Summary of product characteristics	67 (72%)
Internet	28 (30%)
Training courses, seminars	17 (18%)
Other	11 (12%)

Figure 1: Pharmacists' confidence in their oral chemotherapy knowledge (n = 93)



This study revealed that pharmacists' self-assessed level of knowledge about oral anticancer therapy was quite low—mean 2.8; Likert scale. Pharmacists deemed themselves most knowledgeable about special handling of oral anticancer therapy (3.5) and drug indications (2.9) and least knowledgeable about general dosing principles (2.6) and interactions (2.5).

This is the first report of different aspects of oral anticancer drugs among Estonian community pharmacists. The findings of this study cannot be compared with other European countries, mainly because there are no published reports on this topic. In North-America, however, similar small surveys have been conducted in the US and Canada [15-16]. In 2008, O'Bryant and Crandell surveyed community pharmacists' knowledge and attitudes toward oral chemotherapy in the US. As in our study, they reported a low level of comfort in dispensing oral anticancer medications—mean 2.4; Likert scale [15]. Alongside self-assessment using the Likert-type scale, pharmacists' knowledge of oral anticancer drugs was evaluated using a multiple choice questionnaire. Based on these, and more precise results, pharmacists were least knowledgeable about adverse effects (45% of responders) and special handling (25% of responders). Abbott et al. questioned community and hospital pharmacists in one Canadian province. They found that pharmacists' knowledge about different aspects of chemotherapy was also limited [16]. A big proportion of responders (41%) admitted that they do not understand chemotherapy cycles. Additionally, pharmacists were not familiar with targeted anticancer drugs (39% of responders) as well as with their side effects (59% of responders). Many pharmacists (21–53%) did not feel comfortable dispensing oral anticancer drugs with respect to safety, handling, dosing and indications.

Table 5: Topics where more information and training would be needed

Topics	Responses (n = 70)
Interactions (drug–drug, drug–herbal, drug–food)	23 (33%)
All aspects about oral anticancer drugs	18 (26%)
Side effects	17 (24%)
Complementary supplements (food supplement/herbal medicine products)	9 (13%)
Administration of oral anticancer drugs	8 (11%)
Oral anticancer drug regimens	6 (7%)
Pharmacology (mode of action)	4 (6%)
General advice, e.g. about lifestyle	2 (3%)

Any oncology pharmaceutical service is based on facilities for obtaining, interpreting and distributing information relevant to all issues relating to cancer management [17]. Therefore, every pharmacist providing a pharmaceutical service including the supply of oral chemotherapy must be able to find and distribute high quality information. Community pharmacists, however, are not expected to become as deeply specialized in cancer medicines as oncology pharmacists in a hospital setting. They should rather be able to give general but useful information to support cancer patients. For this, the ability to find and use appropriate information sources should be essential [18].

Our study revealed that the vast majority of pharmacists use PIL (81%) and/or SmPC (72%) as their main information sources

Figure 2: Relationship between dispensing frequency and pharmacists' confidence in their knowledge (n = 93)

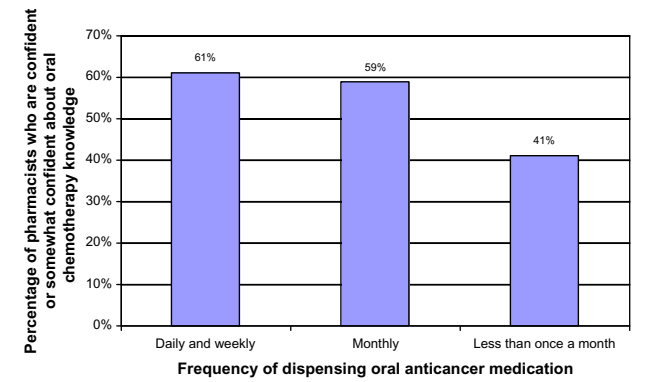
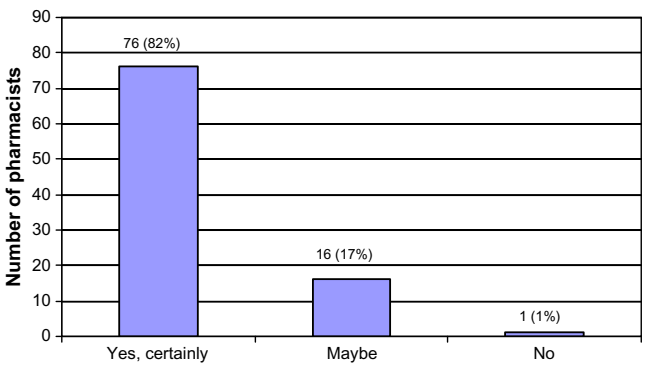


Figure 3: Pharmacists' opinion about the need for special training programme (n = 93)



about oral anticancer drugs. Next to these sources, the use of the Internet (30%) was frequently mentioned. Approximately one third of responders used trustworthy Internet sources like www.raviminfo.ee (website in Estonian, PIL available) and www.ravimiamet.ee (website in Estonian, PIL and SmPC available). Next to these, however, less reliable (www.google.com, www.yandex.ru, www.wikipedia.org) and less informative Internet sources that are oriented for patients (www.rinnavahk.ee) were described. It is not clear from our study, whether these less informative sources were used to find additional scientific information (e.g. information about specific drug–drug interactions) or because of other reasons, such as inability to read in English and/or to find evidence-based medical information. In fact, none of the pharmacists mentioned trustable, evidence-based and continuously updated medical information sources like PubMed (www.ncbi.nlm.nih.gov/pubmed), UpToDate (www.uptodate.com), Micromedex (www.micromedex.com) or Clinical Pharmacology (www.clinicalpharmacology.com) database. Also, several other selected websites, e.g. www.cancernetwork.com, which are developed especially for oncology professionals and researchers were not described [19]. Some responders stated that they have received information concerning oral anticancer drugs through educational activities (18%). Currently, there are no special courses in Estonia about different aspects of oral anticancer medications. Therefore, the educational activities mentioned are mainly those organized by pharmaceutical companies. These training courses and seminars possess several limitations, such as focus on a particular drug, and biased information that is not objective.

This study showed that nearly half the community pharmacists who responded (48%) are not sufficiently confident about their oral chemotherapy knowledge to provide adequate service for cancer patients. A similar proportion of responders (44%) felt themselves somewhat confident and only 8% were strongly confident about their current knowledge. A study carried out in Canada revealed that 32% of pharmacists were not sufficiently confident to educate cancer patients about oral anticancer medicines, whereas a quarter of responders (25%) were confident. It must be noted that hospital pharmacists were also involved in this study (19% of all study group), so these improved results may be related to the higher proportion of more experienced personnel [16]. This is also supported by our study, where higher confidence was seen among those pharmacists who dispensed oral anticancer medicines most often (weekly and daily).

More than a quarter of pharmacists (26%) declared that they would need more information and training in all aspects of oral chemotherapy. Specifically, areas where pharmacists felt least confident were drug interactions (33%), side effects (24%), complementary supplements (13%), and administration issues (11%). Similar areas, although in different proportions, were mentioned by Canadian pharmacists [16]. These areas of least confidence encompass broadly all aspects of safe and effective oral anticancer medicine use and point clearly towards the need for additional education and training.

Participation in structured continuing professional development should be essential for every practicing pharmacist to maintain and improve his/her competence for providing contemporary pharmaceutical care [20]. Therefore, practicing community pharmacists should have a plan for continuing professional development to be able to provide anticancer medication management and direct patient care for cancer patients. The need for special training concerning oral anticancer medicines was clearly stated in our study. The vast majority of community pharmacists questioned (82%) expressed their marked interest in a postgraduate educational programme. Similarly, O'Bryant and Crandell found a great interest among pharmacists in participation in additional educational courses—mean 4.2; Likert scale [15]. Also, Abbott et al. reported that 45–63% pharmacists require education on different aspects of oral anticancer drugs [16].

Training programmes may provide not only specific knowledge about medications but may also have additional benefits. For example, postgraduate education is related to better career progression and job satisfaction. Padiyara and Komperda reported that approximately 45% of pharmacists with postgraduate training indicated they were highly satisfied with their employment, compared to 33% of pharmacists without postgraduate training [21].

At the moment, postgraduate training is not provided by the University of Tartu, the only professional body for obtaining pharmacy degrees in Estonia. Some seminars and lectures are arranged by professional pharmacy organizations but those are available primarily for their members. Furthermore, there are no educational activities provided specifically on topics of oncology pharmacy/anticancer drugs. The lack of postgraduate educational activities—general and cancer specific—may be related to the current situation where continuing education is not mandatory for licence renewal of pharmacists. However, a change in this situation is being discussed by the Estonian Ministry of Social Affairs.

Conclusion

As a result of an ageing population and a growing incidence of cancer, more and more patients are in need of effective anticancer therapies. To cope with the increasing number of patients, there has been a shift from inpatient to outpatient cancer care. Along with this, the use of oral anticancer medicines, dispensed through community pharmacies, has substantially increased. For that reason, community pharmacists must be educated and knowledgeable in the area of oncology and anticancer medicines.

The results of our project clearly indicate limited confidence among Estonian community pharmacists in different aspects of oral anticancer medicines and the provision of pharmaceutical care for patients with cancer. However, community pharmacists strongly expressed the need for and interest in additional postgraduate educational programmes related to these anticancer medicines.

Based on the results of this study, an education programme covering all aspects of oral anticancer drugs should be developed and implemented in Estonia. Educational activities must be supported by pharmacy employers, pharmacy advocacy groups, and provincial and national healthcare authorities to assure viability and sustainability of a postgraduate educational programme that guarantees broad-based access to community pharmacists.

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Occupational risk of handling monoclonal antibodies: a risk-assessment method

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Abstract

Objective: Little is known about the occupational risk of monoclonal antibodies. They are a heterogeneous group of molecules, making it difficult to define their toxicity after chronic low-dose exposure. In the Hospital of Parma in Italy, intravenous cytotoxic therapies and some monoclonal antibody infusions are admixed in a pharmacy compounding facility – the UMaCA laboratory. The aim of this work was to produce a risk-assessment document for monoclonal antibody compounding.

Method: A working group composed of UMaCA pharmacists and chemical safety consultants from the Health and Safety Department was formed to evaluate the risk of monoclonal antibodies and to establish safety procedures. An algorithm for the calculation of the chemical risk (MoVaRisCh) was used to evaluate the maximum hazard to which operators may be exposed.

Results: Safety data tables were built for every monoclonal antibody handled in UMaCA, based on summaries of product characteristics, safety datasheets and published toxicity warnings. No monoclonal antibodies showed carcinogen or mutagen properties. Overall, on the basis of existing research, a medium-high risk was assigned to monocloncal antibodies. The use of MoVaRisCh has shown that as a result of current preventive measures, workers are protected from dangerous substances.

Conclusion: Monoclonal antibody therapies should be compounded using procedures to preclude exposition and cross-contamination with cytotoxic agents. Results showed that preventative and protective measures applied in the UMaCA laboratory adequately protected healthcare staff, especially for the inhalation route. Further data, including specific studies on humans and warning in safety data sheets, are necessary and strongly advisable so that guidelines on monoclonal antibodies occupational hazards can be developed.

Keywords: Monoclonal antibodies, occupational risk

Introduction

The health and safety risk of handling anticancer drugs is well established, however, little is known about the occupational risk of monoclonal antibodies (mAbs). These are not classic cytotoxic agents, as they do not address (directly or indirectly) nucleic acids, and their exact cellular and molecular mechanism of action is not fully understood. They have long plasma half-lives and long exposure times. As they are a heterogeneous group of molecules, it is difficult to define their exact toxicity after chronic low-level occupational exposure.

On the basis of the original definition in 1990 of the American Society of Health-System Pharmacists, the National Institute for Occupational Safety and Health (NIOSH) defined a substance as dangerous when it is carcinogenic, teratogenic, genotoxic, or when it can cause reproductive or developmental toxicity or severe organ impairment at low doses [1]. According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Humans Use, it is not mandatory to test genotoxicity or carcinogenicity on mAbs because they are biotechnology-derived pharmaceuticals, and standard tests are not appropriate [2]. The International Agency for Research on Cancer does not classify these molecules according to their risk [3].

The potential risks from long-term exposure of mAbs are unknown because they have only been in clinical use for a short period of time. Current data on the safety of mAbs are derived from preclinical studies on animals, but human toxicity profiles should be considered superior to any data from animal models or *in vitro* systems. Safety data extrapolated from their therapeutic use could be misleading because of different doses and routes of exposure between patients and healthcare staff. A great concern about mAb safety is related to their antigenicity. The allergic potential depends on the content of non-human protein in the molecular structure and could be more pronounced in immunocompetent people than in immunocompromised people [4].

In 2004, NIOSH generated a list of hazardous drugs in healthcare settings, and this list is updated periodically [1]. It was suggested that each organization should create its own list of drugs considered to be hazardous, based on the definition of dangerous drugs or when the mechanism of action may suggest a concern. The National Patient Safety Agency (NPSA) issued a safety alert in 2007, requiring all drug preparations, including mAbs, to be risk assessed, and the identified risks managed accordingly [5]. A proper method of evaluating the handling hazard of mAbs is not yet available.

In the Hospital of Parma, Italy, intravenous anticancer therapies have been admixed in the pharmacy in a centralized compounding facility (the UMaCA laboratory) since 2008, in accordance with Italian Regulations [6] and Ministry of Health Recommendations, which have been implemented in the Emilia-Romagna region [7]. The aim is to prevent errors in treatment, reduce healthcare staff exposure, and optimize the management of innovative high-cost drugs. Some mAb infusions, e.g. infliximab for

non-malignant disorders, are also admixed in the UMaCA laboratory, allowing vial sharing, so that wastes and costs are minimized. As exact toxicity data are missing, mAbs are handled in a safety cabinet in a separate sterile admixtures laboratory to avoid cross-contamination with cytotoxic molecules. Pharmacy staff wear personal protective equipment.

The aim of this study was to produce a risk-assessment document based on current knowledge to evaluate the hazard related to mAbs handling in the UMaCA laboratory and to determine proper safety measures.

Method

A working group was formed by pharmacists of the Pharmacy Service and chemists of the Prevention and Protection Service, Health and Safety Department. Summaries of product characteristics (SPC), safety data sheets (SDSs) and published toxicity warnings about mAbs were collected, and a literature review was undertaken.

In the Hospital of Parma, a software program (Log80) is used for traceability (prescription, compounding and administration) of anticancer therapies, and allows data extrapolation and processing. A chemical risk-assessment model, called MoVaRisCh, was applied. MoVaRisCh is a mathematical model approved by the technical groups of the regions Emilia-Romagna, Toscana and Lombardia to assess the chemical risk related to low-level exposure activities, as required by Italian legislation on occupational health and safety management [8]. A chemical risk is determined by the hazard of the substance or agent involved and by the relative exposure, according to the general formula:

$$\text{Risk (R)} = \text{Hazard (H)} \times \text{Exposure (E)}$$

Hazard of a chemical substance depends on intrinsic properties that can cause adverse effects when an organism, system or population is exposed to the agent. In this model, a score associated with the R-phrases of SDS is assigned to the parameter H, taking into account the most dangerous property. Exposure depends on chemical properties, amount of handled substance, type of process, type of control, exposure frequency, and distance from the source of emission. Type of molecule, amount and times of exposure can be extracted from the compounding software Log80 for each worker. A score is assigned to parameter E through an algorithm for every route of exposure, e.g. inhalation or dermal. The risk R is then calculated through the formula. The model fixes a cut-off of 21: chemicals with $R < 21$ are not hazardous and chemicals with $R > 21$ are dangerous for health. An economic evaluation of the use of closed-system handling devices was also conducted, comparing it with the traditional compounding method (needles and open-circuit devices).

Results and discussion

In the UMaCA laboratory, mAbs compounding is a significant part of daily activity, representing about 15% of the admixed therapies. Between 2009 and 2013, over 5,000 g of mAbs were handled in total.

Gentuzumab ozogamicin and brentuximab vedotin are handled as dangerous agents because of the known cytotoxic properties of their conjugates.

Since June 2013, the non-anticancer mAb infliximab has been compounded in the UMaCA laboratory. Infliximab was included in the 2009 updated list by NIOSH because of emerging safety warnings in the SPC [1]. Evidence from clinical studies and post-marketing experience has shown that people treated with antitumour necrosis factor agents, including infliximab, may develop lymphomas and second tumours, even if rare [9]. Therapeutic doses, however, are much higher than accidental exposure, and an analysis of the handling of antitumour necrosis factor agents revealed no evidence for systemic absorption after casual exposure. Therefore, simple universal precautions were suggested for workers, as an occupational hazard is unlikely [10].

Between 2009 and 2013, information derived from SPC and SDS of mAbs compounded in the UMaCA laboratory were recorded in safety data tables, see Table 1; those treated as cytotoxics were excluded (bevacizumab, cetuximab, infliximab, ofatumumab, rituximab, trastuzumab). Only few data can be found on mAbs safety.

Not one of the analysed mAbs showed carcinogenic or mutagenic properties [9, 11, 12]. Yet, no long-term preclinical toxicity studies were conducted, and mechanisms causing carcinogenicity other than genotoxicity cannot be excluded [3]. Developmental toxicity tests on animals were carried out only for bevacizumab, rituximab and trastuzumab. Bevacizumab showed embryotoxicity and teratogenicity in studies on rabbits, yet no studies on humans were carried out [9, 11, 12]. No clear evidence of developmental toxicity was found for the other mAbs, even if the mechanism of action might suggest a concern. All mAbs have an immunoglobulin G molecular structure, and could possibly cross the placenta through an active specific transporter, thus exposing the fetus to high concentrations of the drug. Data on fertility and pregnancy were not conclusive.

Summary of product characteristics are intended for industrial scale handling of raw material and are not easily translated into clinical settings. Workers in healthcare settings are exposed to lower doses than animal models and only in a discontinued way, thus limiting the possibility of toxicity. After a survey among some pharmaceutical industry laboratories, Pigneret-Bernard et al. [13] concluded that a hazard would be unlikely as no special measures were undertaken for mAbs preparation, even if considerably greater amount were handled than in hospitals.

Occupational exposure limits were defined for bevacizumab, rituximab and trastuzumab, with reported values over 100 µg/m^3

Table 1: Example of a safety data table for bevacizumab [9, 11, 12]	
Active substance – medicinal product	Bevacizumab, Avastin, humanized monoclonal antibody (IgG1).
Carcinogenic and mutagenic properties	No evidence found.
Developmental toxicity	No evidence found.
Effects on fertility	Repeated dose toxicity studies in animals have shown that bevacizumab may have an adverse effect on female fertility: inhibition of the maturation of ovarian follicles and a decrease or absence of corpora lutea and associated decrease in ovarian and uterus weight as well as a decrease in the number of menstrual cycles. Long-term effects of the treatment with bevacizumab on fertility are unknown.
Effects on pregnancy and lactation	As immunoglobulin G cross the placenta, bevacizumab may inhibit angiogenesis in the fetus, causing serious birth defects. A clinical trial in rats and mice revealed, depending on the dose, significant increases in abortifacient effects. No data are available on use in pregnant women. It is not known whether bevacizumab is excreted in human milk. As maternal immunoglobulin G is excreted in milk, bevacizumab could harm infant growth and development.
Hypersensitivity reactions	In some clinical trials, anaphylactic- and anaphylactoid-type reactions were reported more frequently in patients receiving bevacizumab in combination with chemotherapy than with chemotherapy alone. The incidence of these reactions in some clinical trials is common (up to 5% in patients treated with bevacizumab).
Most serious and most frequently observed adverse reactions	The overall safety profile is based on data from over 4,500 patients with various malignancies, predominantly treated with bevacizumab in combination with chemotherapy in clinical trials. The most serious adverse reactions were gastrointestinal perforations; haemorrhage; and arterial thromboembolism. The most frequently observed adverse reactions across clinical trials in patients receiving bevacizumab were hypertension, fatigue or asthenia, diarrhoea and abdominal pain.
Exposure controls/ personal protection	IOEL > 100 µg/m^3. Respiratory protection not necessary during normal operations. Protective gloves; safety glasses.

IgG: immunoglobulin.

[11]. In the SDS, goggles and gloves are advised, but respiratory protection is not necessary. In pharmaceutical industries, occupational exposure limits less than 10 µg/m^3 are fixed for highly potent or toxic drugs.

When evaluating hazardous drugs, the likelihood of exposure has to be taken into account [1]. Dosage forms, routes of exposure and standard drug-preparation procedures should be considered. Given the high molecular weight and protein nature of mAbs, only the inhalation route of exposure could be significant for healthcare staff, even if systemic passage is difficult to predict and seems to be low because only particles less than 5 µm could be absorbed [13]. An accumulation effect, however, cannot be excluded. Parenteral exposure can happen only in the case of an accident.

In the 2012 updated list of hazardous drugs, NIOSH did not include anticancer mAbs. Although some of them fulfilled the criteria for hazardous drugs, e.g. bevacizumab, cetuximab and rituximab, the probability of systemic exposure was extremely low in healthcare settings. Alemtuzumab, which was previously included, was removed. A recommendation was made to categorize substances as dangerous if the mechanism of action can suggest toxic effects. Bevacizumab is among the proposed additions to the list 2014 because, based on data from SPC, it belongs to US Food and Drug Administration (FDA) Pregnancy Category C (potential adverse effect on the fetus based on animal reproduction studies but no adequate and well-controlled studies on humans) [1].

To estimate if healthcare staff were adequately protected from a potential hazard related to mAbs handling in the UMaCA laboratory, the working group produced a risk-assessment document, and applied the MoVaRisCh model. The formula $R = H \times E$ was applied.

As the inherent hazard of mAbs was unknown, the parameter H had to be calculated. R was assigned the cut-off value of 21 (maximum value for non-hazardous agents) and E was derived for the inhalation and dermal routes of exposure. Thus, a value H1 was obtained, which is the maximum hazard against which workers are protected in the analysed conditions of exposure so that the level of risk could remain below the established limit of danger ($R < 21$).

The side effects observed in patients and reported in SPCs were empirically converted into R-phrases, which were assigned a score according to the MoVaRisCh model; therefore, a second coefficient H2 was obtained, which represented the empirical hazard to which workers are exposed. These two coefficients H1 and H2 were then compared, see Table 2.

When H1 is greater than H2, the working conditions are adequate to protect operators against a possible hazard. When

H1 and H2 are similar, the working conditions have to be re-evaluated and could possibly be improved. If H1 is less than H2, the conditions are not sufficient to protect workers, but this was not our case.

From software reports, times of exposure to mAbs of less than 30 minutes per day for each operator, on average, were achieved. The total amount of handled molecules were low, less than 4g per day.

On the basis of published research, a medium to high risk was assigned to mAbs. Langford et al. [4] developed a risk-assessment tool based on relative antigenicity of the different mAbs and on toxic potential from their therapeutic use as reported in SPCs. The obtained health and safety score was combined to NPSA assessment risk score to achieve an overall risk for each mAb. They were divided into two categories: group 1 mAbs (bevacizumab, cetuximab, rituximab, trastuzumab, infliximab) have a moderate-high risk and should be prepared in pharmacy facilities; group 2 mAbs are considered low risk and could be prepared in clinical areas. A German working group applied a risk-assessment algorithm to mAbs for anticancer therapy (Anatomical Therapeutic Chemical classification system L01XC) according to European regulations for dangerous substances, and concluded that mAbs should be handled as hazardous with maximum protection for workers because they have the potential to cause harm to humans [3]. They underline, however, that the assessment applies first to the active drug substance and not to the medicinal product, even if this should be considered toxic. Furthermore, they report that estimated occupational exposure is several orders of magnitude lower than therapeutic doses. A risk classification was carried out in The Netherlands, based on carcinogenicity, teratogenicity and other toxic properties. Monoclonal antibodies were assigned to class 3 (possible risk not likely, as for infliximab, rituximab, trastuzumab) or 4 (possible risk of embryotoxicity, as for bevacizumab, cetuximab), with class 5 being the most hazardous [14].

When toxicological data are incomplete or unavailable, it is prudent to handle drugs as hazardous until adequate information becomes available [1], according to a precautionary principle. Nevertheless, it is important not to overestimate the risk. The use of closed-system transfer devices for mAbs compounding would certainly reduce the handling hazard in clinical areas but the real risk is to be evaluated if the manipulation occurs in pharmacy facilities by trained personnel that follow specific procedures [5]. For the same reason, an accidental injection is unlikely when admixing is performed in a pharmacy facility. The use of closed-circuit transfer devices in the UMaCA laboratory would have represented an increase in costs of about Euros 20.000/year that could be justified only if a hazard is demonstrated.

The results obtained by applying the MoVaRisCh model showed that the working procedures in the UMaCA laboratory efficiently protect healthcare staff against possible hazards related to mAbs handling. Centralization of admixing in a pharmacy facility, the use of a vertical laminar air flow hood and personal protective equipment, the relatively small amount of mAb molecules admixed compared with industrial scale handling, the protein nature of mAbs, which limits a systemic exposure, the great difference between therapeutic doses in patients and hypothetic accidental exposure doses in workers are all factors that make a significant occupational hazard as unlikely.

Conclusion

Because of the paucity of data about safety aspects, mAbs compounding should be made in specialized pharmacy facilities by trained personnel. Specific working procedures, including the use of personal protective equipment, are strongly advisable. Handling mAbs in a separate laboratory, or at least in a different safety cabinet, can avoid cross contamination with cytotoxic agents, for which a distinct risk is known, above all for mAbs used in non-malignant diseases.

An additive effect should be considered, as healthcare staff handles more than one mAb during their work session.

Table 2: Coefficients calculated by the MoVaRisCh model

Monoclonal antibody	H1	H2	Rating
Bevacizumab (Avastin)	6.50	6.50	When P1 is approximately equal to P2, it is necessary to review with care the assignment of the scores before considering the working conditions as adequate.
Cetuximab (Erbitux)	6.50	4.75	Prevention and protection measures are adequate.
Infliximab (Remicade)	6.50	6.50 (*7**)	When P1 is approximately equal to P2, it is necessary to review with care the assignment of the scores before considering the working conditions as adequate.
Ofatumumab (Arzerra)	6.50	4.50	Prevention and protection measures are adequate.
Rituximab (MabThera)	6.50	4.75	Prevention and protection measures are adequate.
Trastuzumab (Herceptin)	6.50	6.50	When P1 is approximately equal to P2, it is necessary to review with care the assignment of the scores before considering the working conditions as adequate.

H1 is the maximum hazard against which workers are protected; H2 is an empirical parameter of hazard to which workers are exposed.
*H2 value of 7 could be calculated for infliximab if the warning of 'possible lymphomas and second tumours development in patients' was considered, assigning the R-phrase 'limited evidence of a carcinogenic effect', but an occupational exposure was not demonstrated and is unlikely.

Software reports are useful to monitor such occupational exposure frequency and to plan a proper medical surveillance programme.

Although we are aware that MoVaRisCh could not be the optimal model to estimate the occupational hazard related to mAbs handling and in the absence of an alternative proper method, our results show that preventive and protection measures applied in the UMaCA laboratory are adequate to protect healthcare staff during mAbs handling in the current conditions of exposure, especially for the inhalation route. This is crucial because the inhalation route is the most likely for mAbs exposure and a hypersensitivity effect cannot be excluded, independently of the dose.

As evidence of harm to healthcare staff can emerge after many years, further data, including specific studies on humans and warnings about handling in SDS, are necessary and strongly desirable to develop guidelines on mAbs occupational risk and possible toxicity profile changes should be estimated in the next future with the use in therapy of biosimilars.

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Lean thinking applied to a chemotherapy centralized preparation unit

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Abstract

Introduction: Most people with cancer are treated by intravenous chemotherapy and receive their treatment in the Chemotherapy Day Unit (CDU). Increased demand for treatment in our cancer centre, the CDU and the Chemotherapy Centralized Preparation Unit (CCPU), has increased waiting times for patients and the level of pressure on staff. To improve the efficiency of the CCPU and its planned renewal, we introduced a business approach based on lean thinking that aims to eliminate 'muda,' or waste, in workplace processes.

Materials and methods: A multidisciplinary workgroup, involving pharmacy staff and staff from the quality department, was established. Step-by-step lean thinking was implemented with a 'define', 'measure', 'analyse', 'improve', and 'control' (DMAIC) approach: value-stream mapping was used to map out essential tasks within the CCPU. Lead times in healthcare operations within the pharmacy department and the CDU (haematology and oncology) were determined during a 5-day study; 5S principles ('sort', 'set-in-order', 'shine', 'standardize', 'sustain') were applied.

Results and discussion: 5S principles were used to organize the different areas in the CCPU and to improve staff working conditions. On the basis of the current value stream mapping (VSM) and through discussions with the different stakeholders, waste processes were identified, and the redesign of a future state process map is under way. Brainstorming meetings were used to propose solutions to the wasteful processes related to the seven 'classical' muda (transportation, inventory, motion, waiting, over-processing, over-production, and defects). A DMAIC approach will be used to evaluate these proposed solutions, based on current lead-times, quality indicators, and patient satisfaction questionnaires.

Conclusion: Lean thinking is still in progress in the CCPU. Effective completion of the identified improvements should free up resources on the ward, which can be redirected towards better patient care. If successful in the pharmacy department, this business approach could be extended to clinical wards.

Keywords: Chemotherapy Centralized Preparation Unit, oncology, value stream mapping

Introduction

Each year, 33,000 intravenous chemotherapy preparations are produced and administrated in the Cancer Centre Henri Becquerel in Rouen, France. Patients are treated for haematological cancer, e.g. lymphoma, leukaemia, myeloma; and oncological cancer, e.g. gynaecological, ear, nose and throat, and breast cancers. They receive their treatments in the Chemotherapy Day Unit (CDU), which has a capacity of 16 patients a day. In order to meet the increased demand for treatments (up by 13.8% in 2012), a range of 80–200 intravenous chemotherapies are prepared daily, with an average of 137 a day for the CDU. The financial budget for this activity is set, with a cap on recruiting additional staff. Therefore, the workload of pharmacy and nursing staff is too high, and they are under too much pressure to ensure the lowest risk of errors. From the patient's perspective, waiting times have increased, which causes frustration; at worst, medication errors that may affect the patient are made, which would have previously been detected.

The aim of this project is to improve the efficiency and quality of medical care. This can be achieved by reducing waiting times for patients and minimizing medication errors through improved working conditions among pharmacy and nursing staff. Additionally, the aim is to streamline production in the chemotherapy unit, thus eliminating wastage. Therefore, a multidisciplinary workgroup comprising a quality engineer, pharmacy staff and the CDU doctors was established. This workgroup holds weekly meetings. The chosen method, 'lean thinking', has been used in the Japanese car industry. More recently, lean health care has been used by hospitals in Europe in the medical [1], biological [2] and pharmaceutical sectors [3]. Only a few French hospitals have experimented with the lean healthcare approach.

Following an audit four years ago by the Regional Association for the Improvement of Working Conditions (Association Régionale d'Amélioration des Conditions de Travail, ARACT) of Haute-Normandie, pharmacy staff began meeting weekly to discuss ways of improving work life. A year later, the five lean concepts were introduced into the process between the CDU and the pharmacy [4, 5]. This project has been structured with a 'define' 'measure', 'analyse', 'improve' and 'control' (DMAIC) approach.

Step one: definition of the project

Initially, the multidisciplinary workgroup consisted of a pharmacist, a CDU doctor and a quality engineer. Later, a pharmacy student, a quality assurance trainee, and an executive joined the project group.

The aim of lean health care is to avoid financial, spatial and temporal wastes ('muda' in Japanese) in the manufacturing and administration process, to work continuously and smoothly without overstock, and to make continual improvements (called kaizen). The seven muda are transportation, inventory, motion, wait, over-processing, over-production, and defect.

A process improvement begins each time with an analysis of the process. Value stream mapping (VSM) is a good tool for this first step. It documents the different steps in the process and captures time elements. In order to analyse waste, a structural diagram was built to show material and information flows, and therefore to highlight the time the process needs and the time it usually wastes. Compared with customers' expectations, the process steps can be separated into value added and non-value added steps. Value-added activities must be maintained; they directly address customers' expectations. Non-value added activities should be removed and entitled 'waste' [6]. They represent the core performance loss that generates delays. The VSM identifies relationships between the different stakeholders (Chemotherapy Centralized Preparation Unit [CCPU], CDU and Pharmacy).

Step two: measure of indicators

The different steps in the process were identified by VSM, and each of those steps had to be analysed in terms of time. The goal of this time study was to measure waiting time for patients and the total non-value added time. A 5-day study was then organized to measure all times between the CCPU and the CDU. The average time was calculated for each step, and abnormal times were identified. The project group created two collection grids for the CCPU and the CDU. At the pharmacy, the people who produced the schedules are not members of CCPU staff. For the CDU, the collection grid was given to patients. A blank field stands for patients' opinions on this grid. Results will serve as a database representing the working conditions before lean implementation. For this study, an information display set was installed in the waiting room of the CDU.

The VSM diagram, see Figure 1, illustrates the process, and shows the different statekholders involved. The colour blue details a patient's pathway through the CDU, from a patient's reception, to chemotherapy administration, via the consultation, the prescription, and the premedication.

Beige represents the pharmacy, and includes the CCPU and its links with the medical device unit, the pharmacist office, and the clinical trials sector. Steps in the infusion preparation process have been identified, from pharmaceutical validation to dispensation. For each step, the number of operators required and storage responsibility is specified. All physical or network relationships between the different areas and entities (stakeholders, patients and suppliers) were determined. On the basis of this analysis, the duration of the different steps was determined, and 'wasted' and 'useful' times were represented in red and green, respectively); this preliminary work was required in order to proceed to the next phase of study. Duration of 'useful' steps may decrease with practices, but it seemed more appropriate to reduce non-value added time. The total duration of non-value added time was calculated for each patient, with an average of 1 hour, and extending up to 3 or 4 hours. Optimal care was identified at this stage. The VSM highlighted areas needing improvement. For example, at the start of the study, the pneumatic sending system needed improving and the return flow for unused chemotherapy needed to be secured.

Step three: analysis

To understand the maximal values, e.g. a medical consultation up to 4 hours, the workgroup needed some additional medical information, which had not been noticed on the grid.

For example, in the pharmacy, the lead-time between prescription and pharmaceutical validation should be zero. Here, on average, the time was about 6 minutes, with abnormal times up to 24 minutes. This abnormal time is frequently observed in the morning between 8:45 a.m. and 9:15 a.m. This may be attributed to the fact that the pharmacy student responsible for validation starts work at 9:00 a.m.; CDU doctors begin earlier in the morning. Therefore, at the request of a CDU doctor, a modification to the computer software enabled medical validations to be made the day before to avoid delays on the morning of sterilization.

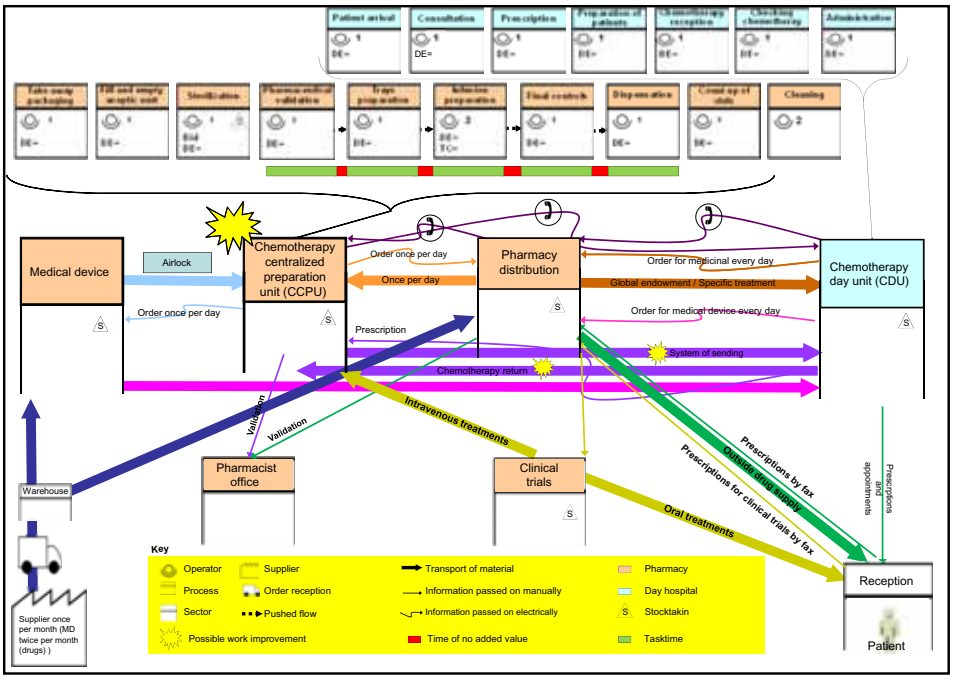
In the CDU, patients attend for appointments either too early or too late by up to 15 minutes. Their advanced arrival does not mean that the doctor sees them ahead of their appointment. This adds to their boredom of waiting. The delay between patients' arrival and their consultation with the doctor can be more than 1 hour. The delay between the delivery of the infusion to the ward and its administration can also be over 1 hour.

We completed this study with a brainstorm about the seven muda: transportation, inventory, motion, wait, over-processing, over-production, and defect. As a result of the brainstorming with pharmacy staff, some solutions were proposed to reduce time wasting: (1) to change the cytotoxic drug's storage area with the system 'kanban' (full/empty); (2) to introduce a visual management of the pharmacists' presence (with a board on the office door); (3) to create an interprofessional working group with the CDU to discuss medical validations earlier in the day to reduce late prescriptions in the morning; (4) to diminish unnecessary and distruptive phone calls by training teams to the CCPU by allowing them to access information; and, finally (5) to introduce continuous pharmaceutical presence to reduce delays with clinical trials. The results of the brainstorm need to be classified and prioritized according to feasibility, ease of implementation, and the importance of expected results.

Step four: improve and control (ongoing)

A reflection of the 5S principles ('sort', 'set in order', 'shine', 'standardize', 'sustain') was conducted. These principles aim to optimize the workplace by simplifying toolsets and clarifying the physical layout of processes. The application of this system to the CCPU yielded a number of improvements. The main improvement was the removal of some unused equipment, and elimination of some old procedures. It gave the pharmacy staff the opportunity to discuss the workspace organization. At first, each workstation was discussed, and all unnecessary pieces of equipment were removed. Where it was unclear whether or not a piece of equipment was necessary, it was put aside in another

Figure 1: Value stream mapping of the chemotherapy centralized preparation unit



room for ease of access. Then, the staff agreed to organize everything into its agreed place. Thirdly, the cleaning step 'shine' was easy because of the type of equipment, as was standardization of equipment and materials. Finally, this year will see the arrival of a new safety cabinet to prepare lean chemotherapy with a short sterilization, several times a day, with efficient storage. A kaizen worksite is under development, for example, to reduce the delay of pharmaceutical morning validations. The pharmacy student starts working at 8:30 a.m., at the same time as the doctors of the CDU. The organization of morning sterilization was discussed again with the staff.

Results and discussion

Lean improvements, using the DMAIC approach, are still in progress. The definition of the project and the measure of indicators have been completed; the project is now between analysis and improvement. With the aid of VSM, the time study, and the muda brainstorming, a list of areas for improving the UPCC was devised. Some improvement tracks are being implemented. More should be done to develop a structured action plan and to prioritize the tracks. This action plan must be validated by a multidisciplinary workgroup and involves a discussion about patient programming. The choice was made not to compare data obtained with benchmarking but to make basic improvements and a similar study will be conducted in a few months to evaluate the effectiveness of actions taken. Indeed, it is difficult to find an institution with similar processes that would have conducted and provided this type of study. Therefore, a new date must be scheduled to evaluate the effectiveness of actions taken. The interviews of patients showed a lack of knowledge of the different steps of their care; they underestimated the activities carried out by the pharmacy because of its lack of visibility. A multidisciplinary project to create posters for display in the waiting room of the CDU is in progress. All stakeholders must agree with the principle that non-value-added time can be redistributed to improve patient care [6].

The purpose of lean health care as has been applied here is not to eliminate jobs but to redistribute personal time to other tasks. It can reduce the risk of error by instituting a more relaxed working environment [3]. To ensure proper implementation, this work must be carried out with the support of the institution's management and unions. Staff involvement is important, as it will increase acceptance of proposed remedial actions. The composition of the multidisciplinary project group is also a key point [7].

This approach presents different risks. Progression may be limited by the degree of training and of the openness of staff to change [8]. Visual management will assist in staff comprehension. The time-study data, however, are subject to bias, as measurements were made by staff assessors using stopwatches, which caused stressed among staff being assessed [9]. Despite the formation of a multidisciplinary working group, the main areas of action involve investment and time management from the healthcare team of the CDU. Because of the duration of this approach (18 to 24 months) [7, 9], there is a risk of weariness from the different teams involved.

A number of ideas have been proposed for improvement; however, these will require significant staff mobilization, including the collection and analysis of the time-study data. It is important that this work does not practically affect existing workload, and no time or resources have been allocated to carry out this work, apart from the presence of the quality student. The time spent in steps of diagnosis and measurement may be perceived by the team as lost time. Nevertheless, this project began only a year ago, and already a lean philosophy is in operation within the team. The deployment of lean in the Centre Henri Becquerel strengthens the managerial policy of the institution in its desire to open up its services and work in multi-professional groups. It can provide assistance in the expansion of the CDU, a target in the medical-scientific project of the cancer centre.

Conclusion

During a period of cost containment, lean thinking is an original approach that can help to improve waiting times and staff working conditions. At the moment, this project has achieved

a good overview of current lead times of the different processes. This will serve as a basis for reducing identified wasted times. Today, the 'improve and analyse' steps are ongoing. Some measures have already been implemented, such as the 5S principles in the CCPU. These methods will be implemented in the pharmacy and in the new CCPU. It will be interesting to compare time baseline data with data obtained after the implementation of all the chosen measures so that improvement can be evaluated [7]; however, it is important that those data are collected under the same conditions. Improvements that we proposed at the end of this study still need to be validated with the different stakeholders.

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'iMedicPlan' for compliance: can it improve life?

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Single agent anti-mucositis protocol for oral and gastrointestinal mucositis and other implications on current concepts regarding chemoradiation induced mucositis and its management from a phase IV post-market surveillance of ProThelial – high potency polymerized cross-linked sucralfate (HPPCLS)

Ricky W McCullough, MD, MSc

Abstract

Introduction: The side effect of chemoradiation induced mucositis impacts adherence and reduces survival due to dose reductions in treatment, interruptions and cancellations. Current concepts regarding mucositis management are formed by mucositis guidelines supporting the use of 12 interventions that have fractional clinical effects on mucositis and even less effects in reducing the cost of care or enhancing survival of the mucositis patient.

Objective: This report contrasts the limitations of current concepts of mucositis management with the utility of high potency polymerized cross-linked sucralfate (HHPCLS), a single anti-mucositis agent with expanded therapeutic outcomes. These outcomes include complete, rather than fractional, effects on mucositis regardless of: (a) its location in gastrointestinal tract; (b) the agent causing mucositis; or (c) the clinical setting of cancer treatment.

Methods: Review current concepts regarding mucositis management as seen in the Multinational Association of Supportive Care in Cancer (MASCC) clinical guidelines. Discuss attempts by oncology pharmacists to implement these guidelines in part as a standardized protocol. Juxtapose these multi-interventional approaches to the use of a single-agent (HPPCLS) in a recent multi-institutional phase IV observational study.

Results: Guideline supported, multi-interventional management of mucositis provide incomplete and fractional effects. HPPCLS provide statistically significant outcomes comprised of complete prevention, rapid and complete reversal without regard to mucositis location in the GI tract, agent causing it or the clinical setting of its occurrence.

Conclusion: Current concepts supporting multi-interventional management of chemoradiation induced mucositis are challenged by the elimination of mucositis using a single agent. A HPPCLS anti-mucositis protocol for complete prevention and rapid treatment of oral and GI mucositis is suggested for practice.

Keywords: Gastrointestinal mucositis, MASCC guidelines, oral mucositis, polymerized sucralfate

Introduction

Mucositis is a major side effect for many patients prescribed chemoradiation treatment for cancer. Using current interventions, mucositis is impossible to completely prevent or completely reverse once established regardless of its cause. Rapid and complete restoration to normal mucosa during active chemoradiation treatment has never been reported. Instead, most therapeutic options for mucositis provide incomplete effects of minimal reductions of mucositis incidence or palliation of mucositis discomfort. Neither of these outcomes substantially lowers the cost of care.

Pain is the most significant symptom reported by patients, however the problem related to mucositis extends far beyond that of pain. In 44% of patients, intestinal mucositis caused by myeloablative chemotherapy (high dose melphalan) in human stem cell transplant patients lead to febrile bacteremia unrelated to neutropenia [1]. This represents a fourfold increase in the risk of systemic bacterial infection compared to patients with minimal or no intestinal mucositis [1]. Because of its pain and associated anorexia, mucositis becomes a major obstacle for adherence to cancer treatment. Patient-reported severity of mucositis escalates as high as 40% [2] in successive cycles of chemotherapy. Dose reductions are required in subsequent cycles of chemotherapy in 25% of patients if they develop any grade of any type of mucositis (oral or gastrointestinal) in the previous cycle of chemotherapy. Counter-intuitively, dose reductions are more common in patients with less severe Grade 1–2 oral mucositis (13%) than in those with more severe Grade 3–4 oral mucositis (10%) [3]. To continue therapy in 60% of patients with Grade 2 and 3 oral mucositis, dose reductions are required, while in an additional 30% of such patients, chemotherapy has to be discontinued [4, 5].

Given that optimal chemoradiation therapy maximizes survival, any dose reduction, interruption or cancellation directly impacts survival. This logical assumption of decrease survival due to unplanned treatment interruptions or modifications has been verified with radiotherapy. In a retrospective study of 1,267 patients receiving radiation therapy, 11% are subject to treatment modification or interruptions [6]. These deviations from optimal dosing were associated with significant survival outcomes [7]. While no breaks in radiotherapy provide 65% survival rate in those patients with head and neck cancer, breaks during the first 3 weeks were associated with 61% survival, breaks during middle 2 weeks with 25% survival and breaks during the last 2 weeks of radiation with 18% survival [8]. Besides the obvious toll in morbidity and mortality, the incidence of oral and gastrointestinal mucositis increases overall cost of cancer care by 35–45% in the US [3, 9-12] and in Europe [13, 14]. Thus, complete elimination of mucositis would therefore reduce the current costs of care, reduce morbidity and in some patients enhance their survival.

Clearly, the clinical management of the mucositis side effect is an urgent need. It is a challenge for oncology pharmacists and other practitioners. The question raised once in the past remains ever real today: 'Can anything be done about oral mucositis?' [15]. Indeed, the history of managing mucositis is long and arduous. Efforts for better nursing assessments have led to enhanced surveillance and some incremental clinical improvements [16, 17]. Periodic audits commissioned by medical working groups of clinical associations have helped raise the profile of this side effect [18-20]. But the better known and more constant endeavour through the years has been the annual publication of mucositis guidelines by the mucositis working group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) [21-24].

Indeed, current concepts on the management of oral and gastrointestinal mucositis have been shaped by MASCC guidelines, which either support or declined to support the use of interventions reported in the literature. The context of supportive guidelines include: (a) the type, dosing and method of administration of an intervention; (b) the intent of use (prevention versus treatment); (c) the location of mucositis (oral versus gastrointestinal); (d) the treatment modality causing mucositis; and even (e) the clinical treatment scenario wherein support for use of the intervention was derived. Efficacy of supported interventions is held by these contextual components and it is understood that any single guideline is to be practiced within the conditions of these contextual components. Thus, there remains the dilemma of whether efficacy is preserved should any one component be altered by the real world situation of clinical practice. Therefore, generalizability and transference into practice, that is, the practicality of these guidelines, have been debated by oncology pharmacists in the past [25]. A standardized protocol incorporating multiple guidelines has achieved moderate success [25]. Yet efforts to date have yielded interventions that provide only limited and fractional benefit. As declared in 2003, by JP Donnelly et al. [15]: 'it has seemed very unlikely that a single agent will be sufficiently pleiotropic to both prevent oral mucositis from starting and accelerate recovery of the oral mucosa.'

Responding to this declaration and in contradistinction to current mucositis interventions, are the statistically significant clinical outcomes demonstrated by high potency polymerized cross-linked sucralfate (HPPCLS) prescribed to patients registered in a phase IV post-marketing study. These outcomes included: (a) complete prevention of oral and esophageal mucositis; (b) complete and rapid restoration of oral mucosa and esophageal function during chemoradiotherapy; and (c) complete and rapid elimination of signs and symptoms of small bowel and colonic mucositis sustained throughout chemoradiation treatment. There will be a brief review of the phase IV study, though outcome results have been reported elsewhere [26-28]. In this report, specific focus will be given to the implication these results have on prevailing concepts regarding mucositis and its management.

To accomplish this, there will be an initial review of current MASCC guidelines, their practicality and generalizability as well as past efforts to incorporate multiple interventions into a practicable anti-mucositis protocol. Then, following a brief review of outcomes from the single agent (HPPCLS) study, current concepts of mucositis management will be addressed. In conclusion, a single agent HPPCLS protocol is suggested for review and examination by oncology pharmacists to address the incidence of mucositis in their respective institutions.

Review of current MASCC mucositis guidelines

The current concepts regarding the management of mucositis are embodied in the construct of the MASCC guidelines. Interventions supported by MASCC define efficacy in the context of required elements of practice. That is, interventions are supported based on efficacy defined by treatment modality causing mucositis, anatomic location of mucositis, the type of cancer under treatment and other contextual arrangements. The guidelines themselves are generated from a review of published reports categorized by weight of evidence. The guidelines are then presented as a series of recommendations and suggestions either for or against the use of an intervention within a specific cancer treatment scenario. Each guideline is based on the outcome analysis of randomized controlled trials that have been peer reviewed [21-23]. Of the 8,279 papers identified, 1,032 were retrieved for evaluation with eventually 570 articles qualified for final inclusion in the 2014 MASCC guidelines [24]. Table 1 lists all MASCC guidelines supportive of interventions, their respective intent of use, whether for prevention or treatment and other contextual elements that defined their efficacy.

The 2014 guidelines have two recommendations and five suggestions favouring the use of seven different interventions to manage gastrointestinal mucositis (GIM). Four interventions are supported for the prevention of GIM and three for the treatment of GIM. There are three recommendations against the use of other interventions in managing GIM.

For oral mucositis (OM) ulcerations, there are four recommendations and three suggestions favouring the use of five different interventions for management of ulcerations. All seven supportive positions are for interventions to prevent the onset of OM. There are none recommended for the treatment or reversal of OM. For oral mucositis pain, there is one recommendation and four suggestions favouring five different interventions.

Countering these supportive positions for the management of OM, there are five recommendations against the use of four different interventions and five suggestions against the use of five different interventions intended to either treat or prevent OM varying cancer treatment scenarios.

Table 1: MASCC guideline recommendation/suggestions for 2014

Intervention	Dose/Timing	Route	Indication	Intent	Cancer treatment	Other controlling conditions
Gastrointestinal mucositis						
Amifostine	Unmentioned	IV	GIM-Esophagitis	Prevention	NSC Lung Cancer	Concomitant Chemoradiation
Sulfasalazine	500 mg bid	Oral	GIM-Enteropathy	Prevention	Unmentioned	Pelvic Radiation
Octreotide	> 100 gm	SQ	GIM-Diarrhoea	Treatment	HSCT	Std/High dose Chemotherapy
Probiotics	UM	Oral	GIM-Diarrhoea	Prevention	Pelvic Malignancy	Chemoradiation Therapy
Amifostine	> 340 mg/m^2	IV	GIM-Radiation Proctitis	Prevention	Unmentioned	Receiving Radiation Therapy
Sucralfate	Unmentioned	Enema	GIM-Chronic Radiation Proctitis	Treatment	Unmentioned	Patients with rectal bleeding
Hyperbaric O2	Unmentioned		Radiation-induced Proctitis	Treatment	Solid Tumour	Radiation for solid tumour
Oral mucositis (Stomatitis)						
Cryotherapy	30 min prior	Oral	Oral Mucositis	Prevention	Unmentioned	Receiving bolus 5FU
Cryotherapy	Unmentioned	Oral	Oral Mucositis	Prevention	HSCT	High dose Melphalan ± Total Body Radiation
LLLT	650.0 nm	Oral	Oral Mucositis	Prevention	HSCT	High Dose Chemotherapy ± Total Body Radiation
LLLT	632.8 nm	Oral	Oral Mucositis	Prevention	HNC	Radiation ± Chemo
Palifermin	Protocol	IV	Oral Mucositis	Prevention	HSCT	High Dose Chemotherapy Plus Total Body Radiation
Benzydamine	0.5%	Oral Rinse	Oral Mucositis	Prevention	HNC	Moderate Radiation < 50 Gy Without Chemotherapy
Zinc	Unmentioned	Oral	Oral Mucositis	Prevention	Oral Cancer	Radiation or chemotherapy
Oral Hygiene	Unmentioned	Oral	Oral Mucositis	Prevention	All Cancers	All treatment modalities in all age groups
Pain attenuation						
Morphine	Unmentioned	IV	Mucositis Pain	Treatment	HSCT	High Dose Chemotherapy ± Total Body Radiation
Fentanyl	Unmentioned	Transdermal	Mucositis Pain	Treatment	Unmentioned	High Dose Chemotherapy ± Total Body Radiation
Morphine	2% solution	Oral Rinse	Mucositis Pain	Treatment	HNC	Chemoradiation
Doxepin	0.5% solution	Oral Rinse	Mucositis Pain	Treatment	Unmentioned	Unmentioned

5FU: 5-fluorouracil; bid: twice daily; HNC: head and neck cancer; HSCT: human stem cell transplant; IV: intravenous; LLLT: low level laser therapy; NSC: non-small cell; Std: standard; SQ: subcutaneous.

The problem of transference of controlled trial settings into clinical practice

Structure of the guidelines is derived from the contextual elements in which the controlled trials were performed. The conversion of conclusions from clinical trial data into guidelines, by design requires, for the practice of those guidelines, the transference of controlled trial parameters (necessary for appropriately powered clinical studies) into the uncontrolled environment of daily clinical practice. Table 1 lists the intent of intervention, the cancer treatment utilized and other trial critical conditions that generated the efficacy data for each intervention. Seldom will exact contextual parameters required for clinical trials that defined the efficacy of the intervention be reproduced in the daily routine of clinical practice. Thus, there remains a lingering question over each guideline as to transference. That is, will the efficacy of an intervention observed in a rigid trial

setting actually persist if that intervention is used in the shifting environment of clinical practice? Even further, the question arises as to the impact on the efficacy of intervention previously defined by a controlled setting, when the use of that intervention is switched to the uncontrolled setting of a busy oncology practice.

It is this conundrum that challenges the practicality of any guideline constructed purely from data extracted from a controlled trial setting, a setting wherein the multiple contextual conditions of the trial are unlikely to be reproduced in the real world. To identify interventions that are likely not to work, guidelines are great tools. To identify interventions that show efficacy in an artificially controlled environment, it is difficult to predict an intervention's efficacy in uncontrolled settings where many factors of the environment differ. And again, we are speaking of only fractional efficacy.

Practicality of mucositis guidelines

Despite their usefulness, the practicality of a mucositis guideline is limited. As seen in Table 1, the recommendation of each intervention is crafted around a specific cancer treatment setting, implying that such interventions may not be useful against mucositis occurring in different settings. This underlying implication limits practicality. Guideline utility that is confined by 'treatment-setting' limits the generalization of each guideline, and by extension, imply the requirement of a new guideline for every possible cancer treatment scenario. The multiplicity of variables that inform each guideline – the anti-mucositis agent, its dosing, its means of administration, the three types of anti-neoplastic modalities used, their independent dosing, together with the type and stage of cancer under treatment – severely limit general application each guideline. The practicality is challenging for practitioners and clinical pharmacists who manage mucositis occurring in clinical settings where any one combination of contextual components may occur. Under such conditions, 'pocket-ready' guidelines for the management of OM and GIM, remains impracticable.

Regarding MASCC guidelines – definition of treat and prevent

The terms 'to treat' or 'to prevent' in the MASCC guidelines are symbolic, meaning 'toward treatment' and 'toward prevention'. They do not mean, as implied, complete reversal or complete prevention of occurrence. Complete versus incomplete reversal or prevention of OM and GIM is substantively meaningful to patients, as they are left with the reality of persisting mucositis and its interference with treatment adherence, self-nutrition, and survival. There are two interventions recommended or suggested 'to treat' gastrointestinal mucositis. Neither of these interventions is associated with complete reversal (full treatment) of GIM. As with all interventions supported by the guidelines, none are associated with patient-relevant complete prevention or complete reversal of OM or GIM. Terms used in the guidelines such as 'to treat' or 'to prevent', mean fractional reversal and fractional prevention by report and in practice. To the patient who must tolerate optimal cancer treatment for a cure, mucositis treatment or prevention is experienced as entire with total lack of persistence of any sign or symptoms of disease. Likewise to payers, in terms of cost of care, fractional treatment and fractional prevention may not provide a meaningful impact on the pharmacoeconomics of managing mucositis.

Guidelines for oral mucositis interventions

Of the guidelines for interventions to manage oral mucositis (OM), none are for treatment; seven are for fractional prevention and four for palliation of pain. Of the seven interventions recommended or suggested 'to prevent' OM, each only fractionally lowers but do not completely eliminate the incidence of severe grades of OM (Grades 3, 4). None of the seven can prevent or reduced the incidence moderate grades of OM (Grades 1, 2). The guidelines supported the use of standard potency non-polymerized sucralfate as an enema for the treatment of chronic radiation-induced proctitis in patients with rectal bleeding. However, its use was not supported for the treatment of GIM, and not supported for the prevention or treatment of OM. High potency polymerized cross-linked sucralfate has yet to be reviewed by MASCC/ISOO.

Clearly, from current guidelines, no single intervention satisfactorily addresses the incidence and persistence of mucositis throughout the entire length of GI tract during chemoradiation treatment. Thus after three decades of search, options to mitigate the impact of OM and GIM remain limited to a few, that is, 12 interventions, with, fractional clinical efficacy and minimal impact on the cost of care or survival.

Standardized protocol incorporating multiple MASCC interventions

Considering that 'the standard of care under the MASCC guidelines was palliative treatment rather than preventative or curative measures', a group of oncology pharmacists implemented a standardized protocol for prevention and management of mucositis at the Memorial Sloan Kettering Cancer Center in New York [25]. Table 2 lists the interventions utilized by Bhatt et al. which was a 'multi-front, multi-agent' routine standardized for patients receiving myeloablative chemoradiation. The protocol achieved meaningful institution-based reductions in the incidence and severity of two grades of mucositis (Grade 1 and 3) as well as reductions in the average length of hospital stay for patients undergoing bone marrow transplant. However, complete prevention, complete reversal and elimination of oral mucositis eluded this protocol as well. Grade 1 and 3 oral mucositis persisted in over 75% of the patients. There was no change in incidence of GIM, as all patients still required parenteral nutrition due to the persistence of intestinal mucositis [25].

The protocol in Table 2, is labour-intensive. It required 'around-the-clock' use of seven different interventions (cryotherapy, oral brushing, chlorhexidine, normal saline mouthwash, Caphosol mouth rinse, magic mouthwash, Cepastat (phenol) lozenges and palifermin). Each intervention, individually, was known to have fractional impact on oral mucositis. Yet the additive effect

Table 2: Published anti-mucositis protocol for haemato-poietic stem cell transplant patients [25]

1. Crytotherapy 30 minutes prior to and throughout Melphalan infusion
2. Brushing with soft tooth brush for oral hygiene: every 12 hours
3. Chlorhexidine gluconate mouthwash swish 30 seconds: every 6 hours
4. Normal saline mouthwash swish 30 seconds: every 6 hours
5. Caphosol mouthwash swish 30 seconds: every 6 hours
6. Magic mouthwash swish: every 6 hours
7. Cepastat (phenol) lozenges: every 2 hours

of their combined use still failed to completely eliminate or completely prevent mucositis.

Review of HPPCLS as a single agent for oral and GI mucositis

Purpose of section: exploring the significance of HPPCLS effect on mucositis

Discussed thus far are the interventions supported by MASCC guidelines, the practicality of the general use of such guidelines, as well as the experience of an anti-mucositis protocol designed to incorporate seven interventions simultaneously. Despite these efforts the problem of mucositis was only fractionally affected. Well over 75% of affected patients remain vulnerable to dose reductions, interruptions or cancellations of cancer treatment and unavoidable direct consequence of reduced cancer survival. Juxtaposed to the efforts of the MASCC mucositis panel [21-24] and attempts to standardize multiple interventions into a single protocol [25] are the therapeutic outcomes associated with the use of HPPCLS.

A description of the phase IV surveillance study is provided to give context to the clinical findings of HPPCLS. The purpose of this section however is not to restate HPPCLS outcomes reported elsewhere [26-29], but rather to explore the significance these outcomes hold for the clinical management of oral and gastrointestinal mucositis caused by chemoradiation.

There are four notable points of significance from the study. The **first** point of significance is that the sizes of HPPCLS treatment effects were large. Unlike other interventions, the effect sizes of HPPCLS treatment outcomes qualify as a Glasziou treatment effects [30]. This means that the ratio of the rate to achieve a disease-free state using the intervention compared to that using either placebo or the natural course of disease is greater than 10. All interventions supported by the MASCC guidelines demonstrated treatment effects that were only fractionally distinct from placebo (comparators) or from patient-reported duration of mucositis [31], having rate ratios less than 1. Generally the differences of effect size between MASCC interventions, their comparators and the patient-reported time for disease reversal were separated by a per cent range under 100 base points. On the other hand, the sizes of the HPPCLS treatment effect were well over 3,700–8,200 base points when compared to the effect size associated with the 'time effect' or patient-reported duration of the natural course of the disease [31] (see analysis of results). The **second point** of significance is that HPPCLS provided both prevention and treatment of mucositis, with statistically significant effect. The **third point** was that HPPCLS achieved mucositis reversal or prevention throughout the entire length of the GI tract, from the oral cavity to the colon. The **fourth point** of significance is that HPPCLS was associated with a complete, non-fractional, effect on mucositis. Rather than the incremental improvements in prevention or treatment associated with MASCC supported interventions, HPPCLS provided patient-relevant elimination of mucositis. That is, there was either complete prevention of mucositis occurrence or complete and rapid (2–3 days) reversal of mucositis once contracted. Complete prevention, rapid and complete reversal should positively impact patients' adherence to optimal cancer treatment, the costs of care among patients with mucositis, and likely survival.

Description of phase IV post-marketing surveillance of HPPCLS

The following is a brief description of data captured from an ongoing phase IV mucositis registry reporting the therapeutic outcomes of 66 consecutive patients enrolled over a 10-month period between February and December 2014. The description includes, the study objective, conduct, results and analysis.

- **Objective of phase IV study** – As required for therapies authorized by the US Food and Drug Administration (FDA), manufacturers are to conduct post-market surveillance to proactively monitor for unanticipated adverse reactions or treatment outcomes. To this end a mucositis registry was established in February 2014. It continues to date. This report captures outcomes of the first 66 patients on the registry.

- **Conduct of the study**

Ethical approval – As the registry was purely an observation of current clinical practice, there were no elements of intervention of care that required review by an ethics committee. Observations were collected without invoking risks of harm to patients or clinicians.

Oncologist selection – Oncologists, nurse practitioners and physician assistants were self-selected based on their voluntary response to national outreach efforts of specialty pharmacies that provided information and access to HPPCLS.

Patient selection – Inclusion criteria were any patients identified by clinicians as either having or being highly vulnerable to develop mucositis. Exclusion criteria were any allergy or prior adverse reaction to sucralfate. No distinctions were made as to type or stage of cancer or to the modality and dosing of cancer treatment used. Neither patients nor insurers were required to pay for any physician assigned samples.

Named patient samples – HPPCLS was allotted to patients weekly. A 75 mL container of HPPCLS was provided to each patient selected by clinicians. HPPCLS is a white paste

of 10% sucralfate with yogurt-like consistency and strawberry flavouring. HPPCLS differs from standard sucralfate in being polymerized by a weak acid and cross-linked by chelated cations. Three hours following administration, this polymerized cross-linked version of sucralfate achieves and maintains a surface concentration of sucralfate that is 800% greater on normal lining and 2,400% greater on ulcerated inflammed lining. Each dose ranged from 2.5 mL to 10 mL of paste depending on the severity of mucositis experienced or anticipated.

Instruction of use – Doses were self-administered three times daily for the first day then twice daily thereafter. Each 2.5 mL to 10 mL dose was self-administered by patients using the tongue to apply dose to inside surfaces of the mouth and lips. Cotton tipped swabs were used for application if not possible by tongue. Following application, patients then gargled for 10 seconds, held in mouth for 15 seconds and then expectorate or swallowed if so instructed by clinicians.

FDA ruled that HPPCLS was safe to swallow in children 14 years or older and in adults in doses of up to 1 gram (10 mL) four times daily for 56 continuous days.

Grades of mucositis – To determine the grade of oral mucositis, a functional patient-reported mucositis scale of the World Health Organization (WHO) was used [32] and is shown in Table 3. The severity of mucositis-related gastrointestinal toxicity was assessed using grading scales developed by WHO and the European Organisation for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) [33] and is shown in Table 4. Grade and function related to difficulty with eating, drinking, swallowing, nausea, vomiting and diarrhoea was identified by the clinical staff prescribing HPPCLS and confirmed by patients in follow-up phone calls by registry attendants.

Outcome collection – Registry attendants collected outcome data through calls made to clinical practices and to patients within four to seven days of patients' initial use of HPPCLS. Questions were asked specifically regarding timing of clearance of symptoms and signs of mucositis, i.e. day 1, day 2, day 3 and day 4 relief.

► Results of study

Mucositis registry – The registry reported was populated over 10 months from February to December 2014 and included 66 unique sequentially registered patients. Outcomes of the first 32 registrants were reported earlier [26] and were combined with a subsequent additional 34 patients also reported elsewhere [28]. There were 39 prescribing clinicians from 32 different oncology practices located in multiple regions of the USA. Of the 66 patients, 48 were males, ages 46 to 92, and 18 were females, ages 14 to 84. Five of 66 patients were lost to follow up (would not return or accept calls) by registry attendants leaving 61 patients to report outcomes. Of the 61 patients, 53 were prescribed HPPCLS to reverse mucositis and eight patients to prevent its occurrence.

Registry metrics – As mentioned, 39 clinicians from 32 institutions prescribed HPPCLS to 58 patients for treatment and eight patients for prevention. Five of the intent-to-treat cohort was lost to follow-up, leaving 53 patients prescribed HPPCLS to treat or reverse mucositis. Between these 53 for treatment and eight for prevention, 78.6% of them (48 patients) were instructed by their oncologists to swallow HPPCLS following tongue application and gargling.

The type of cancers under treatment included unspecified squamous cell carcinoma (SCC) of the head and neck (n = 18), SCC of the tonsil (n = 10), SCC of the tongue (n = 12), SCC of the oral cavity (n = 7), SCC of the larynx (n = 6), esophageal cancer (n = 2), pancreatic cancer (n = 2), colon cancer (n = 2), lung cancer (n = 2), bladder cancer (n = 1), ovarian cancer (n = 1), soft tissue sarcoma (n = 1), lymphoma (n = 1) and metastatic melanoma (n = 1).

Cancer treatment agents causing mucositis included ipilimumab, novilumab, cetuximab, folinic acid, 5-fluorouracil (5FU), irinotecan, oxaliplatin, bevacizumab, pazapanib, carboplatin, cisplatin, paclitaxel, gemcitabine, intensity-modulated radiotherapy (IMRT), and standard non-IMRT. There were no patients in the study who had received myeloablative doses of chemoradiation.

Table 3: Grade scales for the assessment of oral mucositis

WHO Grade	Grade 1	Grade 2	Grade 3	Grade 4
Function	Painless ulcers, erythema or mild soreness not affecting alimentation	Painful erythema, oedema, or ulcers painful to drink fluids and eat solids	Painful erythema, oedema, or ulcers and cannot eat solids	Alimentation is not possible; dependence on intravenous and feeding tube
Clinical exam	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences
Symptoms	Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function	Symptomatic but able to eat and swallow modified diet; respiratory symptoms interfering with function but not with activities of daily living	Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with activities of daily living	Symptoms associated with life-threatening consequences

WHO: World Health Organization.

Table 4: EORTC/RTOG and WHO toxicity criteria acute chemoradiation GI morbidity

EORTC/RTOG scale for GI toxicity				
Toxicity grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Oesophagus	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilation may be indicated	Severe fibrosis; Able to swallow only liquids; may have pain on swallowing Dilation required	Necrosis/Perforation Fistula
Small bowel	Mild diarrhoea; mild cramping; bowel movement 5 times daily	Moderate diarrhoea and colic; bowel movement > 5 times daily	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula
Colorectal	Increased frequency or change in quality of bowel habits not requiring medication, rectal discomfort not requiring analgesics; slight rectal discharge or bleeding	Diarrhoea requiring parasympatholytic drugs, mucous discharge not necessitating sanitary pads, rectal or abdominal pain requiring analgesics. Excessive rectal mucus or intermittent bleeding	Diarrhoea requiring parenteral support, severe mucous or bloody discharge necessitating sanitary pads/abdominal distension (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; gastrointestinal bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
WHO colorectal	Increase of 2–3 stools per day over pretreatment	Increase of 4–6 stools per day, or nocturnal stools, or moderate cramping	Increase of 7–9 stools per day, or incontinence, or severe cramping	Increase of > 10 stools per day or grossly bloody diarrhoea, or need for parenteral support

EORTC/RTOG: European Organisation for Research and Treatment of Cancer/Radiation Therapy Oncology Group; WHO: World Health Organization.

The WHO scale for oral mucositis, see Table 3, and the EORTC/RTOG and WHO Scale for GI Toxicity, see Table 4, were used to assess grades of mucositis. Of the 53 patients with oral mucositis, 8 had Grade 1, 28 had Grade 2, 17 had Grade 3 and none had Grade 4. Of these 53 patients, 41 had mucositis involving oesophagus, small bowel and colon. Of these with alimentary mucositis, there were 20 patients with Grade 2 esophageal mucositis, 10 patients with Grade 2 small bowel mucositis and 11 with Grade 2–3 colonic mucositis.

Outcomes – HPPCLS paste was well tolerated with no patients reporting adverse reactions which met the main objective of the study. Table 5 summarizes the remainder of intervention outcomes. Time of reversal, that is, complete resolution of mucositis was rapid, generally within 2–4 days. This same rapid effect occurred regardless of grade of mucositis or the anatomical location of mucositis. There were 53 patients with mucositis of the oral-pharynx, of whom 20 also had involvement of the oesophagus, 10 had involvement of the small bowel and 11 had concurrent involvement of the colon. Only 12 patients had solely oral mucositis with no involvement of the remainder of the GI tract. Eight patients anticipated to develop mucositis (n = 8) who were prescribed HPPCLS to prevent its occurrence did not develop mucositis throughout their entire chemoradiotherapy treatment.

Tube-feed dependent patients – One patient dependent on gastrostomy feeding tube for several weeks due to Grade 2 GIM (esophageal, small bowel and colonic) caused by 8 weeks on folfirinox (folinic acid, 5FU, irinotecan, oxaliplatin) for stage IV pancreatic cancer, was off tube feed support and self-alimenting in three days on HPPCLS. Eight patients without mucositis were prescribed HPPCLS to prevent certain oral and esophageal mucositis and certain required placement of a prophylactic feed tube. None of these patients developed mucositis during their entire chemoradiation treatment, therefore all eight avoided surgical placement of feeding tube.

Limitation of study – There are several limitations to a study of this type. Firstly, data is from a self-reported registry not designed to investigate efficacy, but rather designed to capture reportable adverse reaction and patients' acceptance of the intervention. In this regard, the study could be viewed as an extended case series covering treatment outcomes over a period of 10 months. Data was subject to selection bias, being derived from a voluntary registry without randomization or placebo or a control group. Patient selection was determined by physicians based on outreach information provided by specialty pharmacies.

- **Analysis of data: statistical measure of efficacy –** Despite limitations of trial design, statistically significant treatment outcomes transpired in patients using HPPCLS. The clinical results of HPPCLS demonstrate a quantifiable effect that is statistically beyond that expected for the natural course of patient-reported mucositis [31]. In all treatment cases of the registry, the rate of complete response of oral mucositis (pain, erosion and function restoration) to HPPCLS was 2–3 days, or 2.5 days. This is compared to 46 to 60 days for myeloablative transplant therapies, 84 days for radiotherapy with or without chemo or 102 days for 6 cycles of myelosuppressive chemo expected for the natural course of chemoradiation induced oral mucositis [31]. These time periods are only fractionally impacted by MASCC supported interventions. As explained by Glasziou et al. [30], the rate ratio derived from comparing the use of HPPCLS to the natural

Table 5: Mucositis locations and time of response to HPPCLS

Patient type	Time for reversal or elimination
Oral/Pharyngeal Mucositis (n = 53)	2–3 days
Esophageal Mucositis (n = 20)	2–3 days
Small Bowel Mucositis (n = 10)	2–3 days
Colonic Mucositis (n = 11)	3–4 days
Tube-Feed Dependence (n = 1)	3 days
Prevention (n = 8) SCCHN	Did not develop mucositis for 42–49 days Radiation

HPPCLS: high potency polymerized cross-linked sucralfate; SCCHN: squamous cell carcinoma of the head and neck.

course of mucositis in the three most common cancer treatment scenarios would be calculated as follows.

Rate for ProThelial ÷ [0.5 ÷ days for mucositis to naturally clear] ⇒ Rate Ratio [1 ÷ 2.5 days] ÷ [0.5 ÷ 46, 60, 84 or 102 days] ⇒ 36.7, 48.2, 67.8 or 81.6

The magnitude of the clinical response to HPPCLS compared to the natural course of mucositis generated rate ratios beyond '10', the number required to secure assumption of efficacy beyond the effect of confounding by biases. The magnitude of clinical response associated with HPPCLS had rate ratios of 37, 48, 68 or 82 depending on the anticipated duration of mucositis depending on the cancer treatment scenario involved. These rate ratios mean that clinical effect of HPPCLS was 3,800% to 8,300% greater than otherwise would be expected from the natural course of mucositis disorder or historical controls. More significant than this, was the observation that the use of HPPCLS was associated with complete, non-fractional, prevention oral mucositis and rapid and complete elimination of mucositis.

Discussion

For the most part the effect size of treatments and placebos for any one condition are on the same order of magnitude, that is, they differ from each other quantitatively by less than 100 base points [34]. MASCC supported interventions are of this category. Additionally, MASCC recommendations and suggestions are expressed as guidelines that are effective and applicable within a particular clinical scenario of cancer treatment. Unstated, but understood in the practice of these recommendations is that the burden is on practitioner to speculate on the efficacy of a MASCC-supported intervention if used in clinical situations that differ from the guideline scenario. Thus, generalizability and transference of guidelines into clinical practice remains a challenge. Aside from that, all current interventions for mucositis whether supported by MASCC guidelines or used in institutional practice [25] provide only fractional effects on the prevention and reversal of oral mucositis. No single intervention has efficacy simultaneously to both treat and prevent mucositis. Additionally, no one intervention has demonstrated multi-anatomical efficacy against mucositis throughout the GI tract. Efficacy is either for oral or gastrointestinal mucositis but generally never both.

Despite obvious design limitations of the 66 patient mucositis registry study, the clinical outcomes seen with HPPCLS have never been associated with any anti-mucositis intervention. Additionally, therapeutic reach of HPPCLS has not been observed with other interventions. To exemplify this, Table 6 compiles HPPCLS outcomes among 11 different patients. In these patients with either oral, esophageal, small bowel or colonic mucositis that was rapidly and completely reversed during cancer treatment. In three of these patient examples mucositis was completely prevented during cancer treatment and the placement of prophylactic gastrostomy tube was averted.

HPPCLS had the same effect in prevention and reversal of mucositis regardless of its cause. Anti-neoplastic agents used included targeted immunotherapies (ipilimumab, novilumab, cetuximab, bevacizumab, pazapanib), non-targeted anti-neoplastic agents (folinic acid, 5FU, irinotecan, oxaliplatin, carboplatin, cisplatin, paclitaxel, gemcitabine) and two forms of radiotherapy (IMRT, standard RT). These treatment modalities have different mechanisms of action that lead to mucositis and different anatomical sites of mucositis occurrence within the GI tract. Still HPPCLS demonstrated capacity to completely and rapidly reverse mucositis regardless of the agent causing it and regardless of the anatomical location of its occurrence. This observation challenges the implications of the MASCC guidelines that differing causes of mucositis occurring in different anatomical locations under specific cancer treatment scenarios will likely require different anti-mucositis interventions. This is not supported by the treatment outcomes reported for HPPCLS.

Given its singular mechanism of action, the therapeutic target for HPPCLS must be the same for all forms of mucositis occurring in all anatomical locations of the GI tract. HPPCLS is a non-systemic topically active agent. Its likely targets include extracellular membrane-related macromolecules tasked with epithelial repair and maintenance. The prevention of mucositis by HPPCLS further implies that extracellular macromolecules are likely engaged in the maintenance of epithelial integrity long before signs and symptoms of mucositis are perceived by patient or clinicians.

The clinical outcomes of HPPCLS for this phase IV surveillance study challenges several unstated but implicit concepts regarding mucositis and its management, namely: (a) oral mucositis is possibly distinct from gastrointestinal mucositis; (b) mucositis caused by differing anti-neoplastic agents likely require different anti-mucositis interventions; (c) the four stages of mucositis provide indispensible targets for prevention and treatment therapies; and (d) separate anti-mucositis

Table 6: Eleven patient case series from phase IV post-market surveillance of ProThelial

Age/Gender	Cancer type	Time from start of cancer treatment	Institution	Grade of mucositis	Location of mucositis	Therapeutic outcome
Complete reversal during chemoradiation						
49 yo male	SCC Tonsil	4 weeks of Cetuximab plus Radiation	Swedish Covenant Hospital, Chicago IL	Grade 3	• Oropharyngeal	2–3 day Elimination
56 yo male	SCC Oropharyngeal	4 weeks unspecified Chemoradiation	Radiation Oncology, Ocala FL	Grade 3	• Oropharyngeal	2–3 day Elimination
88 yo male	SCCHN	3 weeks Cetuximab + Radiation	Radiation Oncology, Ocala FL	Grade 3	• Oropharyngeal	2–3 day Elimination
52 yo male	Stage IV Pancreatic	2 weeks Folfirinox	Lexington Oncology, West Columbia SC	Grade 2	• Oral Mucositis • Burning Mouth Syndrome (BMS) • Esophageal Mucositis	2–3 day Elimination (Held in mouth longer to relieve BMS) **Swallowed ProThelial**
49 yo male	Stage IV Pancreatic	8 weeks Folfirinox	Vanderbilt, Tennessee TX	Grade 4 Feed-Tube Dependent	• Esophageal • Small Bowel (SB) • Colonic Mucositis	2–3 day Elimination of Esophageal Mucositis 4 day Reversal SB/Colonic Off tube feeding 3 days **Swallowed ProThelial**
49 yo female	Stage IV Metastatic Melanoma	4 weeks Ipilimumab plus Nivolumab	Yale-New Haven CT	Grade 3	• Oral • Small Bowel • Colonic Mucositis	3–4 day Elimination **Swallowed ProThelial**
62 yo male	SCC Oesophagus	6 weeks Taxol/Carbo + Radiation	St Frances Cancer Center Hartford CT	Grade 3	• Esophageal Mucositis	2–3 day Elimination **Swallowed ProThelial**
52 yo female	Recurrent Ovarian Cancer	2 weeks	University Pittsburgh Medical Center PA	Grade 3	• Oral Mucositis	2–3 day Elimination **Swallowed ProThelial**
Complete prevention during chemoradiation						
93 yo male	SCC Tongue	0 weeks Radiation	Kansas Radiation Oncology	Anticipated Grade 4	100% Anticipated Requirement of Feeding G-Tube	G-Tube Averted None Required While on ProThelial **Swallowed ProThelial**
55 yo male	SCC Tongue	0 weeks Radiation	Kansas Radiation Oncology	Anticipated Grade 4	100% Anticipated Requirement of Feeding G-Tube	G-Tube Averted None Required While on ProThelial **Swallowed ProThelial**
68 yo male	SCC Tongue	0 weeks Chemo + Radiation	Kansas Radiation Oncology	Anticipated Grade 4	100% Anticipated Requirement of Feeding G-Tube	G-Tube Averted None Required While on ProThelial **Swallowed ProThelial**

IV: intravenous; Reversal: mucositis elimination; SCC: squamous cell carcinoma; SCCHN: squamous cell carcinoma of the head and neck; yo: year old.

interventions are necessary to optimally manage oral and gastrointestinal mucositis. The treatment effects of HPPCLS confront each of these concepts of mucositis management by providing statistically significant clinical outcomes that weaken the premise of each concept.

Certainly, the multi-interventional protocol approach of Bhatt et al. [25] achieved improved outcomes over a single intervention approach. Yet 75% of patients persisted with oral mucositis and 100% of them sustained intestinal mucositis requiring parenteral nutrition. From this preliminary study, the clinical

Table 7: Proposed single agent protocol using ProThelial for chemoradiation induced mucositis

Management goal	Cancer therapy	Loading dose	Maintenance dose through to 1 week post-cancer therapy
Treatment Grade 1, 2	Chemoradiation	2.5 mL to 5 mL TID × 1 day [250–500 mg]	2.5 mL to 5 mL BID [250–500 mg]
Treatment Grade 3, 4	Chemoradiation	10 mL TID × 2 days [1,000 mg]	5–10 mL BID [500–100 mg]
Prevention Grade 1, 2	Chemoradiation	2.5 mL to 5 mL TID × 1 day [250–500 mg]	2.5 mL to 5 mL BID [250–500 mg]
Prevention Grade 3, 4	Chemoradiation	10 mL TID × 2 days [1,000 mg]	10 mL TID [1,000 mg]

Prevention regimen: start first day of cancer treatment; BID: twice daily; TID: three times daily.

outcomes of HPPCLS may provide a starting point for a single-agent protocol to manage chemoradiation induced mucositis occurring in any location throughout the GI tract.

Conclusion

Mucositis is a major side effect to chemoradiation and a key contributor to dose reductions, treatment interruptions or cancellations. Optimal cancer treatment provides evidence-based survival rates that cannot be reproduced in patients where mucositis interferes with delivery of optimal therapy [6-8].

Clinical oncology pharmacists and those managing mucositis are positioned to enhance the patient's adherence to optimal cancer treatment regimens. Fractional benefits of using MASCC supported interventions leaves a substantial population of patients vulnerable to the consequences of mucositis, and forces payers to cover the increased cost of those consequences.

With the passage of time, this new intervention, HPPCLS, will be tested by use in a wider group of clinicians in the US and in Europe. Should current preliminary outcomes hold, then meaningful advances in cancer care with corresponding savings in costs should follow. Table 7 is a guidance to aid the practice of a single agent protocol for the management of chemoradiation induced mucositis.

The pain and nutritional hindrance caused by oral and gastrointestinal mucositis is disheartening to cancer patients. It is financially expensive for insurers, disruptive to optimal treatment, and likely impacts survival [3, 6–8]. HPPCLS warrants consideration as a potential tool for those managing the side effects of chemoradiation, particularly mucositis.

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‘iMedicPlan’ for compliance: can it improve life?

Thomas Klose, PhD; Martin Wolf; Oliver Buchta, MBA; Michael Putzker, PhD

An iPhone and iPad application named ‘iMedicPlan’ has been developed by Dr Fresen Pharma from Koblenz, Germany. The application is designed to assist patients in complying with their medication. This tool generated much scientific, socio-political and medical interest on its first official presentation at the American Society of Clinical Oncology in Chicago, USA on 29 May 2014 [1].

Introduction

The German healthcare system creates substantial costs that must not be borne by the patient. Little attention has been paid to patient compliance. In Germany, costs associated with patient follow-up visits totalled an estimated Euros 18.65 billion in 2011 (Euros 314.5 per person and year) [2]; and Euros 257.6 billion in the US in 2009 (Euros 888.4 per person and year) [3]. Therefore, the potential for cost savings is enormous. The rise of chronic disease has resulted in demographic shifts that mandate new strategies for improving counselling and support.

Materials and methods

The novel application for mobile devices may optimize patient compliance by providing the following features:

i. Reminders to support the regular use of medication, check-ups, and vaccination recommendations (according to the German permanent vaccination commission Robert Koch Institute (STIKO))
ii. Advice about medication intake adverse reactions (based on ABDA database [Arbeitsgemeinschaft Bundesvereinigung Deutscher Apothekerverbände])
iii. Preparation of a medication dosage schedule
iv. Management of all health-related contacts, e.g. physicians, pharmacists, clinics
v. The ability to track and store medical diagnostic data for patients with certain issues, e.g. weight, Body Mass Index, blood pressure, glucose and lipid levels, complete blood counts for patients suffering from diabetes, high blood pressure, cancer, or both.

In January 2014, the German online survey software ‘polldaddy’ (http://mwkoblenz.polldaddy.com/s/kundenbefragung-adherence-zum-medikationsplan-1) was used to conduct a customer survey about the idea of developing an application (app) for smartphone, tablet, and other mobile devices in order to assist patients with medication compliance. Encouraged by consistently positive feedback, a questionnaire of 10 points was

Figure 1: Presentation of the elements of iMedicPlan on Apple smartphone and tablet platform

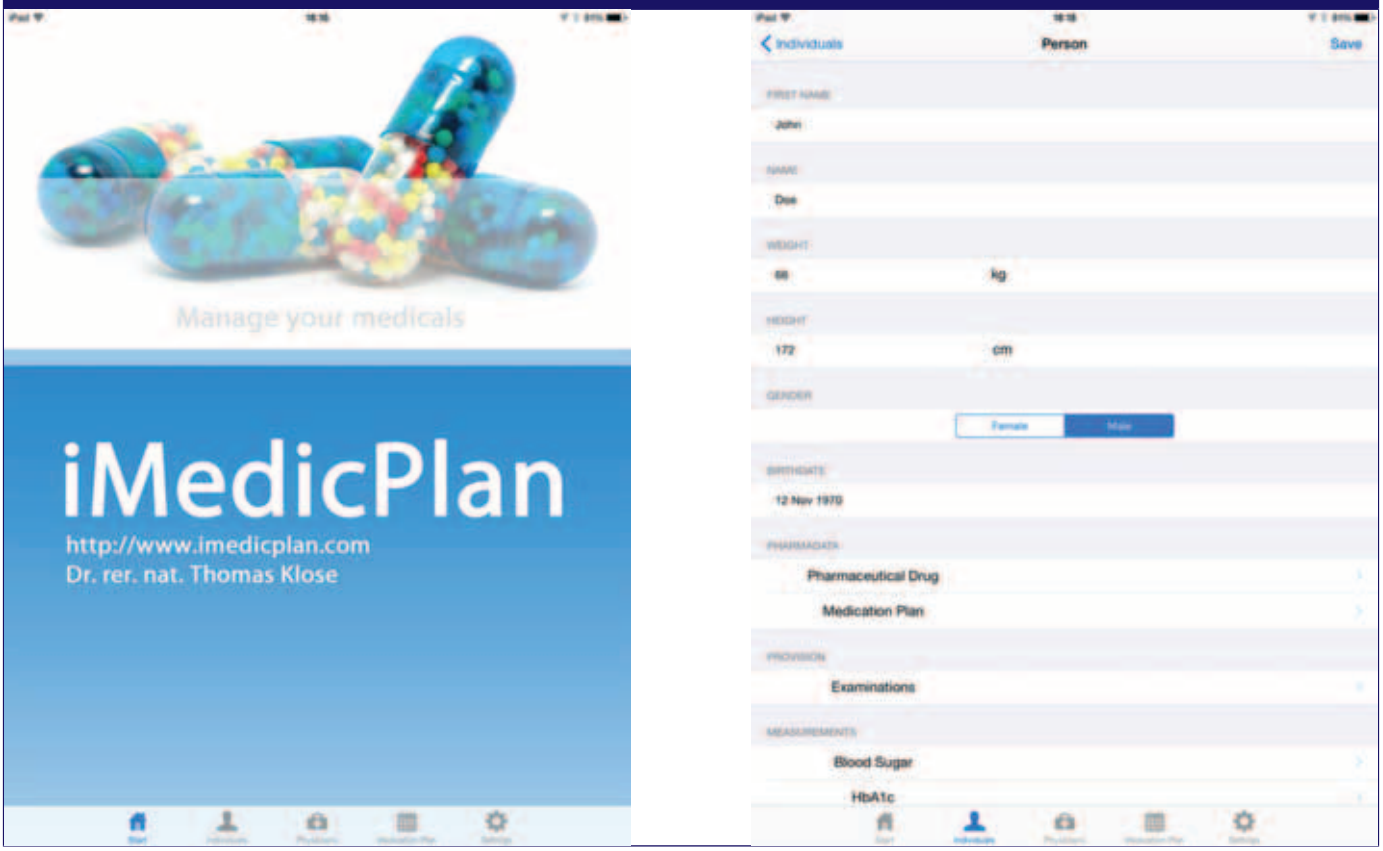
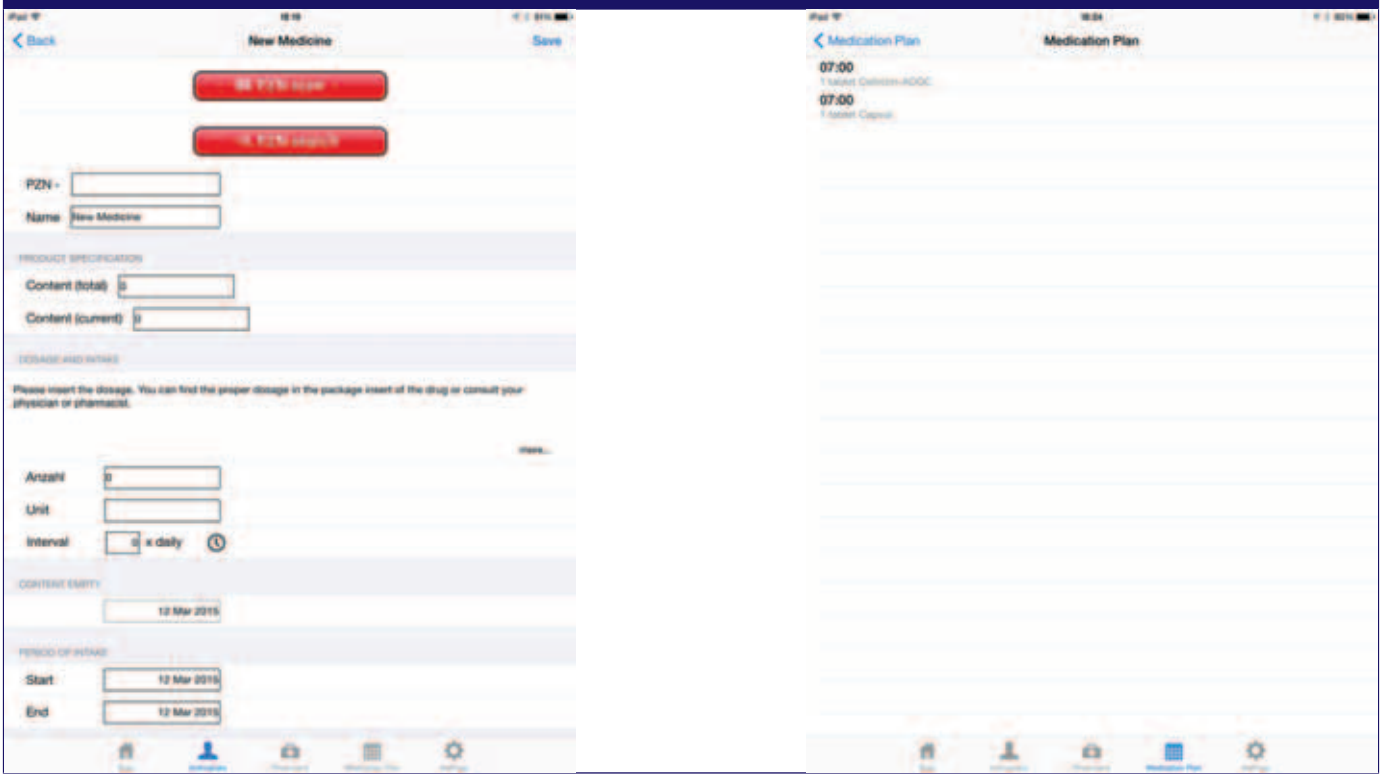


Figure 1: Presentation of the elements of iMedicPlan on Apple smartphone and tablet platform (*Continued*)



designed in order to determine the general acceptance of such a free of cost tool. A total of 123 patients agreed to take part in an inquiry. Participants commented on the questions either online via Facebook or by means of personal interview in several retirement homes and elderly care centres performed by pharmacy staff. Neither active recruitment was carried out nor any reimbursement given. The language of the survey was German [4].

Results

Analysis of the results of the questionnaire revealed that 41 (33.3%) participants reported problems with their medication. A total of 92 (74.8%) patients relied solely on their memory; only 12 (9.8%) received outside help; and 42 people (34.1%) said that a technical tool would appeal to them (34.1%). Overall, 62 (50.4%) respondents were smartphone users (iOS, Android operating system), and 12 (9.8%) of those were prepared to use a free downloadable compliance app.

Conclusion

Among patients taking medications long term, there seems to be significant interest in an application to help healthcare planning. For the younger generation, the monitoring of contraceptive intake would be an additional add-on use of such an application. Overall, patients with proper medication intake can expect better quality of life. At the same time, the healthcare system could experience significant savings, particularly for expensive drugs.

A discussion held with the US Food and Drug Administration (FDA) on 9 February 2015 [5] about the question of whether an app is considered a medical device emphasizes the importance of this issue. Following the development of the first computing watch in 2015 (Apple iwatch), even more interest in the app presented in this study may be expected, as compliance data will be available imminently.

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References 1–5 can be found on page 20

A German initiative towards more patient safety in oral anticancer therapy

Introduction

Fewer visits to the oncologist, self-administration and storage in the patient's home: with oral chemotherapy on the rise, community pharmacists have an increasingly important role in counselling patients about anticancer therapy.

Dorothee C Dartsch, PhD

At one time, the treatment of chronic myeloid leukaemia was a complicated, time-consuming parenteral therapy with interferon, and offered little hope of sustained survival. Then came the discovery and market availability of imatinib in 2001, which fundamentally changed the treatment of chronic myeloid leukaemia; now, treatment can be managed conveniently with tablets by the patient at home, and nearly nine out of 10 patients treated with imatinib go on to live for at least five more years [1].

The number of oral anticancer agents has grown continuously since then. Today, about one-half of all newly developed anticancer drugs are available orally [2]. Patients appreciate the ease of handling, increased independence from medical facilities and being reminded less of their disease [3].

The main disadvantage of oral anticancer therapy is patient adherence; patients need to be willing to take their medication and capable of doing so exactly as prescribed by the oncologist. Parenteral and oral therapy require different amounts of will and capability: the tablets and capsules must be swallowed regularly and precisely in the right dose in spite of the nausea and emesis, and the severe skin reactions that may occur as side effects as described in the package inserts, or experienced as real adverse drug reactions. Also, most treatment regimens are complex, with specific time intervals between administration and meals and alternating days of therapy and days of pause. Therefore, counselling and comprehensive explanations about the benefit, risks and singular traits of oral anticancer therapy are pivotal for the empowerment of patients in oral anticancer therapy.

In an article addressing adherence in tumour therapy, US health services researchers concluded that visits to the medical oncology facility will be insufficient to ensure adherence to oral anticancer agents [1].

In countries in which oral anticancer drugs are dispensed by community pharmacies, direct contact between the patient and the pharmacist at the point of dispensing the prescribed drugs offers the patient pharmaceutical advice that complements and affirms the advice of the physician. This opportunity should not be missed.

In Germany, parenteral cytostatic infusions are prepared in specialized pharmacies equipped with the technology to ensure safe and sterile handling of the materials. Naturally, these pharmacies are more concerned with, and are, on average, more knowledgeable in the field of anticancer therapy than regular pharmacies, given the fact that antineoplastic chemotherapy is a widely neglected topic within the curriculum of undergraduate pharmacy programmes and needs to be covered by (voluntary) postgraduate education. Therefore, pharmaceutical staff in these specialized community pharmacies may expect to be better prepared to counsel patients in oral therapy than non-specialized community pharmacies. Oral anticancer drugs, however, are dispensed routinely by community pharmacies in Germany, whether they are specialized or not. The important question, therefore, is where do patients go to obtain their prescriptions for oral anticancer drugs and what do they expect from the dispensing pharmacy?

In a written and anonymous opinion survey of patients undergoing oral chemotherapy carried out by the German Society for Oncology Pharmacy (*Deutsche Gesellschaft für Onkologische Pharmazie,* DGOP), patients were questioned about their latest 'dispensing event'. A total of 427 patients from 31 community pharmacies throughout Germany participated in the survey. Seventy-four per cent of patients returned their questionnaires. Patients were asked about the kind of dispensing pharmacy visited, the counselling received, both in general and specifically about the anticancer drug, specific information desired, and satisfaction with the consultation. Most participants were aged between 65 and 74 years, 53% were female, and 84% held a statutory health insurance. Four out of five patients (83%) always received their medications, including oral chemotherapy, from the same community pharmacy.

For 70% of patients, the main criterion for the selection of this one pharmacy was accessibility. Only 27% of patients filled their prescriptions from a pharmacy specialized in cancer treatment; the remaining patients selected a non-specialized community pharmacy. Over one-third of all patients did not receive any advice about their oral anticancer therapy, although about one-half of these patients would have welcomed such advice, especially about side effects, diet and complementary, and alternative treatment options. As the number of participating pharmacies was low, and as patients were recruited via the pharmacy, a selection bias and overestimation of aspects such as the percentage of counselled patients cannot be ruled out. Strengths of the study were the anonymity of the interview and

the design as a real-life observational survey. The results of this opinion survey confirm that all community pharmacies must be able to offer competent pharmaceutical advice to cancer patients to ensure patient safety. Consequently, knowledge, skills and supporting tools need to be present in every single pharmacy.

Aspects to be included in the consultation with the patient

Patients will only be adherent if they are fully convinced of the benefit of their oral anticancer therapy. In addition to prolonged survival, this may also be improved quality of life. Some patients have incorrect notions about their anticancer tablets; for example, that they are less effective, less toxic than an infusion, or both, or that their treatment regimen is just the 'last try' before palliative treatment. Other patients feel isolated because they are left to deal with their medication alone and visit the oncologist infrequently, or feel like guinea pigs trying new agents [4]. Such misconceptions should be identified by questions such as 'How do you feel with your therapy?', and corrected as quickly as possible because they are a threat to adherence.

Further topics that should be included in counselling to ensure patient safety are presented in Table 1.

Initiative 'Oral Anticancer Therapy – Safe and Effective'

The DGOP is offering nationwide support for community pharmacists who engage in counselling patients in oral anticancer therapies. To this end, the society launched the initiative 'Oral Anticancer Therapy – Safe and Effective' towards the end of 2011 together with the German Cancer Society (*Deutsche Krebsgesellschaft*).

Elements of this initiative are practice-oriented training programmes run by committed and experienced speakers throughout the country and an online database that enables quick access to the essential drug information about orally available anticancer drugs required for the pharmaceutical counselling.

Table 1: Issues that should be included in patient counselling to ensure treatment adherence

Pharmaceutical aspects	Clinical aspects
Medication regimen	Drug–drug and drug–diet interactions
Drug handling	Adverse drug reactions and their prevention
What to do when administration of tablets is missed or doubled	Verification of the prescribed dosage
Special precautions, e.g. slowing of reactions, contraception and sun screen	Check for absence of contraindications

The training programmes are based on a curriculum and designed for a contact time of 8 hours altogether. The curriculum is subdivided into three parts: basics of cancer therapy (2 hours), applied oncology pharmacy (4.5 hours) and handling of oral anticancer drugs (1.5 hours).

Part I, basics of cancer therapy: covers terminology, epidemiology, tumour development, and principles of cancer therapy. Part II, applied oncology pharmacy: addresses methods of dosage individualization, side effects and their prevention as well as interactions.

Part III, handling of oral anticancer drug: explains aspects of storage, administration via enteral tubes, handling of excreted materials, disposal of waste, and cleaning.

Slide sets devised by experts within the DGOP are available to speakers. For convenience, the contents are uniformly practice-oriented. Currently, there are about 50 speakers prepared to offer the training units.

Training is also offered at scientific meetings, such as the well-known 'Northern German Cytostatics Workshop' (*Norddeutscher Zytostatika Workshop*, NZW). In September 2015, the 'NZW Sued' will be flanked by the second meeting on oral anticancer therapy in Munich. The lectures and workshop are specifically designed for the community pharmacist and will offer both an introduction to, and reinforcement of, knowledge and skills in this important field. Topics include adherence, adverse drug effects, their management, medication safety, as well as working in the inter-professional team and the limits of pharmaceutical counselling. In addition to these lectures, workshops are offered in which theoretical aspects relevant to pharmaceutical counselling are actively transferred to case-based problems. The language of the meeting is German. Further information can be found at www.orale-krebstherapie.de

In Germany, the pharmaceutical support system (PoB-DGOP, *Pharmazeutisch-onkologisches Betreuungstool der DGOP*) is a database that provides pharmacists with a quick overview of the elemental drug information for each agent, based on drug monographs available for oral anticancer agents. Moreover, it creates concise medication administration plans, diary-like tables patients can use to document their daily condition, individualized information leaflets for patients and clinical information for oncologists. It also stores relevant patient pharmaceutical data and facilitates documentation of the counselling process. The monographs are updated on a regular basis by pharmacists who have taken over responsibility as drug-monograph managers. Registration and use of the database are free of charge and available exclusively to pharmacists.

A network of pharmacists, oncologists and physicians of other medical specialties, as well as nurses, are needed to ensure the safety of patients in oral chemotherapies and to increase their quality of life. As pharmaceutical competence is essential in

To continue on page 5.

ASCO 2015: New immunotherapies at high cost

Cost of cancer drugs should be part of treatment decisions. Currently, it is the pharmaceutical companies who set the price of medications that they make.

Background

Generally, the immune system plays an important role in controlling and eradicating cancer. During an immune response, the immune system turns on to attack cancer cells. The immune system also has ways to turn off. This limits the immune response and prevents damage to normal tissues. Immunotherapies of advanced cancer were the prominent topic of the 2015 Annual Meeting of the American Society of Clinical Oncology (ASCO).

Professor Dr med Günther J Wiedemann, MD, PhD

Professor Dr med Wolfgang Wagner, MD, PhD

T lymphocytes (T cells) are immune cells that can kill cancer cells. Some cancer cells bind to receptors on activated T cells and turn them off. **Immune checkpoint inhibitors** are cancer treatment drugs that prevent immune cells from being turned off by cancer cells. This allows T cells to infiltrate a tumour and stop it from growing.

The **checkpoint inhibitor proteins** (checkpoint receptors) PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic T lymphocyte-associated antigen) are located on T cells, and interact with their ligands in antigen-presenting cells, i.e. PD-L1, PD-L2, to inhibit T cell activation and proliferation. This negatively regulates T cell effector mechanisms and restricts immune responses to cancer cells. PD-1 is highly expressed on T cells from patients with tumours, and causes tumour-related immunosuppression. Prior research suggested that patients who had detectable PD-L1 levels in their tumour (PD-L1 positive tumours; commercially available test) typically had better responses to PD-1 receptor inhibition. At present, however, we do not know reliable response-predicting tumour biology for immunotherapy.

Checkpoint receptor inhibition directed against the interaction of PD-1 with PD-L1 on tumour cytotoxic T cells has emerged as an effective therapeutic option for some patients with various cancers, including melanoma, renal cell cancer, and non-small cell lung cancer.

Nivolumab, pembrolizumab and ipilimumab are immune checkpoint inhibitors that block two different immune checkpoints PD-1 and CTLA-4, respectively. Both treatments essentially boost the immune system's ability to kill cancer cells. Prior research has shown that these immune checkpoint inhibitors can improve survival for patients with melanoma and lung cancer. Ipilimumab, nivolumab and pembrolizumab are US Food and Drug Administration (FDA) approved for use as single agents in patients with unresectable or metastatic melanoma that no longer responds to other drugs.

The prolonged benefit of immune checkpoint inhibitors is explained by the fact that immunotherapy works by activating the immune system rather than targeting the tumour directly. It is not yet clear how long patients need to be treated to fully activate the immune system, and the minimal duration of therapy probably varies from patient to patient.

PD-L1 status and identification of mismatch repair deficiency may help define optimal treatment

The PD-1 protein on immune cells attaches to another protein called PD-L1, which is sometimes found on the surface of tumour cells. Prior research suggested that patients who had detectable PD-L1 levels in their tumour (PD-L1-positive tumours) typically had better responses to PD-1 therapy. **Mismatch repair (MMR) deficiency leads to an accumulation of genetic mutations in a tumour. MMR deficient tumours are highly responsive to checkpoint blockade with anti-PD1**. MMR deficiency is represented in 4–5% of many cancer types and responses were seen in colorectal, endometrial, stomach, small bowel and bile duct cancers. MMR deficiency is easily determined using a commercially available test.

A phase II study identified the first **genomic marker – MMR deficiency** – to predict response to the anti-PD-1 antibody **pembrolizumab**. This marker predicted responses across a range of cancers. Among patients with colorectal cancer (CRC), 62% of those with MMR-deficient tumours experienced tumour shrinkage, while no responses were detected among those without this abnormality ('MMR-proficient'). The response rate among patients with other MMR-deficient cancers was similar – 60%.

MMR deficiency is found in 15–20% of sporadic (non-inherited) CRCs and in nearly all CRCs associated with Lynch syndrome, which constitutes up to 5% of all CRCs. MMR deficiency is also found in other tumour types including stomach, small bowel, endometrial, prostate and ovarian cancer.

Testing for MMR-deficiency is widely available and may enable oncologists to identify a larger population of patients who might benefit from pembrolizumab and other PD-1 drugs.

Undesired side effects

Because immune checkpoint inhibitors prevent T cells from being turned off, these drugs affect the balance of the immune system. In addition to the desired drug effect of infiltrating tumours, activated T cells can affect any organ system, but they typically involve the skin, the gastrointestinal, hepatic and endocrine system. These undesired drug effects occur in about 10–20% (grade 3) and 60% (grade 1–2) of patients on these drugs. There is no strong correlation between the occurrence of an immune-mediated adverse event and long-term outcomes to immune checkpoint-blocking antibody therapy. Patients who stop immunotherapy because of adverse effects can still have excellent long-term outcomes.

Immune-related side effects usually occur six to 12 weeks after starting treatment and may include diarrhoea (immune-mediated colitis), rash, difficulty breathing (autoimmune pneumonitis), pruritus, nausea, anaemia, arthralgia, vomiting, constipation, jaundice (immune-mediated hepatitis)), immune-mediated nephritis and renal dysfunction, autoimmune hypothyroidism and hyperthyroidism, and fatigue. Temporary use of **immunosuppressive medications** (corticosteroids, tumour necrosis factor alpha antagonists, mycophenolate mofetil, or other agents) can suppress these autoimmune adverse effects. If this influences the antitumour response is being investigated. When appropriate immunosuppressive treatment is used, patients generally completely recover from immune-mediated adverse events.

Immunotherapy in brain metastases

Traditionally, the central nervous system (CNS) was considered an immunologically privileged site because of the restriction of the circulation of lymphocytes and antibodies by the blood-brain barrier. There is evidence, however, that activated T cells can patrol the CNS in an antigen-independent and unrestricted manner and then return to the systemic circulation. Several studies have confirmed that **T cells can cross the blood-brain barrier**, thereby supporting the strategy of T cell responses as an antitumour approach.

Metastatic malignant melanoma

A randomized phase III trial indicates that initial therapy with **nivolumab alone** or in **combination with ipilimumab** is significantly more effective than **ipilimumab** alone. This study randomly assigned 945 patients with previously untreated, advanced melanoma to receive ipilimumab, nivolumab, or the combination of the two. After a follow-up period of at least nine months, the median progression-free survival was 2.9 months for ipilimumab, 6.9 months for nivolumab, and 11.5 months for the combination. The differences between the combination and ipilimumab groups, and nivolumab and ipilimumab groups were statistically significant. The response rates were also substantially higher in patients receiving the combination therapy (57.6%) and nivolumab (43.7%) alone, as compared to ipilimumab (19%). But the results also warrant caution – the nivolumab and ipilimumab combination used in this study came with greater side effects, which might offset its benefits for some patients (Jedd D Wolchok and co-authors, Memorial Sloan Kettering Cancer Center; Abstract LBA1).

Metastatic non-small cell lung cancer

A randomized phase III trial indicates that **nivolumab** is beneficial in patients with metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy (LBA109; Luis Paz-Ares and co-authors, Hospital Universitario 12 October, Madrid, Spain). The study randomly assigned 582 patients to treatment with nivolumab or docetaxel. Response rates were higher in the nivolumab group compared to the docetaxel group (19.2% vs 12.4%). Responses also lasted significantly longer in the nivolumab group (17.1 months vs 5.6 months, on average). The median overall survival was 12.2 months in the nivolumab group compared to 9.4 months in the docetaxel group.

Value = Outcomes/Cost: cost questions raised

In a main lecture at the ASCO 2015, Craig Reynolds compared the impact of interventions on survival with cost in patients with metastatic non-small cell lung cancer:

- Early palliative care (Temel, et al. NEJM 2010) plus 2.7 months/US$6,000/year
- Bevacizumab (ECOG 4599) plus 2 months/US$115,000/year
- Ramucirumab (ASCO 2015) plus 1.4 months/US$121,000/year
- Nivolumab (ASCO 2015) plus 3.3 months/US$140,000/year

The conclusion: cost of cancer drugs should be part of treatment decisions.

Delivering affordable cancer care

Human life is priceless, and to think otherwise is to detract from the dignity of the patients. But, pharmaceutical companies now control the drug development agenda and, as a result, are able to price drugs whatever they think the market will bear, said Dr Leonard Saltz, Chief, Gastrointestinal Oncology Service at Memorial Sloan Kettering Cancer Center in New York, at his Plenary Session. He emphasized that all resources are finite and society must decide how best to distribute healthcare resources.

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