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Because there is a need

Klaus Meier
Editor-in-Chief
President of ESOP

EJOP

Nearly 13 years ago the *New York Times* reported an incident that had occurred at the Dana-Farber Cancer Institute in Boston, USA, a Harvard teaching hospital. Two patients receiving standard chemotherapy for advanced breast cancer at one of the most prestigious cancer hospitals in the US were given massive overdoses of two chemotherapy drugs. One patient died, and the other suffered permanent heart damage.

The patient who died, Betsy A Lehman, was an award-winning health columnist for *The Boston Globe*. The news of the mistake was all the more unsettling because Ms Lehman, as a health reporter, was presumably knowledgeable about her treatment and would have chosen her hospital with care. Ms Lehman, who was 39, died after doctors apparently refused to heed her warnings that something was drastically wrong and ignored the results of tests indicating heart damage.

A pharmacist and several doctors as well as nurses were involved in this treatment and had not been able to anticipate the grave error in treatment.

The reasons for such an incident have often been discussed at conferences and in quality circles.

As oncology pharmacists we have learned a lot, but we have to understand that not everywhere was our knowledge and contribution valued. We still have to grow in our knowledge and we have to be partners in the healthcare process.

So the American Society of Clinical Oncology put out a statement in July 2006 via its official journal, *Journal of Clinical Oncology,* to the effect that "healthcare plans should aspire to meet certain common goals to ensure access to quality cancer care". We were pleased until we got to point 7 "multidisciplinary cancer care" in which the members of a multidisciplinary team listed did not include a pharmacist.

The ESOP seized the opportunity and in 2006 published the Ljubljana Declaration in which it stated: "The close cooperation between oncology physicians and oncology pharmacists is vital for optimal patient care. Professional, close and timely collaboration will in particular ensure economic use of resources and improve safety."

In 2007, European oncology physicians and nursing societies together with the ESOP founded the new European CanCer Organisation, ECCO. This organisation will irrevocably cement the multidisciplinary approach in Europe.

In addition, we have learned that not only education but also willingness have to be our watchwords.

The word has to become flesh and make its dwelling among us. To improve our practise we have to act and we are asking you all to support our online survey (also enclosed as print insert) on the role of oncology pharmacists in patient education in CML treatment. Its aim is to benchmark on the national level and between the countries. We must have a clear understanding of all our needs in order to become better oncology pharmacists through all our future activities. The survey asks about work and experience, knowledge and needs. Thank you to Professor Alain Astier and Dr Christophe Bardin for their great support to complete this survey.

Pan-European survey on the role of European oncology pharmacists in patient education in CML treatment

The ESOP announces a survey: Defining the role of European oncology pharmacists in patient education in CML treatment.

ESOP is seeking to establish the current role of European oncology pharmacists in patient education, particularly in the treatment of chronic myeloid leukaemia (CML). The survey also investigates the wider role of oncology pharmacists in the multidisciplinary team and patient education; so please take part even if you don't currently have any patients with CML. The reason for this benchmarking exercise is to identify the needs and interests of oncology pharmacists so appropriate training and support can be devised.

For more information, please visit the ESOP website: www.esop.eu. The survey is now available online at www.ejop.eu/survey Please complete it by 3 March 2008. Thank you for your cooperation.

Oncology pharmacists study hard in Spain

The 52nd National Congress of the SEFH (Spanish Society of Hospital Pharmacists) took place in Tenerife, Canary Islands, on 25-28 September 2007. For more details, visit the SEFH website: www.sefh.es

Although it is a general congress this year the main topic of the programme was: "Pharmacotherapy in the genomics and communication age: challenges and opportunities" covering several interesting topics for oncology pharmacists such as: therapy individualisation, adjuvant therapy in breast cancer, controversies with the launching of biosimilars, new drugs for multiple myeloma treatment, etc.

During the first weekend of October 2007, 20 hospital pharmacists working in oncology sat for the BCOP (Board-Certified in Oncology Pharmacy) examination set by the BPS (Board of Pharmaceutical Specialties) from the US. This is the fifth time this examination has been held in Spain and at this moment Spain has 49 hospital pharmacists who have obtained this certificate. At the moment, Spain is second only to the US in certified oncology pharmacists, followed by Canada with 19, Korea 14, Singapore 7; and Australia and the UK with six certified pharmacists each.

Areas of expertise that must be mastered to earn a Board-Certified Oncology Pharmacist (BCOP) credential

1. Optimise drug therapy for patients with cancer through the design, recommendation, implementation
2. Monitoring, and modification of individualised pharmacotherapeutic plans in collaboration with the healthcare team
3. Contribute to the care of patients with cancer through research, the application of research results, and education
4. Ensure the safe, effective, and appropriate use of medications in patients with cancer through the implementation of guidelines and the development and modification of pharmacy policies and systems
5. Raise awareness among the public and healthcare providers regarding cancer-related issues (risk factors, prevention, screening and treatment)

Maria José Tamés, PhD, Hospital Pharmacist specialising in Oncology

Developments in oncology pharmacy in Croatia

The most important development is that oncology pharmacy will, as of Spring 2008, be taught as a subject within the clinical pharmacy postgraduate course at the Faculty of Pharmacy of the Zagreb University. This is the result of suggestions put forward by the Working Group on oncology pharmacy, and is supported by the oncology section of the Croatian Medical Association (CMA). This represents a meeting of minds between pharmacists, the Ministries of Education, Science and Health and medical professionals in order to improve overall medical and pharmaceutical care for the benefit of our patients.

My doctoral thesis was on cytotoxic drug management and served as one of the basic documents upon which the decision to establish the new subject matter in the postgraduate course was taken. In Croatia, one other pharmacist is presently working on a master's thesis and another on a doctoral thesis related to oncology pharmacy, indicating the ever growing interest professionals are displaying in this field.

Dr Pavlica drawing attention to the 2007 Osijek Oncology Congress

The oncology section of the CMA and the oncology pharmacy Working Group of the Croatian Pharmaceutical Society have good links with international oncology associations. Every two years we arrange a congress, which this year was held in the city of Osijek, Croatia, 29 March-1 April 2007. The Faculty of Pharmacy and Biochemistry of the Zagreb University and the Croatian Chamber of Physicians were also involved in its organisation. Prominent international professionals in medical oncology and oncology pharmacy gave lectures on gastrointestinal tumours, targeted biological solid tumour therapy, adjuvant breast cancer therapy, lung and pleural tumours, supportive therapy for oncology patients, molecular and experimental oncology, tumour treatment in elderly patients, liver metastasis treatment and handling of antineoplastic drugs.

The oncology pharmacy working group was led by Professor Alain Astier who also presented a number of lectures. The congress attracted favourable media interest and was able to reward the best posters and publicise the work of ESOP. Third prize went to Mr Zelic of the Pozega General County Hospital with the topic of extravasation.

Apart from this Congress, oncology hospital pharmacists met on several other occasions in the course of the year. Contact was established in Prishtina (Kosovo), Bosnia Herzegovina and Montenegro. In Prishtina, we now have regular meetings within the Chemotherapy Society; relationships with colleagues in Bosnia Herzegovina and Montenegro will develop further.

The Zagreb Tumour Clinic is currently under reconstruction and the pharmacy will be given new space, which will contain a central antineoplastic drug preparation unit. We are looking forward to it becoming fully functional in May 2008 and hope that colleagues from abroad will visit it.

Vesna Pavlica, PhD
Hospital Pharmacist specialising in Oncology

New approaches, new treatments

Genetic fingerprinting and predictive tests of many kinds made headlines at the European Cancer Conference (ECCO 14) held 23-27 September 2007 in Barcelona, Spain. Some of the radiotherapy presentations were particularly interesting.

Adjuvant radiotherapy after radical prostatectomy in patients with prostate cancer

Professor Wolfgang Wagner MD, PhD

Within five years of radical prostatectomy, 15-16% of patients with pT3 prostate carcinomas show increasing Prostate Specific Antigen (PSA) levels, a sign of local tumour progression. Adjuvant radiotherapy for positive margins aims to reduce residual tumour cells in the prostatic bed, thus possibly reducing the biochemical progression rate. A large number of retrospective investigations have been conducted, but at ECCO 14 results were presented from three randomised prospective studies. Of these, an EORTC (European Organisation for the Research and Treatment of Cancer) study and a SWOG (South West Oncology Group) study have been published. One further study is available only in abstract form at present. D Bottke from Sweden presented results that form a well-documented indication for adjuvant radiotherapy for pT3 carcinoma with positive margins, whether PSA is undetectable or if measurable levels persist after radical prostatectomy. The recommended total dose should be at least 66 Gy. Although no randomised data exist at the present time, adjuvant radiotherapy for patients with pT2 prostate cancer and positive margins has been seen to help individual patients. On the after hand, statistically there is no survival advantage for irradiated patients. There is still no consensus on whether adjuvant radiotherapy is superior to salvage radiotherapy for this group of patients. The rate of severe late side effects is low.

Breast cancer gene predicts outcome and response to treatment in lung cancer

Researchers have found that the breast cancer susceptibility gene, BRCA1, plays a significant role in non-small cell lung cancer (NSCLC). Predictive of outcome, it may also prove to be a valuable tool in choosing the best therapy.

The Conference heard that analysis had shown that NSCLC patients who had high levels of expression of BRCA1 had nearly double the risk of dying early from the disease than patients with low levels of BRCA1 expression.

In addition, Dr Rosell, Chief of the Medical Oncology Service and Scientific Director of Oncology Research at the Catalan Institute of Oncology (CIO), in Barcelona, Spain, said that earlier studies in breast cancer and the CIO study into NSCLC had linked low levels of BRCA1 expression with high sensitivity to cisplatin-based chemotherapies, while high levels of BRCA1 expression were linked with lack of response to cisplatin, but an increased sensitivity to antimicrotubule agents (taxanes) that prevent cancers growing by stopping cell division.

This will be tested in a prospective adjuvant chemotherapy clinical trial on 450 patients, and another trial in January 2008 for 700 patients with metastatic disease. Different chemotherapy regimens will be given, based on the patients' BRCA1 levels.

Dr Rosell concluded: "Our findings represent a drastic change from the currently accepted view that cisplatin-based adjuvant chemotherapy can reduce the risk of relapse in resected NSCLC patients. On the contrary, our results indicate that cisplatin will be ineffective in patients with high BRCA1 levels, though they will benefit from treatment with docetaxel or vinorelbine. Implementation of this concept in clinical practice could lead to major improvements in lung cancer treatment."

Radical salvage prostatectomy

Further interesting information was presented by J Eastham concerning surgery for progression after failed radiation therapy. One of the most difficult problems facing urologists and oncologists is the evaluation and management of patients with biochemical recurrence after definitive local therapy. The initial challenge is to determine whether the PSA originates from local recurrence of cancer, from distant metastases, or from both. If the recurrence is local only, there is an opportunity for cure by additional treatment to the primary site. After radiation therapy, the interpretation of an elevated PSA can be difficult. Because the prostate remains in place, a detectable serum PSA level might represent only normal prostate or inflammation of residual prostate tissue. In addition, as radiation kills prostate cells, the serum PSA level may actually rise and may not begin to fall until several months after radiation therapy has been completed. The average time to reach a serum PSA nadir (minimum) following radiation therapy is eighteen months, but it can take as long as two to three years. While there is no defined nadir representing cure after radiation therapy, the ideal serum PSA nadir should be 0.5 ng/mL or lower. The higher the nadir, the more likely that cancer will recur. Regardless of the lowest serum PSA after radiation therapy, a persistently rising level is ominous and often suggestive of recurrence. The ultimate goal of early detection of local recurrence of prostate cancer is to offer effective salvage therapy.

Salvage radical prostatectomy is technically challenging. Reported short-term and long-term complication rates exceed those of standard radical prostatectomy, but with appropriate patient selection and surgical expertise, this procedure has become less hazardous for the patient. Overall, mean estimated blood loss and operation time do not differ significantly from the values for standard radical prostatectomy. Up to 15% of patients in reports dating from the 1990s had rectal injuries, and as many as 25% had some other early complication of surgery, such as ureter transection, prolonged anastomotic leakage, or pulmonary embolism. Rectal and other intraoperative injuries were especially common in patients who had had pelvic lymphadenectomy.

In the past 10 years, however, the morbidity of the operation has improved substantially. With today's surgical techniques, salvage radical prostatectomy is technically feasible, with intraoperative and immediate postoperative outcomes similar to those with standard radical prostatectomy.

Preoperative serum PSA levels, but not clinical stage or biopsy grade, had a positive correlation with the course of the disease. Data presented suggested that the lower the serum PSA level at the time of salvage surgery (preferably < 4.0 ng/mL), the more likely the cure. Patients should be in good health with a life expectancy greater than ten years and have no evidence of metastatic disease. As outcome continues to improve, patients may become more willing to accept this treatment option after failure of definitive radiation therapy. Improved methods of identifying treatable recurrent prostate cancer while it is still confined to the prostate are needed.

Cancer cells in blood may identify risk of recurrence in breast cancer

Cancer cells circulating in the blood, (circulating tumour cells CTCs), are known to be associated with a bad prognosis in women with metastatic breast cancer. Now, for the first time, scientists have shown that they can detect CTCs before and after chemotherapy treatment and hence may be able to identify those patients likely to have a recurrence of their cancer after such treatment in future.

Previous work has already shown that detecting CTCs in bone marrow has predictive value, said Dr Jückstock from University of Munich, Germany. But it is much simpler, and more patient-friendly, to take blood samples for analysis. "For those patients who have an increased risk of recurrence (i.e. circulating CTCs), we could prolong or alter the chemotherapy regime to give them a better chance of recovery. For those who are likely to respond well to treatment, we could reduce the length of treatment and use less aggressive therapies, thus sparing unpleasant side effects" he said.

Results from further research are expected in the next five years.

Risk of second tumour

Hooning et al. demonstrated that young breast cancer patients treated with post-lumpectomy radiotherapy experienced an increased risk of contralateral breast cancer, specifically in the case of a positive family history of breast cancer. This finding questions the rationale of breast-conserving therapy in mutation carriers and warrants further research. The radiotherapy-associated risk of contralateral breast cancer increased with decreasing age at first treatment. Treatment with adjuvant chemotherapy (cyclophosphamide, methotrexate and fluorouracil) exerted a protective effect on the risk of developing contralateral breast cancer in the first five years of follow-up. Another group investigated Hodgkin's lymphoma (HL) survivors: they have an increased risk of breast cancer after treatment, especially those irradiated in the breast area at a young age. They assessed the cumulative risk after 25 years, comparing radiotherapy to the breast area and radiotherapy plus gonadotoxic therapy. A cohort of 1,155 women was treated in the period between 1965 and 1995 before the age of 51. The risk of developing breast cancer was compared with the general population and standardised incidence ratios and absolute excess risks were calculated. The absolute risk at 30 years was assessed using Kaplan-Meier risk estimation techniques. Cox regression analyses were performed to study effects in relation to gonadotoxic therapy. The risk of breast cancer remained elevated up to more than 30 years after treatment, which suggests a need for lifetime surveillance. Additional gonadotoxic therapy lowered the risk of breast cancer in patients irradiated to the breast area.

Dose and volume sparing

Taylor and Powell (United Kingdom) reported on the difference between IMRT (intensity-modified radiotherapy) in comparison to conformal radiotherapy in reducing normal tissue doses and side effects. They demonstrated that IMRT reduces the dose to normal structures by up to a massive 40% and it is possible to increase the external beam dose to the tumour by 20% whilst keeping normal tissue doses at less than with conformal radiotherapy. For radiotherapists this is very important information.

Molecular fingerprint of drug resistance can predict response to treatment

Docetaxel is one of the most effective chemotherapy treatments in advanced breast cancer. "However, up to half of all patients treated with this drug develop resistance, and hence the treatment fails," said Dr Iain Brown, from the University of Aberdeen, Scotland.

Scientists there decided to look for a specific genetic make-up in patients where docetaxel treatment had failed, hoping this might explain why they became resistant to it. They identified a set of genes that appear to control response to docetaxel in vitro. "At the moment we have only tested this in cell lines," said Dr Brown, "but we believe these results may translate into the clinical setting and benefit the patient."

The scientists will start collecting tissue samples from patients within the next six months. "If we find the same results in

patient samples, we expect that a simple test for docetaxel resistance could be developed and in clinical use within the next five years," said Dr Brown. Such a test would mean that those who would not benefit from docetaxel chemotherapy could be spared its side effects, and also reduce costs for healthcare providers.

"The changes we have found may represent common drug resistance mechanisms in breast cancer cells," said Dr Brown. "So we are looking at these findings in other cancer types, especially those which are also treated with docetaxel, to see if the results may have a potential in other areas".

New chemotherapy regimen prolongs survival in childhood brainstem gliomas

Childhood brainstem gliomas (BSGs) are rare but can be very difficult to treat successfully and they have poor survival rates. However, a team of Spanish researchers have found that a chemotherapy regimen of irinotecan and cisplatin (I/C) produced rapid clinical responses and shrank the tumours by more than 20% in all six children enrolled in a clinical trial.

Dr Jaume Mora told ECCO 14 that this was the first time that such a response had been achieved in children with high grade gliomas, while in low grade gliomas the response was comparable with the best achieved by other chemotherapies. All six children were still alive at one year, although the disease had progressed in three children with the most life-threatening tumours. The usual average survival rate for BSGs is between 4-15 months.

Irinotecan and cisplatin were given once a week for four weeks for a total of four cycles. Children with the high-grade tumours were also given anti-angiogenic therapy (bevacizumab) and radiotherapy. Dr Mora said: "All patients had complete and rapid clinical responses to the I/C regimen. No chemotherapy has ever achieved this grade of early response in high-grade BSGs."

Despite the promising early response the high-grade patients are progressing however.

New type of drug shows promise in melanoma

An experimental drug that attacks cancer in an entirely new way has shown promise in treating advanced melanoma, doubling time to progression of the disease.

STA-4783 is the first in a new class called oxidative stress inducers. It works by increasing the amount of reactive oxygen species (ROS), such as hydrogen peroxide and superoxide, in cells. When the level exceeds the antioxidant capacity of cells, the cells are in a state of oxidative stress. Cancer cells naturally operate with a higher level of ROS and oxidative stress than normal cells. However, too much oxidative stress for too long results in cell death. STA-4783 kills only tumour cells because the additional stress pushes cancer cells, but not healthy cells, over the critical threshold. Melanoma is one of several cancer types that are known to have a higher level of oxidative stress.

The study also indicated that STA-4783 might boost the efficiency of chemotherapy drugs that induce cell death, or apoptosis, because it appears to lower the hurdle for activating that process.

A large study in melanoma patients across Europe is now under way to further investigate the drug's potential.

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Early results show axitinib safe in renal cancer

Axitinib — a selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2 and 3 — has shown promise for people with metastatic renal-cell cancer in a phase II study, published in November's *Lancet Oncology* (2007;8:975).

All 52 patients with metastatic renal-cell cancer, whose previous cytokine-based treatment had failed, received axitinib at a starting dose of 5 mg twice a day on an empty stomach. Complete or partial response to the drug was seen in 23 patients.

The median time to progression in the French study was 15.7 months and median overall survival, 29.9 months. Thirteen patients had stable disease for 24 weeks or longer.

Axitinib, from a class of drugs known as VEGF inhibitors, works by starving tumours of blood and nutrients necessary for growth, a process called anti-angiogenesis. Genentech's widely-used cancer drug Avastin was the first approved medicine to work in this way.

The investigators found severe treatment-related side effects in 28 patients. Diarrhoea, hypertension and fatigue occurred in at least 10% of patients. The drug is showing promise against advanced pancreatic, thyroid and non-small cell cancers as well.

Pictures of life beyond cancer

A photographic exhibit which tells the inspiring stories of women who are using art, music, dance, and a passion for life to help them fight breast or ovarian cancer is touring medical congresses, museums and other venues around the world.

Ana and Fernanda from Portugal, Caridad from the Philippines and Helen from Scotland are some of the women who stepped forward to act as role models for women everywhere who will not let cancer define them. Their stories are also helping to raise awareness of breast and ovarian cancers, and the importance of early detection in ensuring the most effective treatment. Having faced up to the fears and challenges of their own diagnosis, the women show how they have rediscovered old interests and developed new skills, with the help and support of family and friends.

"A picture is certainly worth a 1,000 words and these photographs of real people who have had cancer and lived through it say so much more than data and statistics," says Susan Knox, Executive Director of the European Breast Cancer Coalition, Europa Donna.

She explains that cancer still carries a stigma in some parts of Europe, making people afraid to talk about their disease: "These photographs will help people to see that cancer is a battle which can be won, and that those who have the disease can still live happy, dynamic and fulfilling lives."

The black and white images for the exhibit, *Courageous Journeys: International Images of Women's Fight Against Cancer*, were taken by renowned fine art photographer and physician, Arthur Myers, through an educational initiative supported by Schering-Plough Corporation.

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Ana has confronted her fears of dying, after being diagnosed with stage II breast cancer at the age of 36, thanks to support of family and friends.

Fernanda, diagnosed with stage II breast cancer at 64, discovered her own inner strength and takes advantage of all the good moments of life – the smile of a nurse, a phone call from a good friend or a visit from her beloved grandchildren.

Helen focused on being positive when diagnosed with ovarian cancer at 52, and continues to follow her plan to enjoy life – watercolour and oil painting, and taking up the harp – a lifelong dream.

For Caridad, her ovarian cancer, diagnosed when she was 71, has been a journey of resurrection, enabling her to regain her passion for life – and dancing!

Photographer: Art Myers ©Schering-Plough Corporation

Dasatinib in the treatment of chronic myeloid leukaemia

Dasatinib is one of a new generation of tyrosine kinase inhibitors. It has great potential to retain its activity where imatinib meets resistance and is generally well tolerated. Now is the time to get a better idea of its place in clinical use.

Chronic myeloid leukaemia

Chronic myeloid leukaemia (CML) is a malignant clonal disorder of haematopoietic stem cells that results in increased numbers of myeloid cells, erythroid cells and platelets in the peripheral blood and myelogenous hyperplasia in the bone marrow [1].

Jerzy Lazowski
PharmD

Epidemiology

Leukaemias are responsible for 2.5% of all human cancers and CML specifically represents 15 (7-20%) of all leukaemias with a global prevalence of 1-2 cases/100,000 inhabitants/year. It occurs most often in Germany, Italy, Switzerland, UK and the US. CML occurs in both sexes, however slightly more often in men than women (ratio 1.4:1). It is observed in all ages, but most often between 50 and 60 years (median 53 years). Mortality increases with age beginning with 0.1/100,000 inhabitants/year aged 50-64 and up to more than 8/100,000 inhabitants/year in people aged over 80 years.

Pathophysiology

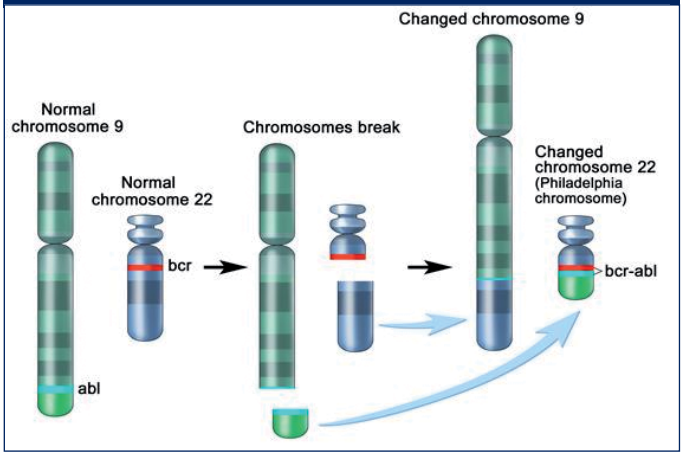
The natural history of CML is typically progression from a benign, extended phase (CP), often through an accelerated phase (AP), to a rapidly fatal blast crisis within 2-5 years. CML is considered to be an acquired disease, and predisposing factors have not yet been identified [1] (Table 1).

Table 1: Characteristics of chronic myeloid leukaemia phases

Chronic phase CML (all factors present)
< 15% blasts (immature blood cells) in peripheral blood (PB) and in bone marrow (BM)
< 20% basophils in PB
< 30% blasts + promyelocytes in PB and BM
platelets ≥ 100,000/mm^3
no extramedullary involvement (other than liver or spleen)
Accelerated phase CML (at least 1 factor present)
15-30% blasts in PB and BM
≥ 20% basophils in PB
≥ 30% blasts + promyelocytes in P and BM
platelets < 100,000/mm^3 (unrelated to therapy)
clonal cytogenetic evolution
Blast phase CML (at least 1 factor present)
≥ 30% blasts in PB or BM
extramedullary infiltrates of leukaemic cells (other than spleen and liver)

The vast majority of patients (95%) with CML have a genetic mutation called Philadelphia chromosome (Ph+), due to reciprocal translocation between the long arms of chromosomes 9 and 22. This leads to creation of a BCR-ABL fusion gene that encodes the production of the bcr-abl protein, a tyrosine kinase that influence all growth, differentiation and survival and is responsible for neoplastic transformation of haematopoietic cells seen in bone marrow and blood of CML patients. Cells containing Philadelphia chromosome replicate rapidly producing the characteristic pattern.

Figure 1: The t(9,22) chromosome translocation in CML



Treatment

The ultimate aim of the treatment of CML is to eliminate leukaemia cells having mutant BCR-ABL genes; however the more immediate goal is to control the signs and symptoms of the disease.

Prior to the introduction of interferon and imatinib, the treatment of CML relied on conventional methods (e.g. radiation therapy and cytotoxic agents such as busulfan or hydroxyurea). With conventional treatment, CML was a fatal disease with median survival of four years for patients with CP-CML and six months in the blast phase. The introduction of interferon in the mid-1980s replaced conventional treatment. As a single agent, interferon prolongs survival compared to conventional treatment, and a combination of interferon and cytosine arabinoside is effective in patients previously refractory to interferon alone. However, the majority of patients develop resistance or intolerance to interferon. The recent

introduction of imatinib, a small molecule inhibitor of tyrosine kinase, the first drug rationally designed for CML, revolutionised the treatment of this disease (in interferon-refractory patients and as first-line therapy) and improved tolerability over interferon. It competitively inhibits bcr-abl kinase activity and blocking the effects of bcr-abl fusion protein helps to destroy leukaemic cells. As with interferon, achievement of a cytogenetic response to therapy with imatinib is associated with haematological and cytogenetic responses as well as survival benefit [2, 3]. The occurrence of resistance to imatinib is also well described now [4, 5].

The most common cause of imatinib resistance is the development of point mutations in the ABL kinase domain of BCR-ABL. This leads to amino acid substitutions that prevent the binding of imatinib. Imatinib-resistant patients have inadequate treatment options, which include increasing the drug dosage (which often is not tolerable), interferon or chemotherapy. In addition to imatinib resistance, some patient develop adverse effects to the drug and therefore are intolerant to therapy. Even more limited options are open to these patients, including interferon and chemotherapy [5].

Combating imatinib-resistant CML is an important challenge, a promise contained in a new generation of tyrosine kinase inhibitors, such as dasatinib. At present, transplantation of allogeneic haematopoietic stem cells remains the only known curative treatment in CML. The widespread application of this modality is limited by donor availability and the high toxicity of the procedure in older patients, which limits the age of eligibility to ≤ 65 years [6].

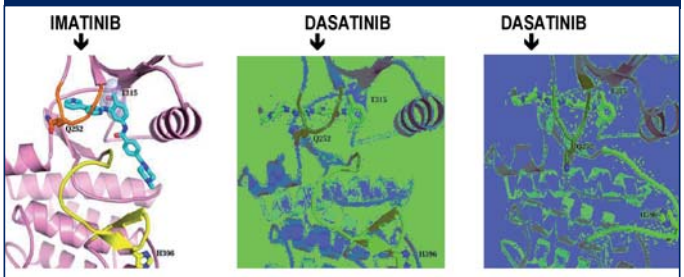
Dasatinib

Marketing Authorisation for dasatinib (Sprycel, from Bristol-Myers Squibb) was granted by the EMEA in November 2006 for the treatment of adults with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesylate, and also for treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia and lymphoid blast CML with resistance or intolerance to prior therapy [7].

Mechanism of action

Dasatinib is a potent inhibitor of five critical oncogenic kinases (i.e. BCR-ABL, SRC, cKIT, platelet-derived growth factor, and ephrin A receptor kinase) that are linked to multiple human malignancies. In contrast to imatinib, which binds only to the inactive conformation, dasatinib, a distinct chemical entity, binds to both the active and inactive conformations of the ABL domain of BCR-ABL. This is the reason for dasatinib's increased binding affinity over imatinib, and its activity against almost all imatinib-resistant kinase domain mutants. Dasatinib has 325-fold greater potency compared with imatinib against cells expressing wild type BCR-ABL, and is

Figure 2: Differential binding of imatinib and dasatinib to the ATP binding site of the ABL kinase domain of BCR-ABL



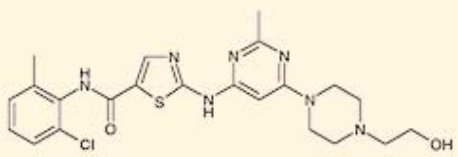
Source: Dasatinib (BMS-354825), Oncology Drug Advisory Committee (ODAC) Briefing Document NDA. 21-986, 02 June 2006.

Chemistry

Systemic name

N-(2-chloro-6-methylphenyl)-2-[[6-[-4(-hydroxyethyl)-1-piperazynyl]-2-methyl-4-pirymidinyl]amino]-5-thiazole carboxamide monohydrate

Chemical structure



BMS-354825

Origin: chemical, synthetic
Administration: p.o. (formulation: tablet)
Dosage: 75 mg twice daily

Originator

Bristol-Myers Squibb

Development status

- treatment of adults with chronic, accelerated or blast phases of chronic myelogenous leukaemia with resistance or intolerance to prior therapy including imatinib mesylate
- treatment of adults with Philadelphia chromosome positive acute lymphoblastic leukaemia and lymphoid blast chronic myelogenous leukaemia with resistance to prior therapy

Basic pharmacokinetics

Bioavailability: ?
$T_{1/2}$: 3 – 5 hours
T_{max}: 0.5 – 6 hours
V_D: 2505 L
Plasma protein binding: 96%
Metabolism: substrate CYP 34A
Elimination: faeces
Hepatic and renal impairment: no clinical studies conducted

effective against all imatinib-resistant kinase domain mutations tested to date except T315.

Dasatinib also has the potential to overcome imatinib resistance that results from divergent mechanisms including BCR-ABL overexpression, activation of alternative signaling pathways involving the SCR family kinases and multidrug resistance gene overexpression.

Clinical efficacy

Chronic phase of CML

Recently published [8] initial results of an international, multicentre phase 2 clinical trial of 186 patients with imatinib-resistant (n=127) or intolerant (n=59) chronic phase CML (CP-CML) confirmed earlier studies with respect to the efficacy and safety of dasatinib (70 mg twice daily) [8]. Complete haematological response was observed in 168 of 186 patients (90%). These response rates proved to be long-lasting (range1.1+ to 10.6+ months) with only seven (6%) of the 111 patients with imatinib-resistant disease and one (2%) of 59 patients with imatinib-intolerant CP-CML who achieved complete haematological response with dasatinib subsequently progressing (Table 2).

Table 2: Criteria for cytogenetic and haematological responses

Complete haematological response
- complete normalisation of peripheral blood counts with leukocyte count < 10 x 10^9/L
- platelets < 450,000 /mm^3
- no immature cells in peripheral blood
- no signs and symptoms of disease with disappearance of palpable splenomegaly

Cytogenetic response*
- *complete*: no Ph(+) cells in BM
- *major*: 1-35% Ph(+) cells in BM
- *minor*: 36-95% Ph(+) cells in BM
- *no response*: > 95% Ph(+) cells in BM

Molecular response
- *complete*: no transcripts BCR/ABL
- *major*: <0.10 transcripts BCR/ABL

***Only achieving complete or major cytogenetic response positively influences survival of patients with Chronic Myeloid Leukaemia**
J Natl Cancer Inst. 1997;89:1616-20

Dasatinib also induced marked cytogenetic responses in these patients. Major cytogenetic responses (MCyRs) were evident in 97 (52%) of 186 patients: in 50 (39%) of 127 patients with imatinib-resistant disease and 47 (80%) of 59 patients who were unable to tolerate imatinib. Subsequent analysis revealed that 38% of patients with no prior cytogenetic response to imatinib and 44% of patients who received doses of imatinib exceeding 600 mg/day achieved MCyR with dasatinib. MCyRs were long lasting; responses in 96% of patients with imatinib-resistant disease and 100% of patients imatinib-intolerant CP-CML at seven months' follow-up. Marked molecular responses were also evident with dasatinib. The median ratio of BCR-ABL to ABL transcripts fell from 66% at a baseline (n=149) to 2.6% (n=26) at nine months' follow-up.

Progression-free survival rate was 92.4%. After a minimum of eight months' follow-up, 15 patients (8%) with imatinib-resistant disease and one patient (0.5%) with imatinib-intolerant CP-CML had experienced disease progression and died. Nine of these 16 patients had shown evidence of a response prior to progression.

The trial confirmed good tolerability of dasatinib, with only 16 patients (9%) having discontinued treatment as a result of adverse events at eight months' follow-up. Cytopenia was common, but generally reversible and could be managed effectively with dose adjustments. Non-haematological events were generally mild to moderate in intensity (grade 1 or 2): headache, gastrointestinal disorders (diarrhoea, nausea), fatigue (asthenia and dyspnea were most common). Dose reduction or interruption were used effectively to treat cases of neuropathy, dyspnea, elevated activity of liver enzymes, headaches, bone pain, rash, renal failure, cardiac abnormalities and diarrhoea.

In another recently published [9] multicentre phase II trial, patients with CP-CML were randomised 2:1 to 140 mg dasatinib (n=110) or 800 mg imatinib (n=49). With a median follow-up of 15 months, complete haematology responses were observed in 93% and 82% of patients receiving dasatinib and high-dose imatinib respectively. Dasatinib resulted in higher MCyR rates (52%) than high-dose imatinib (33%); this included complete cytogenetic response (CCyR) in 40% and 16% patients respectively. Major molecular responses were also more frequent with dasatinib (30% vs. 16%). Treatment failure ratio and progression-free survival both favoured dasatinib. Superficial oedema (42% vs. 0%) and fluid retention (45% vs. 30%) was more prevalent with imatinib while pleural effusion was more common with dasatinib (17% vs. 0%). Grade 3 to 4 non-haematological toxicity was minimal.

Accelerated phase CML

Efficacy of dasatinib in the therapy of accelerated phase CML (AP-CML) was proved by Guilhot F et al. [10] in a phase II open label study of 107 AP-CML patients with imatinib resistance or intolerance. At eight months' follow up, 81%, 64% and 33% of patients were in overall, major and complete haematological responses respectively while 33% and 24% attained MCyR and CCyR. Of 69 patients who achieved major haematological response, seven progressed. Seventy-six per cent of patients were estimated to be alive and progression-free at 10 months. Response rates for the 60% of patients with baseline BCR-ABL mutations did not differ from the total population.

Blast crisis phase CML

At the end of 2006, Cortes J et al. [11] published results of

multicentre phase II clinical trials of dasatinib in patients with imatinib resistant or intolerant blast crisis CML: myeloid blast crisis (MBC) (n=74) and lymphoid blast crisis (LBC) (n=42). At eight months' follow-up, dasatinib had induced a major haematological response (MaHR) in 34% and 31% of MBC and LBC-CML patients, and MCyR in 31% and 50% of these patients, respectively. The majority (86%) of these MCyR were CCyR. Responses were both rapid and sustained: 88% and 46% of MBC and LBC-CML patients achieving MaHR had not progressed at eight months' follow-up. Response rates were similar in patients with and without BCR-ABL mutations known to confer resistance to imatinib.

In summary, the authors concluded that the results of their study demonstrated that potent, multi-targeted kinase inhibition of BCR-ABL and SRC family kinases with dasatinib induces haematological and cytogenetic responses in a large proportion of patients in imatinib-resistant or intolerant blast crisis. Given the poor survival of patients with CML blast crisis, the progression-free survival achieved to date with dasatinib is clinically meaningful. Responses achieved with dasatinib in blast crisis CML may open a window of opportunity to allogeneic stem cells transplantation for many of these patients.

Adverse reactions

Data collected during phase I and phase II clinical studies, including 911 patients treated with Sprycel revealed a broad spectrum of toxicity of the drug. They showed that almost all patients experienced adverse drug reactions at some time, although most of them were mild to moderate and were easy to manage. Drug discontinuation due to adverse reactions was necessary only in 6% of patients in CP-CML, 5% in accelerated phase, 11% in myeloid blast phase and in 6% in lymphoid blast phase of CML or Ph+ acute lymphoblastic leukaemia.

Apart from anticipated haematological effects directly related to the pharmacological activity of dasatinib (febrile neutropenia: 7% of patients; gastrointestinal bleeding: 6% and thrombocytopenia: 5%) the most frequent reactions included fluid retention events, such as pleural effusion (14%) and oedema (15%); gastrointestinal events including diarrhoea (34%), nausea (19%), vomiting (13%) and anorexia (11%); headache (23%) and musculoskeletal pain (14%).

Interactions

As dasatinib is metabolised primarily by cytochrome C-450 enzyme 3A4, drugs that increase its activity (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital) may decrease dasatinib plasma levels and alternative agents that cause less enzyme induction should be used, or increasing the dose of dasatinib should be considered. On the other side, drugs that inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, indinavir, etc) should be avoided or the dose of dasatinib should be reduced.

Dosage and administration

The recommended dosage of Sprycel is 140 mg/day administered orally in two divided doses (70 mg twice daily), one in the morning and one in the evening with or without a meal. Tablets should not be crushed or cut; they should be swallowed whole. In clinical studies, treatment with dasatinib was continued until disease progression occurred or it was no longer tolerated by the patient. The effect of stopping treatment after achieving a complete cytogenetic response has not been investigated. If adverse reactions appear it is possible to discontinue the drug completely or periodically, as well as to decrease the dose to 50 mg or 40 mg twice daily.

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Spillages and occupational exposure to cytotoxic drugs in an oncology centre

Healthcare workers must be aware of the problems of external, even non-visible, contamination of vials of cytotoxic compounds, and take suitable precautions whenever handling them. ESOP calls on manufacturers to ensure the highest standards of cleanliness.

Introduction: Data on the number of spillages that occur in the oncology clinic are relatively limited. We evaluated the accidents due to cytotoxic spillages in the Bank of Cyprus Oncology Centre between 2004 and 2006.
Methods: All cytotoxic spillages were reviewed that occurred between 2004 and 2006 in the Bank of Cyprus Oncology Centre and were reported to the pharmacy under the monitoring programme, which was modelled on the ESOP recommendations.
Results: A total of 111 spillages occurred during the three-year surveillance period. The majority of spillages occurred in the two inpatient wards of the Centre (92), while the rest were reported from the day care unit (17) and the pharmacy (2). The vast majority of spillages involved the drug fluorouracil. Seventy-two percent of the spillages were associated with the drug administration process. The most frequently reported types of exposure for the staff were due to possible inhalation (44%) and skin contact (16%).
Conclusion: Spillage accidents are thought to be unavoidable in the oncology setting. However, instituting a structured surveillance programme including periodic staff training and using a spill kit based on the ESOP recommendations, can significantly minimise the exposure of the healthcare personnel to cytotoxic or other potentially harmful drugs.

Background

Exposure to cytotoxic drugs at the oncology clinic setting is of major concern to nurses, pharmacists and other healthcare professionals. As a result of the potential exposure to cytotoxic agents, special care is required on the part of healthcare workers handling chemotherapeutic agents. Employees with repeated occupational exposure to the above agents should receive training and be knowledgeable on how to handle these medications safely. In addition, spill kits should be available in all areas where cytotoxic drugs are prepared, dispensed, administered, transported and disposed of.

Stavroula Theophanous-Kitiri MSc

Elpidoforos S Soteriades, MD, MSc, DSc

At a meeting in Hamburg, Germany, all ESOP delegates decided to introduce a spill kit, which would be the same for all European countries. Four forms were prepared (how to use the spill kit, an incident report form, the content of the spill kit, a warning notice). The members considered that it would be more user-friendly, if the spill kit forms were translated by the delegate member of each country into their own language. Thus the forms were translated and finalised. The spill kit is now available in many different languages. Each European delegate has the responsibility at national level to train everyone from his/her country who wish to be able to use the spill kit in the right way

In order to deal with spillages is an emergency situation every hospital must have a written policy and provide appropriate training to its staff in advance, in order to reduce contamination of employees. The spill kit in the Bank of Cyprus Oncology Centre was introduced in 2004 based on the ESOP initiative.

The response to a spill

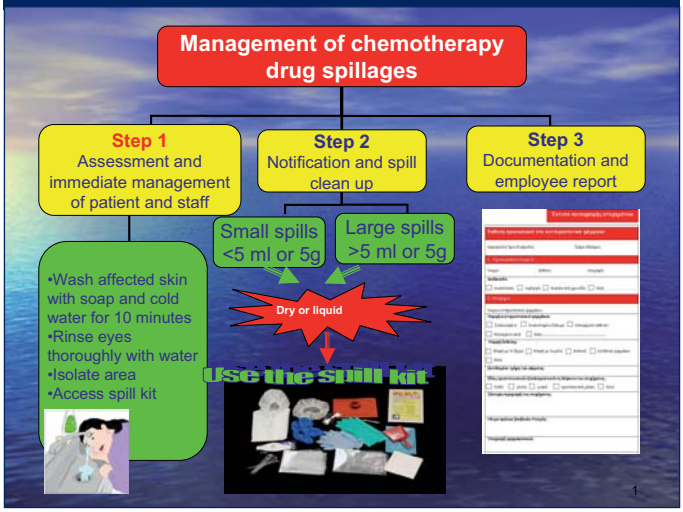
In every incident of cytotoxic spillage, personnel decontamination has priority and must always take place first. If skin is contaminated with cytotoxic drugs it must be washed immediately with soap and cold running water for at least five minutes. Contamination in the eyes must immediately be rinsed with water or normal saline solution for at least 10-15 minutes and an ophthalmologist must be consulted.

Spills are categorised according to their size (small or large) and type (liquid or dry). Small spills are defined as spills of less than 5 mL or 5 g occurring outside a Biological Safety Cabinet (BSC). Large spills are defined as spills greater than 5 mL or 5 g occurring outside a BSC. In every case a spill kit must be used in order to clean up a spillage. The personnel must all wear appropriate Personal Protective Equipment (PPE) (gowns, NIOSH-approved respirator mask, double latex gloves and splash goggles) for either powder or liquid spills. When a large spill occurs, additional equipment should be used since the content of a spill kit is not enough. Liquid spread is limited by gently covering with absorbent sheets or spill-control pads or pillows. If a powder is involved, damp cloths or towels should be used. Specific individuals should be trained to clean up large spills (Figure 1).

Training at the Bank of Cyprus Oncology Centre

The training programme required that all forms in the spill kit be translated into Greek (instructions for how to use the spill kit, incident report form, warning notice, contents of the spill kit). After the

Figure 1: Management of chemotherapy drug spillages



delivery of the spill kit from ESOP in 2004, we trained our staff based on a training course repeated six times in the first year and continued with the new staff in the following years. The courses were attended by doctors, pharmacists, nurses, cleaning staff, porters and other employees dealing with cytotoxic medications.

Our course aims to impart theoretical knowledge for the staff as well as practical skills. Written instructions are given to personnel listing briefly and clearly the actions to be taken in the event of an incident. The practical skills include the removal of three different types of "test contamination" (dry substances, liquid and glass). One member of staff volunteers to remove the "spillage" in the seminar room of our Centre, in the right way while other members of staff watch the procedure. Following the instructions of the trainer, the trainee performs the actions below in the indicated order:

- Secures the contaminated area/puts up a warning notice.
- Marks the area using talcum powder.
- Dons all the personal protective clothing in the indicated order [single-use overall, overshoes, respiratory protection mask (3M), protective gloves, nitrile gloves (two pairs), household gloves, protective eyewear, cap and overshoes].
- As a "dry test contamination", we use well broken mouthwash tablets. We dampen paper with water and the spilt powder is removed by laying the wet paper over it to avoid creating an aerosol.
- As a "liquid test contamination" we use distilled water and clean it up with high liquid binding capacity cloths with one liquid-proof side.
- To remove glass, we break an ampoule of normal saline and an ampoule with a dry powder antibiotic. An additional pair of gloves is used (household gloves). The broken glass is collected up using appropriate aids (scraper, dustpan and cardboard) (Figure 2).
- After the spillage has been collected, the contaminated surfaces are cleaned with 98% isopropyl alcohol followed by a vigorous cleaning with household cleaners.
- The protective clothing is placed in the container in the following order: overgloves, head protection (if the overall does not have integrated head protection), overshoes, overall, and lastly the gloves and the respiratory mask.
- All waste is placed in blue plastic bags and sealed using cable ties.

Figure 2: Personal protective equipment

At the conclusion of the practice, personnel answer a multiple choice questionnaire (on the theory and the practice of removing a spillage) and a certificate of attendance is presented.

Methods of Analysis

In order to evaluate the cytotoxic exposure surveillance programme of the Bank of Cyprus Oncology Centre, we reviewed all reported spillages. All spillages that occurred between 2004 and 2006 at the Centre and were reported to the Pharmacy Department were reviewed by two independent reviewers. A computerised database was created and the data were analysed accordingly.

Results

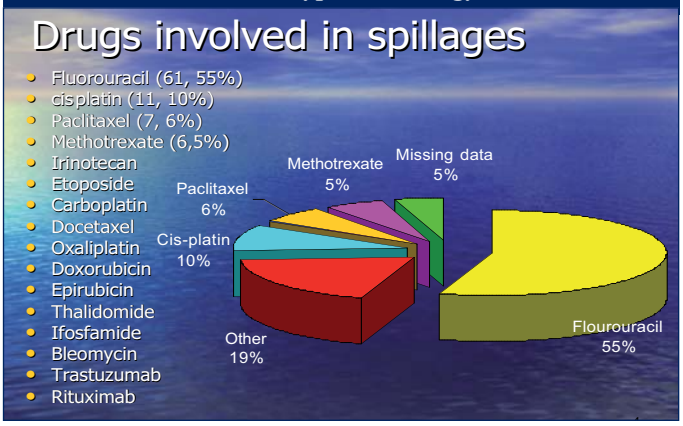
A total of 111 spillages were reported over the 3-year surveillance period. Forty incidents were reported in 2004, 41 in 2005 and 30 in 2006. The majority of spillages occurred in Ward A (54), while there were 38, 17 and 2 spillages in Ward B, day care unit and the pharmacy respectively (Table 1). However, it is worth noting that only 15% of chemotherapy treatment is administered in the inpatient wards (9% in Ward A and 6% in Ward B), while the remaining 85% is administered in the day care unit (as outpatient treatment).

The drugs most commonly involved in spillages were fluorouracil 61 (55%), cisplatin 11 (10%), paclitaxel 7 (6%) and methotrexate 6 (5%). In five cases no data were available about the drug involved. Other medications reported in spillages were irinotecan, etoposide, carboplatin, docetaxel, oxaliplatin, doxorubicin, epirubicin, thalidomide, ifosfamide and bleomycin. Although not cytotoxic drugs, in

Table 1: Cytotoxic spillages reported in the Bank of Cyprus Oncology Centre (2004–2006)

Site	2004	2005	2006	Total
Ward A	15	20	19	54
Ward B	20	12	6	38
Day Care Unit	4	8	5	17
Pharmacy	1	1	0	2
Total	40	41	30	111

Figure 3: Cytotoxic medications involved in spillage reports at the Bank of Cyprus Oncology Centre



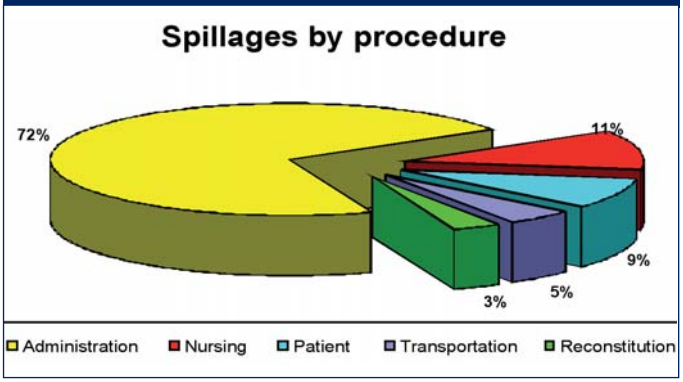
two cases the personnel reported spillages with trastuzumab and rituximab (Figure 3).

Seventy-two percent of spillages occurred due to administration, 11% from patient nursing, 9% due to patient intervention and 8% due to transportation and reconstitution. The majority of spillages occurred at the time the drugs were administered and the most common reasons were leakage from the rubber of the infusion bottle, leakage at the site of connection of the infusion set from the infusion bottle, disconnection of the IV set with the infusion bottle and leakage from the 3-way tab. While nursing patients, the staff reported spillages from patients' excreta, most commonly with urine spread on the linen. In the pharmacy the spillages occurred while moving the vials from shelves (Figure 4).

More than one type of exposure was selected by the staff in the incident reports (24 reports out of 111). The types of exposure were inhalation 63 (57%), environmental 47 (42%), skin contact 22 (20%) and eye contact 7 (6%). The spill kit was used in only 46 out of 111 spillages, while in the rest of the incidents; the employees used gloves and/or other equipment.

From 111 reports, we had missing data in 16 cases. Analysing the data of the 95 cases where more than one protective measure was marked by staff, the following results are listed: gloves were used as a personal protective equipment in 91 spillages (82%), a respirator mask was used in 64 spillages (58%), goggles were used in 57 spillages (51%), a gown in 53 spillages (48%) and in two spillages nothing was used as a personal protective equipment.

Figure 4: Occurrence of chemotherapy spillages



Conclusions

To our knowledge, this is the first report of a cytotoxic spillages surveillance programme in Cyprus. Although the vast majority of chemotherapy treatments are administered in the day care unit, our evaluation showed that far fewer spillages occurred compared to the incidents reported in the inpatient wards. In addition, fluorouracil appears to be involved in the majority of spillages, most likely due to its long infusion period (up to five days). Furthermore, we found that most of the spillage incidents occur during the administration process, while employees do not report using the spill kit at all incidents.

Employees should be educated to use appropriate personal protective equipment to manage spillages based on current guidelines. The spill kit should only be used by persons who have previously undergone a qualified, documented training course about handling cytotoxic medications and using the spill kit. Emergency procedures to cover spills or inadvertent release of hazardous drugs should be included in the overall health and safety programme of all oncology clinics.

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Glucarpidase: a method of rescue from high dose methotrexate

High dose methotrexate is used to treat childhood cancers followed by leucovorin to rescue normal tissues such as kidney, gastro-intestinal mucosa, skin and bone marrow. Voraxaze, a biological product, rapidly hydrolyses MTX into an inactive metabolite to rescue patients from overexposure to MTX.

Introduction

Methotrexate (MTX), an antifolic compound, is one of the most widely used and well studied anticancer agents. High-dose methotrexate (HDMTX) is used in the standard treatment of childhood acute lymphoblastic leukaemia, lymphoma and osteosarcoma [1, 2]. HDMTX is administered (>1 g/m^2) combined with leucovorin (LV) rescue.

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Professor G Vassal

MTX is hydrolysed to 7-OH MTX and is cleared primarily by renal excretion. High doses of MTX cause acute renal dysfunction: MTX and its metabolites precipitate in the renal tubules. The results of this leads to delayed MTX elimination and life-threatening toxicity. Elevation of plasma MTX concentrations increases other MTX-related side effects such as myelosuppression, hepatitis, dermatitis and orointestinal mucositis [2, 3]. Nephrotoxicity is prevented by alkaline hydration. If over-exposure is found by monitoring MTX serum levels, the dose of leucovorin is increased over a prolonged period of time, but it does not completely reverse the toxicity of MTX [4].

Recently a new drug has become available on a named patient basis: glucarpidase [formerly known as carboxypeptidase-G2 (CPDG2)]. Marketed as Voraxaze, it is a recombinant bacterial enzyme that hydrolyses MTX to an inactive metabolite, DAMPA (2, 4-diamino-N10-methypteroic acid). Glucarpidase is a zinc-dependent enzyme isolated from a strain of the bacterium *Pseudomona*. Now a recombinant form cloned from *Pseudomonas* strain RS-16 is awaiting market approval. Glucarpidase rapidly hydrolyzes MTX into inactive metabolite; it may be used as a rescue agent for methotrexate-induced nephrotoxicity [3].

Advantages and disadvantages of different methods of treating HDMTX nephrotoxicity

Leucovorin (LV) rescue prevents the nephrotoxicity due to HDMTX but has no effect on delayed MTX excretion [4].

Glucarpidase decreases the concentration of MTX in extracellular fluids. However a slow process leads to an efflux of intracellular MTX back into the serum and MTX concentrations rise again some hours after infusion of glucarpidase. For this reason LV is always administered in combination, after glucarpidase.

Glucarpidase rapidly hydrolyses MTX into DAMPA. This is less soluble than MTX in acidic pH but is eliminated by an

Mechanism of action

Glucarpidase hydrolyses MTX and 7-OH MTX into DAMPA, a non-toxic metabolite (Figure 1). Glucarpidase is restricted to the extracellular compartment due to its molecular size and does not hydrolyse intracellular MTX [2, 3]. This hydrolysis results in the plasma MTX concentration decreasing by 99% within 15 minutes (Figure 2).

Figure 1: Mechanism of action

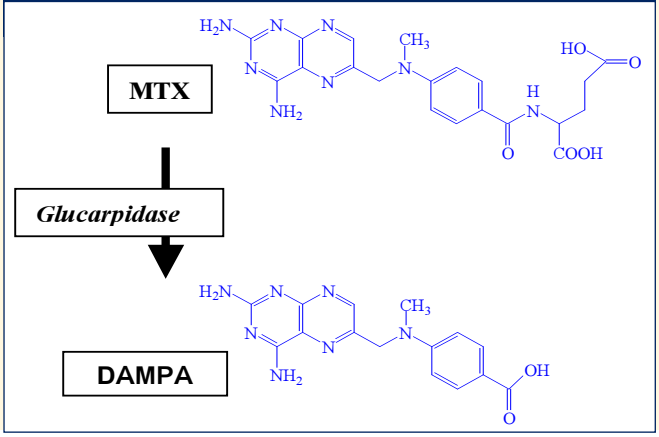
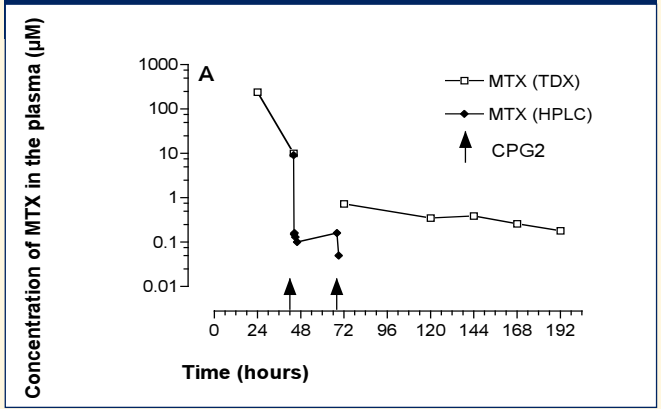


Figure 2 : Decrease in the plasma MTX concentration after glucarpidase infusion [6]



extra-renal route. This is the reason why with glucarpidase, patients continue to need hydration and alkalisation [3, 5]. Haemofiltration or haemodialysis might be used when the patients are oliguric or anuric.

Indications

- plasma MTX concentration > 10 μM less than 42 hours after start of HDMTX infusion

or

- renal insufficiency (serum creatinine ≥ 1.5 x basal values or creatinine clearance < 60 mL/mn/m^2) with delayed elimination of MTX (plasma levels >mean +2 standard deviations within 12 hours of MTX administration)

and

- availability to infuse glucarpidase within 96 hours of starting HDMTX infusion

Posology and administration

Glucarpidase is given at 50 Units/Kg in an intravenous infusion (IV) over five minutes.

It is presented in a lyophilised form. The lyophilised powder is reconstituted with 1 mL of NaCl 0.9%. The solution obtained contains 1,000 units of glucarpidase [7].

Hyperhydration (3 L/m^2), alkalinisation and LV rescue are required when using glucarpidase.

As LV is a competitive substrate of glucarpidase, a study of the interaction between glucarpidase and LV has shown that glucarpidase increases the clearance of LV and reduces its efficacy. Thus LV should be administered at least four hours before or four hours after glucarpidase infusion, to restore reduced pools of intracellular folate.

Undesirable effects

Glucarpidase is well tolerated. Anaphylactic reactions could theoretically occur.

Side effects are infrequent, reversible and minor: paraesthesia, feeling of warmth, tingling in the fingers, flushing, shaking, headache [7, 8].

Special warnings and special precautions for use

Patients must be evaluated for signs and symptoms of toxicity: complete blood counts, liver function and serum creatinine level.

To evaluate the efficacy of glucarpidase, plasma concentrations are determined.

To determine plasma MTX concentrations two methods are used: Commercially available immunoassays such as the Fluorescent Polarisation Immunoassay (FPIA with TDx) are not appropriate to determine MTX concentrations after glucarpidase administration because DAMPA, the metabolite of MTX, cross-reacts with MTX [1]. The concentrations of MTX are thus overestimated.

Therefore the concentrations need to be measured by High Performance Liquid Chromatography (HPLC) because this technique can quantify both MTX and its metabolite DAMPA.

Samples for the determination of MTX concentrations are obtained before and 30 minutes, 24 hours after glucarpidase is given: the blood samples are placed on ice and rapidly centrifuged. To inactive glucarpidase, the serum samples are heated to above 80°C for five minutes in a water bath or treated with 1N HCl to obtain a final concentration of 0.1N of HCl [4].

The results of this monitoring show that glucarpidase causes a decrease in the plasma MTX concentrations of 99%.

The study by Attina and Brugières [9] evaluating the efficacy of glucarpidase showed a rapid reduction in MTX concentration (median 79.3%) for most of the patients. However, a second dose was necessary for five patients. Therefore, it took a median of 12 days for the MTX plasma level to return to its normal limit and renal function normalised with a median delay of 14 days.

Pharmaceutical problems for the management of glucarpidase

The number of glucarpidase (Voraxaze) infusions depends on the concentration of MTX.

Voraxaze is supplied in packs of two vials. Each vial contains 1,000 Units and costs Euros 7,038. The high cost and the way this product is provided explains why it must be well used.

The problem is that shelf life for unopened vials of Voraxaze is 24 months at 4°C. At least two vials are necessary for each patient, so the pharmacist must order two packs of two vials. Currently it is not possible to exchange only one expired vial.

How to obtain glucarpidase in Europe

The manufacturer of Voraxaze is Protherics, which has contracted with IDIS in the UK to respond to the request for products. IDIS will normally be able to deliver Voraxaze within 24 hours of receipt of the order, with a shipment the next day [10].

- The investigator fills in a "named patient basis" form
- The pharmacist faxes this form to the national competent authority
- When the competent authority authorises the request for the product, the hospital pharmacy can order Voraxaze from IDIS.

Conclusion

Voraxaze is an efficient means of rescuing patients from overexposure to MTX following administration of high doses.

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Psychological support of quality of life in cancer patients

Barbara Czerska, PhD

An understanding of the patient's psychological reaction to cancer should colour the attitude of every professional assisting in their care.

Modern cancer treatment is expanding in two directions: improving efficacy and diminishing side effects. Recently oral chemotherapy has also been developing – a method of treatment that protects patients' personal and social relations within their closest sphere. These two aspects of treatment are easing the burden of cancer on the patient.

However the shock of finding one has a possibly life-threatening illness remains similar. When a doctor informs a patient that he or she has cancer, a patient has a real problem to deal with such information. Defence mechanisms are immediately activated. Depending on a patient's personality these could be: disbelief, denial, neglect, not taking note. Disbelief can allow the patient to escape from the problem and reject a possible treatment. My point is that the patient's psychosocial conditioning has a great effect on his/her quality of life.

If, a few weeks after diagnosis, a patient has been able to agree to the next steps of investigation or treatment, we can assume the first psychological hurdle has been overcome. But at this stage it is very difficult to realise that cancer is a chronic illness. This attitude can help to diminish fear of death, although at the same time it reduces the impulse to act heroically [1]. This understanding can be helpful to those who suffer from a recurrence of the problem at a later date. If we do not want a relapse to be a heavy blow, we should concentrate on psychological prophylaxis from the very beginning of the drama. It may reduce the daring will to fight, but it may enable patients to live with cancer calmly, if necessary.

So the patient may do well to adopt an understanding that they have a chronic condition. Changing your self image means changing your habits too. It is an uphill task. And what is a habit? It is a combination of knowledge, skills, and desires. Starting with getting up in the morning up to going to bed at night, we are directed by our habits all day long. Luckily it is like this. Most habits make our lives easier, they are like maps to guide us. The most important habits are those that make our activities more efficient.

At a more advanced stage of the illness one of the most serious problems for the people with cancer is the problem of unremitting fatigue. It is something that cannot be compared to normal tiredness following an effort or work – the tiredness of healthy people. Fatigue, pain and loneliness are all reasons for professional psychological support and further adaptation of lifestyle.

It is not enough to discover something once, just a glimmer, a deed. A constant change is needed. Albert Einstein said once: "Vital problems of our lives cannot be solved on the same level of thinking on which we were when they occurred".

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Combined radiochemotherapy – the state of the art - part two

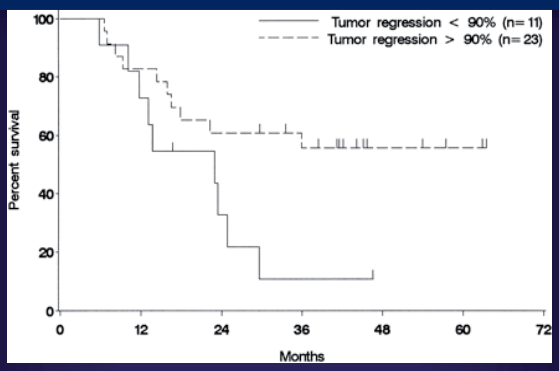
Professor Wolfgang Wagner, MD, PhD

If all factors are optimised, survival in even difficult to treat cancers improves. It is important to keep up to date with the latest guidelines as survival rates nudge upwards. Professor Wagner offers to share the latest thinking if readers would like to contact him.

In stage III advanced non-small cell lung cancer combined radiochemotherapy has become a new standard improving overall survival. There are some prospective randomised studies showing that combined radiochemotherapy followed by surgery will improve resection rate and overall survival. In most studies there is not a significant difference between stage III A and III B. The most important pointer to whether patients will survive is lymph node status after resection. When the lymph nodes specimens are negative patients will have a chance of long term survival (Figure 1).

A meta-analysis from 1995 evaluating 1,780 patients treated with platinum-based induction chemotherapy and preoperative radiotherapy indicated an increase in median survival rate from 10 to 13 months. Nevertheless, the 5-year overall survival rate is disappointing and was calculated to be only 2%. It is unclear whether hyperfractionated radiotherapy or conventional fractioned radiotherapy is superior; a clearly superior chemotherapy regime did not appear either. Today we still do not know whether induction chemotherapy alone is superior to concurrently applied chemoradiotherapy, both given before surgery. All these points must be analysed by work in progress. In patients with small cell lung cancer with limited disease combined radiochemotherapy will improve 3-year overall survival rate (by 5%). This is the result of a meta-analysis published by Pinion et al. in 1992. Up to now the best way to handle small cell lung cancer with limited disease is up-front radiotherapy which will mean that after one or two courses of platinum, combined radiochemotherapy (platinum-based) should follow. Nobody knows whether trimodal therapy with surgery at the end of therapy will improve survival. But what we do know is that prophylactic radiation of the brain will improve overall survival and there is no difference between hyperfractionated or conventional fractionated irradiation.

Figure 1: Stage III non-small cell lung cancer survival is improving with combined radiochemotherapy



Survival (%) from time of diagnosis in patients with negative resection margins (n = 34) according to postoperative degree of tumor regression of lymph nodes in resection specimens. The difference in survival (median, not reached *v* 23 months; 2- and 3-years survival rates, 61% and 56% *v* 33% and 11%) is statistically significant (*P* = .03).

Thomas u. Wagner, JCO, 1999

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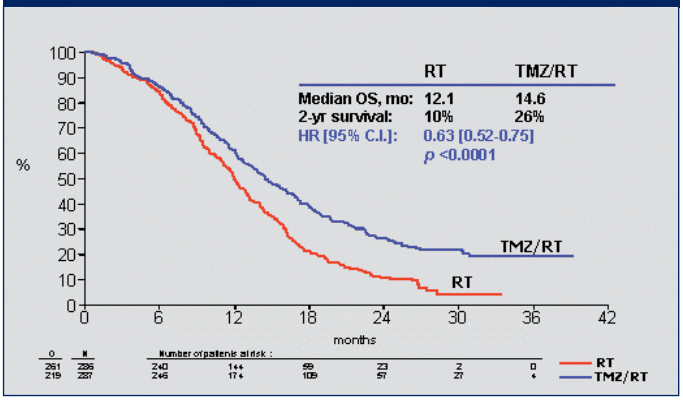
Combined radiochemotherapy has become a new standard too in the therapy of malignant glioblastoma multiforme since 2005. Stupp et al. published their results from an international European-Canadian study concerning concomitant and adjuvant use of temozolomide and radiotherapy for histologically diagnosed glioblastoma multiforme [1]. In this trial they showed that combined radiochemotherapy will improve overall survival from 12.1 to 14.8 months. The treatment schedule consists of one course of radiation with 60 Gy with temozolomide given daily at a dose of 75 mg/m^2. After the end of radiation, four to six courses of chemotherapy are given once a month for five days with a daily dose of 150 to 200 mg/m^2.

In patients with advanced stages of oesophageal carcinoma, combined radio and chemotherapy given concurrently preoperatively will improve the 3-year overall survival significantly. Chemotherapy alone followed by irradiation does not improve outcome. Up to now there are seven randomised studies and one meta-analysis documenting the overwhelming benefit in these patients of treating with combined radiochemotherapy plus surgery compared with surgery alone. In the combined modality the 3-year overall survival rate was significantly better and the local recurrence rate was significantly lower, too. In the surgery arm only the overall resection rate and therapy-related mortality had been favourable compared to the combined modality treatment (Figure 2).

In patients with advanced rectum carcinoma neoadjuvant, combined radiochemotherapy has become standard within the last 20 years. A total dose of 50 Gy is given over a total time of about five weeks and during the first and the last week 5-FU is given at a dose of 1,000 mg/m^2 without a break over a total of 120 hours. We know that prolonged 5-FU infusion will improve survival in comparison with bolus 5-FU during pelvic irradiation and we have learned another lesson – the toxicity of

Figure 2: Significantly improved survival with infused versus bolus 5-FU during pelvic irradiation for advanced rectum carcinoma

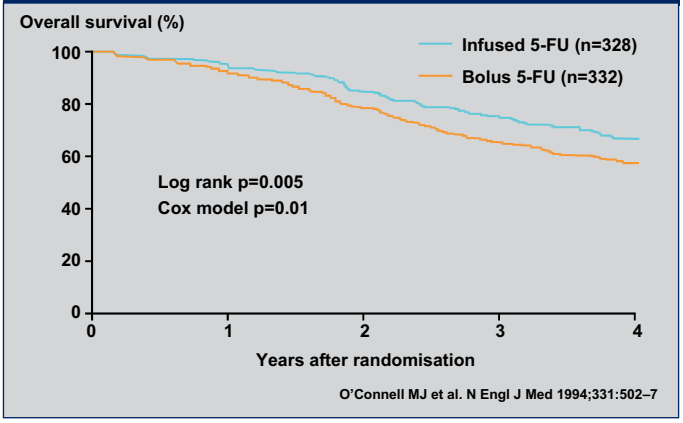


bolus 5-FU application is higher than if it is given over an extended period of time (Figure 3).

Concerning postoperatively applied radiochemotherapy there are some valid data that the local control rate is significantly superior in trimodal therapy (surgery plus radiotherapy plus chemotherapy) in comparison with surgery or surgery plus radiotherapy alone. But the 5-year overall survival rate has only improved in some studies. In other studies these results could not be maintained.

In summary, it is a fact that for many tumours combined radiochemotherapy has become a new standard within the last two decades, improving overall survival rate by about 5% in comparison with chemotherapy or radiotherapy alone.

Figure 3: Overall survival in advanced oesophageal carcinoma is improved with combined temozolomid/radiotherapy compared to RT alone



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News Flash

Does morphine signal death?

Dr Colette Reid and colleagues have explored the factors influencing the decision to accept or reject morphine when first offered to patients with cancer. It suggests that patients interpret the offer of an opiate as an indication that they are dying, rather than a move to enhance their quality of life as they go on with their lives. A qualitative in-depth interview found that participants rejected morphine as a medical intervention to control pain and promote quality of life because they saw it only as a comfort measure for the dying. This, in turn, sometimes led to refusal of pain relief and a reduction in patients' quality of life.

In a study published online, 11 December 2007 in *Annals of Oncology* [1], experts in palliative care also say "the belief that opioids hasten death is widely held" amongst patients and this "has a significant impact on pain management, as patients felt that an offer of opioids signified imminent death". Previous studies have estimated that between 40-70% of cancer patients may not have their pain properly controlled with the right medication for a variety of reasons.

Morphine as a "last resort" was the central theme to emerge from the interviews. The authors write: "Patients with cancer who were offered morphine for pain relief interpreted this as a signal that their health professional thought they were dying. Because participants themselves were not ready to die, they rejected morphine and other opioids as analgesics, despite the pain experienced as a consequence." As a result, unrelieved pain leads to social isolation, loss of role and depression.

The role of healthcare professionals is crucial in helping to change patients' beliefs and attitudes towards morphine. If used properly, morphine can promote quality of life by allowing patients with pain to function better. World Health Organization guidelines for the management of cancer pain state that analgesic treatment choices should be based on the severity of the pain, not on prognosis.

1. Annals of Oncology, doi:10.1093/annonc/mdm462

Supportive care: nutrition problems, alopecia and mucositis

Supportive care is fundamental when treating both the consequences of tumour burden and the result of treatment. Adequate nutrition is a mainstay in supportive treatment; side effects such as alopecia and mucositis should be handled sensitively and appropriately.

Supportive care

Tumours cause many distressing symptoms in patients with cancer and must be adequately managed. Cancer and its treatment not only give direct tumour symptoms but also systemic effects that lower the patient's daily comfort and quality of living if not properly treated.

Professor Per Hartvig PharmD, PhD

Eva Honoré MSc Pharm

Therapy itself gives prominent side effects which profoundly affect suffering and discomfort, reduce the quality of life of the patient and in some instances also limit further treatment. Adequate nutrition is a mainstay and must be reviewed. Methods are continuously evolving to limit the burden of cancer for the patient and everyone has the right to have their symptoms properly managed. Supportive care plans for cancer treatment should be made mandatory [1].

Nutrition of patients with cancer

Many cancer diseases show non-specific symptoms at an early stage. Considerable loss of weight is often the first indication of a tumour. Tumour growth is associated with profound metabolic and biochemical alterations, leading to the onset of the anorexia-cachexia syndrome. Cachexia is a problem during advanced stages of tumour disease and almost 100% of patients are affected near death. It worsens the prognosis of the disease, diminishes the response to cytotoxic drug treatment and increases mortality following surgery [2]. The pathogenic mechanisms of cachexia and anorexia are multifactorial, but cytokines and Tumour Necrosis Factor/cachecin have a significant role, thereby representing possible therapeutic targets. In anorexia energy expenditure is frequently increased while energy intake is decreased, further exacerbating the progressive deterioration of nutritional status. The tumour by its nature and obligate growth continues to consume glucose, amino acids and lipids at the expense of its host. This produces abnormal host intermediary metabolism with increased glucose production and recycling, decreased muscle protein synthesis and elevated fat breakdown. The mechanisms are only partly explained [3].

Patients with cancer may suffer from a sensation of repletion, modified perception of taste, anorexia, nausea or vomiting, swallowing or chewing difficulties, inflammation in the oral cavity and depression. All these factors decrease appetite and food intake. Malnutrition may result despite increased energy consumption. Muscle wasting is the most important feature of cancer cachexia [4] and the principal cause of function impairment, fatigue and respiratory complications. Pharmacological attempts have been made to inhibit the catabolic effect in muscles but results from studies are still scanty and contradictory. Stimulation of muscle anabolism offers a promising therapeutic alternative and might be achieved with short-acting anabolic steroids, although side effects must be carefully considered. Insulin growth factor 1 (IGF-1) plays a role in muscle homeostasis, hypertrophy and regeneration. IGF-1 over-expression at muscular level by gene therapy reverses muscle hypotrophy. It has been speculated that this approach could be valuable in cancer-induced muscle wasting [4].

Change of eating habits in the direction of healthy nourishment may have a positive effect on the patient's condition. A radical change may however be inadvisable since it usually results in eating less. A warning should be sounded about so-called cancer diets. Many are one-sided and may therefore influence the progression of the disease negatively. Everything should be done to increase the appetite and to make eating well-balanced food a pleasant experience. Nutritional support is effective at maintaining bodyweight in cachectic cancer patients, but it has not yet been shown to increase the response to radiotherapy or cytotoxic drug therapy [5].

Mucositis

Mucositis remains one of the most troublesome and frequent side effects of anti-cancer treatment with cytotoxic drugs or radiotherapy. Inflammation of the mucous membranes is named according to its site: stomatitis, oesophagitis, cystitis, etc. It can be extremely painful. Until recently treatment was not particularly successful. The pathophysiology is now better understood and since the disability is often so severe as to be dose-limiting more interest is now being shown from clinicians and drug companies. Analgesics and adequate nutrition are important elements of treatment but anti-infectious treatment must also be considered for manifest ulcerations. Use of oral local anaesthetics is standard.

Guidelines for mucositis treatment have appeared but the first, issued in 2004, rapidly became out-dated. Recommendations contained many negatives, a few "maybes" and very few positive plans. Palifermin (rHUKGF1) was the first drug in its class and also the first in the field to receive a positive recommendation. Evidence has allowed the mucositis guidelines group to make a

recommendation for its use, albeit in a narrower group of patients than regulatory agencies recommend and only in haematological malignancies so far. This is an interesting break-through in the treatment of mucositis although the drug is expensive, not simple to use, and not necessarily safe and effective in all cancer patients [6]. An expansion of the positive recommendation for cryotherapy (ice cubes) has also been issued [7]. Keratinocyte growth factor, molgramostim and transforming growth factor beta may also reduce chemotherapy-induced mucositis [8].

The Multinational Association for Supportive Care in Cancer guidelines for mucositis can be found on www.mascc.org/content/338.html

Alopecia

Alopecia is a weighty side effect during many cytotoxic drug regimens. To lose all body hair is a real sorrow. The patient is reminded visually that he/she is seriously ill. It is felt like a loss of identity, a deep personal feeling that is difficult to address. Relatives and friends may feel confirmation that the patient is sick. It is hard for the patient to challenge this change. Contact with patients suffering hair loss must acknowledge their emotional pain, be participating and generous. Time is necessary for the patient to express his/her concern, sorrow and anger. Decisions require time. It is important to give the patient that time!

Hair cells divide very rapidly and are damaged by the administration of cytotoxics due to the growth of more narrow and fragile hair. It is easily broken when this new hair reaches the scalp. Loss of hair starts about two weeks after cytotoxic drug treatment and all hair falls out within a few weeks. In the case of moderate damage, only a fraction of hair follicles stop growing. Not only the hair on the head is affected, but all other hair on the body including eyelashes, eyebrows and facial hair as well. Not all cytotoxics cause the same degree of hair loss and some drugs do not affect hair growth at all.

Options for treating alopecia are still very limited. Cool-caps can be used at the request of the patient. The scientific evidence for them is weak and it seems logical only to reduce the blood flow to the scalp for cytotoxics with a very short elimination half-life. After discussion with the patient, a wig or scarf might be an acceptable alternative. New hair regenerates rapidly and within one or two months of completion of cytotoxic drug treatment, hair begins to grow on the head. There is no scientific evidence to show that medication may improve hair growth after cytotoxic drugs. It is also important to protect the bald scalp from sunlight [1].

The pharmacological agents under evaluation for cytotoxics-induced alopecia include drug-specific antibodies, hair growth cycle modifiers, cytokines and growth factors, antioxidants, cell cycle or proliferation modifiers and apoptosis inhibitors. Most of these mechanistically different drug principles have been evaluated in animal models so far. Most have an activity only limited to a single cytotoxic agent, whereas calcitrol and cyclosporin A have broader activity.

Conclusions

Inadequate treatment of systemic tumour effects or drug induced side effects may worsen the disease burden in cancer, increase suffering, limit treatment and in the worst case even be life-threatening. The risk that these symptoms may be debilitating must be considered before treatment and adequate management plans must be at hand. Supportive care is an important task for the clinical oncology pharmacist.

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Dispensing of oral chemotherapy in the community: a viability assessment in the UK

Cancer treatment is traditionally prescribed, dispensed and administered in hospital. There is now pressure for oral cancer treatment via local pharmacies to reduce costs and assist patient convenience. Safe and accurate supply of medicines, an 'out-of-hours' service and waste disposal procedures are needed.

Background

In 2005, the Department of Health consulted 143,000 members of the public on their health requirements. The resulting White Paper entitled 'Our Health, Our Care, Our Say' was published in 2006 [1]. The dominant theme arising from the consultation was that people wanted quality health services closer to their homes. The challenge from the White Paper is to find ways to change the way health services are provided to make them closer to patients' homes and more flexible whilst maintaining safety. This requires a shift in emphasis from secondary to primary care.

Community pharmacists are ideally placed to facilitate the movement of some services away from the secondary care setting. This has already been done successfully in the management of chronic diseases such as asthma and diabetes. There are also examples of community pharmacist led anticoagulation services.

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Cancer

The involvement of community pharmacy in cancer prevention originates from the Calman Hine Report in 1995 [2] and the NHS Cancer Plan in 2000 [3]. Dietary advice and health awareness leaflets are available in most pharmacies and smoking cessation programmes are now evident in many. Community pharmacists have also been involved in the provision of drug supplies for terminally ill patients, and with the advent of supplementary and independent prescribing, the pharmacist role can expand further.

Historically however, very few cytotoxic chemotherapeutic drugs have been dispensed from community pharmacies. Reasons for this would be the relatively rare nature of some of the diseases, the close involvement of the secondary care team in the management of the patient, the varied scheduling and toxic nature of the drugs involved. Furthermore, the vast majority of the drugs used to be given parenterally due to their low therapeutic index and toxic potential.

As rapidly advancing technologies ensure better bioavailability and predictable pharmacokinetics, more oral cancer drugs are being developed. This combined with pressure on hospital chemotherapy units and patient preference for oral therapies offer unprecedented opportunities to treat patients outside the hospital environment.

Some of the new oral drugs resemble the conventional cell-damaging predecessors, but there are other small molecules which are relatively non-toxic and exert their anticancer effect via complex molecular mechanisms. Also, as the drugs become more effective, are used earlier in the disease and patients are living longer, cancer is becoming a chronic disease, making it a possibility for certain patients to have their disease maintained in the community with advisory secondary care input in terms of a shared care arrangement. In addition, separating the drug costs from the treatment costs introduces a choice as to how therapy is delivered.

Whilst there would be many barriers to operating a safe community dispensing/monitoring service to patients on anticancer therapy, national drivers such as those set out in the White Paper and changes in commissioning arrangements warrant its investigation. In addition, there is a national framework for Pharmacists with Special Interests that could be adapted to fit cancer [4].

Assessment of barriers and incentives

1. Patient numbers per locality

Consideration of how many patients might be likely to want to access a community pharmacy service for oral chemotherapy dispensing needs to be given. The German model involves a small number of specialist pharmacies. However the German pharmacies are not limited to oral chemotherapy dispensing, but also have aseptic facilities to compound parenteral chemotherapy doses. The UK is unlikely to be able to emulate that model in the near future; the focus must therefore be on opportunities for delivery of oral chemotherapy through community pharmacies.

2. Chemotherapy regimen

The type of chemotherapy to be dispensed is of paramount importance to the safety of any community dispensing scheme. Also of importance is the potential variety of regimens in terms of ensuring that the community pharmacy staff are adequately skilled. Classic sources of error in oral chemotherapy prescribing and dispensing include [5]:

- Incorrect verification of dose (based on BSA, weight, titrated, fixed or banded)
- Pulsed dosing misinterpreted as continuous
- Inability to recognise variations in pulsed dosing for same drug, but for different disease
- Wrong strength tablet/capsule dispensed
- Drugs continued where cessation of treatment was intended
- Inaccurate numbers of tablets dispensed (potential for over or under dose)
- Where more than one drug is prescribed, schedules swapped due to (i) poor labelling or (ii) poor patient understanding
- Where a chemotherapy regimen consists of both parenteral and oral cytotoxic components

With these sources of error in mind, special care should be taken with the following chemotherapy regimens [6]:

- Those involving drugs with a low therapeutic index (i.e. the most toxic)
- Those involving a 'pulsed' schedule
- Those involving more than one drug in different schedules
- Complex regimens for patients who cannot follow complex schedules
- Those given to patients who are very ill

It would be reasonable to assign a risk scoring system to potentially suitable oral chemotherapy regimens based on the above parameters. In addition, dispensing scenarios could be modelled using the National Patient Safety Agency (NPSA) toolkit to identify potential pitfalls and methods where safety could be maximised [7].

Logistically, it would not be efficient to use community dispensing for oral chemotherapy where there is also a parenteral component to the regimen.

3. Availability of the drug

Consideration should be given to the accessibility of each oral chemotherapeutic agent. Unlike a hospital pharmacy, community pharmacies are unlikely to be able to keep stocks of these drugs. For example, a drug that is only available from the main supplier and not via the wholesaler can not be accessed within 24 hours. There is potentially a problem for uncommonly used, high expenditure drugs such as imatinib (Euro 3,000 for a month's supply) in that a community pharmacist will not be able to afford to be left with partially used (non reimbursed) packs.

4. Origin of the prescription

The prescription could be generated by hospital-based cancer clinician or in general practice. In the case of the latter, a GP with a special interest in cancer (GPSI) would be preferable. There have been many cases of oral chemotherapy being inaccurately prescribed in general practice. If a GPSI and a specialist pharmacy are both required, the pool of potential patients is getting smaller still. It would therefore seem appropriate for prescriptions to originate from the hospital.

Preprinted or computerised prescription templates are used in hospitals to reduce the chance of dispensing or prescribing errors. Drugs are reimbursable to community pharmacies from the standard hospital prescription forms (FP10 or FP10HP). Since it would be difficult to convey the full dispensing requirements for some oral chemotherapy prescriptions using the FP10 restricted template, it may be that such prescriptions are unsuitable for community pharmacy dispensing or that an alternative template might be acceptable.

Ideally chemotherapy prescriptions should be checked by a specialist cancer pharmacist. This check could be done within the cancer centre/unit by the specialist oncology pharmacist. To ensure safety, should community pharmacists be required to undertake these checks, they may need to operate according to shared care guidelines [5] or become a *Pharmacist with a Special Interest (PhwSI) in cancer* [4].

5. Requirement for shared care documentation

A shared care partnership standard operating procedure or detailed information sheet, drawn up between the community pharmacist and the secondary care centre would help give reassurance to the secondary care provider and support to the community pharmacist. It should contain details of cancer professionals who could assist in the event of a query. It would also be advisable for the dispensing pharmacist to have access to some details about the patient, and his/her particular previous or concurrent medication. The dispensing record for that patient should be checked at any interaction the community pharmacist has with the patient. In the shared care agreement, it would be the responsibility of secondary care to provide the patient detail and their plan, and the responsibility of the community pharmacist to ensure that records are adequately checked prior to dispensing.

If the community pharmacist is required to give information on drugs to any patient receiving chemotherapy, that information should be agreed in the shared care agreement. The shared care agreement can also ensure that the community pharmacist is adequately appraised of the relevant adverse drug reactions and interactions.

A list of appropriate chemotherapy regimens, approved by the cancer network that can be dispensed in the community and a detailed description of the clinical assessments and intervals that should occur between prescriptions will help to ensure that the patient is managed optimally.

In many cases pharmacies being left with part packs of expensive medicines could be avoided by developing shared care guidelines that involve original pack dispensing. There are schemes that could be extended to chemotherapy dispensing where waste stock is reimbursed. It is unsafe for patients to be given more tablets than required.

6. Training

The *ideal* model to ensure adequate training of community pharmacists in the care of cancer patients is to use the service framework for *Pharmacists with Special Interests (PhwSI)*[4]. It is worth noting that this qualification could effectively

increase the pharmacists' role in many other cancer areas, not merely in the dispensing of chemotherapy. For example, palliative care, smoking cessation and dietary advice.

Definition of a Pharmacist with a Special Interest (PhwSI)

"A Pharmacist with a Special Interest supplements their core generalist role by delivering an additional, high quality service to meet the needs of patients. Working principally in the community, they deliver a clinical service beyond the scope of their core professional role or may undertake advanced interventions not normally undertaken by their peers. They will have demonstrated appropriate skills and competencies to deliver those services without direct supervision".

The competencies necessary for a community pharmacist to be designated as a PhwSI in cancer are yet to be defined. A pilot project may be useful to inform the definition of competencies and a suitable organisation needs to be identified to develop these. Also, when considering the points made below in 7, it may not be practically possible to make such a qualification obligatory, and a lesser training may be required.

7. Continuity of community pharmacy workforce

This is an area of concern; particularly if the PhwSI qualification is considered to be obligatory to the community chemotherapy dispensing service. It is unlikely that an appropriately trained covering pharmacist could routinely be available. A possible scenario would be that chemotherapy could not be dispensed at the premises when the specialist pharmacist is unavailable, and alternative arrangements, possibly involving similar pharmacies could be made. The alternative would be to take the prescriptions back to secondary care.

8. Remuneration

This new work requires a considerable degree of expertise and extra time is required apart from just ordering and dispensing the drugs involved. The additional pre-dispensing checks and responsibility should be paid for, as should the potential wastage on expensive part packs.

9. Handling and disposal of cytotoxic drugs and associated waste

Community pharmacies are also obliged to follow COSHH regulations. There are already purple burn bins available for this purpose

10. Out-of-hours support

There are potentially two types of patients involved in this proposal. The first would be those requiring routine, continuous dose, established chemotherapy for a low grade (chronic) cancer. Examples of this might be hydroxycarbamide for CML or chlorambucil for CLL. There are unlikely to be queries relating to the chemotherapy or disease that are urgent. The primary care out-of-hours services would be sufficient to cover these. The other type of patient might be viewed in the same way as

Table 1: Dispensing oral chemotherapy

Country	Prescribed by	Prescribed			Dispensed			
		Hospital (government)	Hospital (private)	Consulting rooms	Hospital	Community	Both	By consultant
Australia	Consultant	x	x	x		x[1]		
Canada (West)	Consultant	x	x		x			
Canada (East)	Consultant	x	x			x		
Cyprus	Consultant	x	x		x			
Czech Republic	Consultant	x		x	x	x[2]		
Denmark	Consultant	x					x[6]	
Estonia	Consultant	x					x	
Finland	Consultant	x					x[6]	
Germany	Consultant	x	x	x			x[4]	O[3] & IV[3]
Lithuania	Consultant	x					x	
Netherlands	Consultant	x					x	
Slovenia	Consultant	x				x		
Spain	Consultant	x					x	
Sweden	Consultant	x					x[5]	
Switzerland	Consultant	x		x	x			O[3] & IV[3]
UK	Consultant	x			x			
USA	Consultant	x	x	x		x		

1. Shared care agreement.
2 Can be dispensed in community pharmacy but not common. May be given to patient in the ambulance.
3. Oral preps dispensed by consultant in rooms. Parenteral prepared in specific community pharmacies with Laminar Air Flow cabinets.
4. Discussing issues with community pharmacy. Patient taking drugs in pharmacy, or given via ambulatory nurse.
5. Community pharmacies are dispensaries only and are run by the health service and pharmacists are government employees.
6. Patients on wards supplied from ward stock (no pharmacy involvement). Prescriptions dispensed from local community pharmacy.

a secondary care patient on chemotherapy and could be channelled through the secondary care out of hours services.

Summary

The evolution of healthcare policy in the UK and the changing demographics of the cancer patient require solutions to the problem of moving the treatment of patients requiring chemotherapy services increasingly from the secondary to the primary care setting.

There are many barriers to the successful and safe transmission of chemotherapy dispensing from secondary to primary care, but frameworks are emerging to facilitate the move.

The British Oncology Pharmacy Association (BOPA) is committed to forming the appropriate links with political, professional and patient representing organisations to progress this work.

The BOPA has established a workgroup to study the options for the pharmaceutical care of patients with cancer. Although this group was initially formed to look at the supply of oral cancer treatments, all areas of care will be examined.

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ESOP News

ESOP masterclass in Ishöj, Denmark

The very first ESOP masterclass took place from 5-9 November 2007 in Ishöj, just south of Copenhagen in Denmark. The first course in the masterclass gave recent updates on the risks of cytotoxic drug preparation and handling. It also encouraged participants to provide clinical oncology services to the wards by presenting literature sources, information about stability and microbiological contamination of cytotoxic drugs as well as an insight into treatment of infection in cancer, herbal remedies and risks of medical errors. The second course focused on clinical oncology pharmacy practice with supportive care for cancer patients, as well as the new era with individualised therapy in medical oncology. The participants, 22 in the first and 23 in the second course, rated the courses as "very good to excellent" and said they "fulfilled or were better than their expectations". The level of course material and lectures were also considered "adequate".

All participants gave a good opinion of the masterclass

An animated small group discussion during the ESOP masterclass

The two courses were linked by a very joyful dinner in a small restaurant in Köge harbour where colleagues from 15 European countries shared a good time.

Course Leaders:
Professor Per Hartvig and Dr Eva Honoré

Current thinking in antifungal prophylaxis

Recent data show that posaconazole promises to effectively decrease the incidence of invasive fungal infections in patients with acute leukaemia.

Christina T Rieger
MD

Professor Helmut Ostermann
MD

Introduction

Invasive fungal infections (IFI) are increasingly diagnosed in patients with haematological malignancies and allogeneic stem cell transplants. They cause significant morbidity and are an important cause of mortality in these patients. As treatment of IFI is far from optimal, prevention by the prophylactic use of antifungals is an obvious option for these patients. The recent change in epidemiology from *Candida* species to moulds becoming more predominant as pathogens makes it necessary to use agents not resistant to species like *Aspergillus*. Therefore fluconazole is no longer an option for prophylaxis in these patients.

Epidemiology and clinical problem

Immunocompromised patients are at risk of developing opportunistic infections. Bacterial infections, often present as blood-borne infections or clear-cut clinical infections like pneumonia, are quite easy to diagnose. Treatment of bacterial infections in immunocompromised patients with broad-spectrum antibiotics carries a high response and cure rate. Fungal infections however are hard to diagnose, difficult to treat, and still carry a high mortality risk. The diagnosis of IFI relies on clinical signs and symptoms, blood tests, radiological examinations and culture or histology. Although the mortality of IFI may have decreased recently [1], in allogeneic stem cell transplant recipients for example it is still around 20-30%. Furthermore, in recent years the emergence of rare fungi that are often difficult to treat, such as *Zygomycetes* and *non-albicans Candida*, has been observed [2]. Different treatment strategies can be used in IFI. The increasing incidence and the high mortality associated with invasive fungal infections have prompted studies on antifungal prophylaxis. Most of the clinical trials that have been done on antifungal prophylaxis are small, observational and use mostly historical controls.

Risk factors

Risk factors for invasive fungal infections are prolonged neutropenia, which occurs following intensive chemotherapy for acute myeloid leukaemia, allogeneic stem cell transplantation especially when associated with graft-versus-host disease (GvHD), immunosuppression following solid organ transplantation and lengthy corticosteroid use.

As mortality is high once an invasive fungal infection develops, it seems rational to use antifungal prophylaxis in high risk situations. Reported case fatality rates are between 40% and 90% depending on the patient population [3].

Prophylaxis with fluconazole

Fluconazole has an excellent safety profile. It is however still not clear whether its effect relates to the prevention of fungal infections only, as fluconazole is not effective in mould and in various *non-albicans Candida* infections.

Prophylaxis with fluconazole is generally recommended for patients with allogeneic stem cell transplantation. In this patient cohort two studies show a significant effect on mortality [4, 5]. However, the positive results from Haematopoietic Stem Cell Transplantation patients have been accepted for patients with acute leukaemia as well, leading to the widespread use of fluconazole prophylaxis in this patient cohort. Recent data show no advantage from this approach [6]. Therefore fluconazole prophylaxis in acute leukaemia only has a low level of recommendation [7].

Prophylaxis with itraconazole

Itraconazole has the advantage of being effective against *Aspergillus* spp. As these are clinically more important than yeasts in patients with acute leukaemia, itraconazole has been investigated in this indication. Problems associated with itraconazole relate to poor absorption with the capsules and poor tolerability with the oral solution. Furthermore, drug interactions are prominent as with all azoles. Therefore no trials have demonstrated superiority in acute leukaemia. In allogeneic stem cell transplantation two trials have shown a decrease of mould infections; however tolerability and toxicity were important issues. Therefore only a weak recommendation can be given for itraconazole [7, 8]. If itraconazole is chosen for prophylaxis, plasma levels should be measured, especially for the oral formulations.

Prophylaxis with posaconazole

Among the azoles posaconazole has several advantages. It has a broad spectrum of activity against *Candida* and *Aspergillus* spp. and is effective against *Zygomycetes* as well. It is well tolerated; however it is only available in an oral formulation. As with all azoles, it has the potential to interact due to cytochrome P450 metabolism.

Two large randomised trials have proven it to be effective in lowering the incidence of invasive fungal infections and improving survival in patients with haematological malignancies. The first trial was done in patients with acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) receiving intensive induction chemotherapy [9]. Posaconazole prophylaxis was compared

to standard azole prophylaxis, i.e. fluconazole in the majority of patients as well as itraconazole. The incidence of invasive fungal infections reduced from 8% to 2%, mainly due to a decrease in invasive aspergillosis. Overall mortality was lower in the posaconazole group. These results have prompted strong recommendations in guidelines [7]. The number needed to treat to prevent one invasive fungal infection was 14 within the trial.

The second posaconazole prophylaxis trial focused on patients with acute or chronic severe GvHD which develops following allogeneic stem cell transplantation [10]. The control group received fluconazole. Comparable to the AML trial, the incidence of invasive fungal infections reduced significantly from 9% to 5%. There was a trend for a decrease in mortality; however this was not statistically significant. Therefore according to these results a change from fluconazole prophylaxis to posaconazole prophylaxis should be considered in patients following allogeneic stem cell transplantation who develop severe GvHD.

Some questions however remain unanswered regarding posaconazole prophylaxis. As it is only available in an oral formulation and absorption is affected by oral fat intake, patients with severe mucositis or nausea may not tolerate the drug. Furthermore, wide spread use of posaconazole could lead to resistance problems, and for an expensive drug, cost effectiveness should be demonstrated.

Polyene prophylaxis

Topical amphotericin B

Topical prophylaxis with amphotericin B has shown to decrease the incidence of *Candida* mucositis. However, an effect on systemic fungal infections could not be consistently shown. Furthermore, close observation of patients at risk identifies patients with oral candidiasis early. These patients can easily be managed with oral fluconazole. Additionally, when mucositis occurs, a swab should be taken to identify fluconazole-resistant *non-albicans Candida* spp.

Inhaled amphotericin B

As aspergillosis is mostly transmitted as an airborne disease affecting primarily the lungs, local prophylaxis by inhalation should make sense. However, a randomised trial could not show an effect by using this method, which is hampered by poor tolerability as well [11].

Intravenous amphotericin B

Both conventional and liposomal amphotericin B have been employed in prophylaxis trials. However, no trials have been sufficiently powered to show a positive effect. Therefore the use of intravenous amphotericin B is not recommended for prophylaxis [7].

Echinocandins for prophylaxis

Sparse data have been published so far on the use of echinocandins in prophylaxis. One trial compared fluconazole to micafungin in allogeneic stem cell transplant patients and found no difference in mortality or the incidence of IFI compared to fluconazole but a decreased use of empirical antifungal therapy [12].

Conclusion

In summary, antifungal prophylaxis in patients with acute leukaemia or allogeneic stem cell transplantation has gained renewed interest following the publication of new data. Among the azoles itraconazole and voriconazole are suitable, however data are not consistent and for itraconazole poor bioavailability and tolerability poses a problem. Amphotericin B and liposomal amphotericin B can only be used as an IV formulation. Furthermore side effects make their use in prophylaxis difficult. With echinocandins again only IV formulations are available and clinical data for the use in prophylaxis are scarce.

Table 1: European Conference on Infections in Leukaemia recommendations on the use of antifungal prophylaxis in allogeneic stem cell transplants and acute leukaemia [7]

Drug	Level of recommendation*
Allogeneic stem cell transplantation	
Fluconazole 400 mg qd oral/IV	A1
Itraconazole 400 mg IV followed by oral solution	B1
Posaconazole 200 mg tid oral	A1
Micafungin 50 mg qd IV	C1
Polyene IV	C1
Acute leukaemia	
Fluconazole 50 – 400 mg qd IV/oral	C1
Itraconazole oral solution 2.5 mg/kg bid	C1
Posaconazole 200 mg tid oral	A1
Low dose Polyene IV	CII – CIII

* Levels of evidence are listed in accordance to the Oxford Centre for Evidence-based Medicine classification: Levels of Evidence and Grades of Recommendations: www.cebm.net

The best evidence so far points to the use of posaconazole in patients with AML induction treatment until recovery of neutrophils. In allogeneic stem cell transplant patients fluconazole is the standard followed by posaconazole, if severe GvHD develops.

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A good standard of contributions at the SFPO

Frederic Pinguet, PharmD, PhD

The sixth annual meeting of the French Society of Oncology Pharmacy (SFPO) was held in Nice, France, 11-12 October 2007. It attracted more than 400 participants from France and countries as far away as Tunisia. Congratulations to the team!

In plenary sessions, talks were given on topics such as genetics, monoclonal antibody stability, myeloma, pharmaceutical care and fungal infections. Three workshops gave more practical information on prescription analysis, anticancer drug stability and optimisation of cytostatic preparations.

An impressive number of abstracts were presented (more than 100) covering a large range of both basic and pharmaceutical aspects of cancer diseases. Six of them were selected as oral communications and five awards were made, as we were so impressed by the work. Some papers initiated and presented by the SFPO will soon be submitted for publication.

We hope that the different presentations and results of the SFPO 2007 meeting will be available in more detail on the SFPO website by the time this issue of EJOP reaches you. Please consult www.sfpo.com for information about anticancer treatment as well as further conferences and activities organised by the SFPO.

The following study was awarded the prize for the best oral communication.

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Thermal stability of two monoclonal antibodies: cetuximab and bevacizumab

M Paul, A Lahlou, M Carvalho, B Blanchet, Professor Alain Astier, PharmD, PhD

The stability of therapeutic proteins, especially those used in oncology, is a subject of great interest, considering the possible loss of efficacy and emergence of side effects due to thermal or mechanical stress. We studied the aggregation pattern of two monoclonal antibodies (MAbs) bevacizumab and cetuximab exposed to thermal stress. One of the potential harmful side effects caused by aggregates is immunoallergic reactions.

Methods: Commercial vials of cetuximab (Erbitux, 2 mg/mL and bevacizumab (Avastin; 25 mg/mL, diluted to 2.5 mg/mL with phosphate buffer pH 6.0) were sampled and aliquots were kept under sterile conditions at four temperatures: 4°, 25°, 37° and 56°C. For each assay time and temperature, an estimation of the aggregation was performed by turbidimetry at 350, 410 and 550 nm. After centrifugation, the non-aggregated solutions were analysed by size exclusion chromatography (SEC) and ionic chromatography (IC). Each determination was performed in triplicate.

Results: After storage periods of up to 1056 hours (44 days) neither antibody exhibited significant aggregation at 4°, 25° or 37°C. However, at 56°C, aggregation was rapid with the solution becoming opaque after three hours. At 4° and 25°C, the SEC and IC chromatograms did not change: neither soluble aggregates (high MW) nor fragmentation (low MW peaks) were observed. After 72 hours at 56°C the residual amount of non-aggregated cetuximab was 6.4% ($T_{1/2}$ 0.67 hours) but was 99.5% at 4° and 25°C and 98% for 37°C. An identical pattern was observed for bevacizumab. Ionic chromatograms showed no change for either MAb until 276 hours of incubation. However at 37°C, a decrease in the secondary isoform peaks indicated a change in the total ionic charge. The temperature causing half the maximum heat-dependent aggregation (Tm) was 72.5°C for cetuximab with aggregation increasing slowly but significantly beyond 30°C (double sigmoid curve). For bevacizumab the Tm was 69.4°C but without significant increase between 30°C and 60°C (single sigmoid curve).

Conclusion: These preliminary results suggest that, for storage temperatures under 37°C (pH 6.0), no significant aggregation or degradation were observed until 256 hours for either MAb. Cetuximab exhibited a lesser tendency to aggregate on exposure to heat than bevacizumab. Further analysis is needed to demonstrate possible more subtle chemical alterations of the secondary structure (iso-electro focusing, peptide map). However, our results suggest that dilute solutions of bevacizumab and cetuximab can be kept for several days at ambient temperature without significant risk of aggregation.

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Highlights of the NZW-Süd oncology meeting in Ravensburg, Germany

The sixth annual NZW-Süd oncology meeting on 14-15 September 2007 presented a wide range of issues from interactions of herbal remedies with chemotherapy to pharmacogenetic polymorphisms.

Dronabinol in palliative care (Dr Hans-Peter Lipp, Tübingen)

Dronabinol (tetrahydrocannabinol, THC) has been used for many years as an antiemetic agent especially in AIDS patients and in cancer patients resistant to other antiemetics. In recent years some evidence also emerged of positive effects THC has in anorectic tumour patients.

Professor Günther J Wiedemann MD, PhD

Sabine Thor-Wiedemann MD

Newer trials raise some doubt about the value of dronabinol in the palliative setting. Jatoi et al. compared the effects of dronabinol and megestrolacetate alone or in combination in anorectic cancer patients [1]. Megestrolacetate alone was significantly better than dronabinol alone or the combination of both. In a study of Strasser et al. cannabinoids were no better than placebo in treating anorexia [2].

Interactions of herbal remedies and herbal food with anticancer medications (Rainer Nowack, Lindau)

Herbal food and phytopharmaceuticals may affect the pharmacokinetics and pharmacodynamics of anticancer drugs as they can induce or inhibit cytochrome P450 oxidases such as CYP3A4. This may result in unexpected treatment failure or toxic effects.

Well known are the effects of St John's Wort (it induces CYP3A4, resulting in faster metabolism and reduced bioavailability of other drugs) and grapefruit juice (which inhibits CYP3A4, resulting in reduced metabolism and potentially toxic plasma levels of other drugs).

Less known are the effects of very common plants and supplements such as camomile, garlic, soy or peppermint, each of them affecting the CYP450 system (Table 1)[3].

All of these plants and supplements may affect the bioavailability of drugs such as teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib and imatinib.

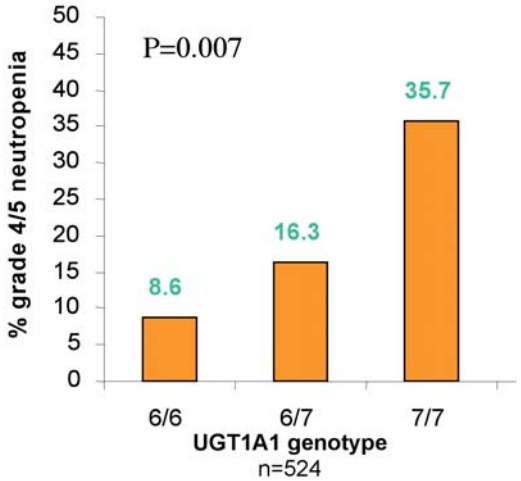
Table 1: Top dietary supplements reported by users of herbal therapy in 2002

Dietary Supplement	Percentage of herbal users reporting product use
Echinacea	40.3
Ginseng (unspecified species)	24.1
Ginkgo biloba	21.1
Garlic	19.9
Glucosamine	14.9
St John's Wort	12.0
Peppermint	11.8
Fish oils, omega fatty acids	11.7
Ginger	10.5
Soy	9.4
Camomile	8.6
Bee pollen or royal jelly	7.0
Kava kava	6.6
Valerian	5.9
Saw palmetto	5.8

Genetic polymorphisms affect the therapeutic efficacy of drugs (Dr Eckart Schnakenberg, Langenhagen)

Genetically determined variations in CYP450 activity may strongly influence the efficacy of drug therapy – ranging from total treatment failure, through normal/expected response to

Figure 1: Percent grade 4/5 neutropenia during irinotecan therapy depending on UGT1A1 genotype



UGT1A1 genotype homozygous for the $[TA]_7$-repeat allele (7/7) homozygous wild-type (6/6) and heterozygous (6/7) n=524

toxic effects. The activity of several enzymes can be determined before therapy to avoid unexpected effects. This can be of vital relevance for an individual patient (Figure 1) [4].

Another example is the therapeutic efficacy of tamoxifen. It depends on the extent to which tamoxifen is transformed into the more powerful n-desmethyltamoxifen. Extensive metabolisers experience better relapse free and overall survival rates This is genetically determined by the CYP2D6 genotype [5].

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8th Annual meeting of Polish oncology pharmacists

Jerzy Lazowski, PharmD

Death is the natural end of life rather than the failure of treatment. The Polish annual meeting considered philosophical questions of death and palliative care.

On 3-6 October 2007, the Oncology Pharmacy Section of the Polish Pharmaceutical Society held its annual meeting in Dzwirzyno near Kolobrzeg on the Baltic coast. The meeting was attended by 115 hospital pharmacists engaged in oncology pharmacy activities. The programme included plenary lectures, oral communications by participants, workshops on preparing cytotoxic drug solutions (Cypro and Cato systems), information about new drugs in oncology as well as social events which always play a very important role in drawing together this community of pharmacists.

"I hear and I forget. I see and I remember. I do and I understand." Workshop at the Polish Oncology Pharmacists' Meeting

The two plenary sessions were the "main course" of the meeting. The first one, which opened the meeting, was devoted to palliative medicine and presented a lot of ideas to think about as we consider the end of our life. Dr Barbara Czerska spoke about the idea of a good death in medicine and culture and its development from the most ancient times. Dr J Jarosz discussed the enormous value of palliative care in terminally ill patients and W Chańska spoke as a philosopher about the pros and cons of euthanasia. The second session was led by representatives of the Polish Office for Registration of Medicinal Products and provided important practical information about conducting clinical trials of drugs in hospitals and the role that the hospital pharmacy and pharmacists should play in them. Two hospital pharmacists spoke next, Dr Zosicz giving a short overview of legal aspects of conducting the trials under Polish and European Union legislation and Dr Zalewska discussing the role of pharmacist in these trials. It too often happens that hospital pharmacies and pharmacists do not take part in these trials and are not even informed about them - despite Polish pharmaceutical law stipulating that pharmacists should be part of the team. Pharmacists should be responsible for keeping the trial documentation and supervising the movement of medicinal products under investigation in the hospital. Omission of a pharmacist may lead to serious negligence in the trials. Practical examples of problems pharmacists may

meet in trials were presented by Dr Grzegorczyk, a pharmacist working for ICON Clinical Research UK Ltd.

We also had the honour of having our great friend Klaus Meier staying with us. During the meeting he gave again the lecture he delivered during ECCO 14 (23-27 September 2007) in Barcelona, Spain on *Collaboration between physicians and pharmacists treating oncology patients in the intensive care unit*.

The final act of the meeting was to elect the Board of the Section. It is now composed as follows: Chairman - Dr Jerzy Lazowski, PharmD (re-elected); Vice Chairmen - Dr Hanna Jankowiak-Gracz, PharmD (re-elected) and Professor Anna Wiela-Hojenska; Members: Agnieszka Jarmolowicz MSc (re-elected), Teresa Pociecha, MSc (re-elected), Julia Bogumila Sobkowiak, MSc and Slawomir Waryszak, MSc. Best congratulations to re-elected and new members of the Board!

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Greek pharmacists visit the Bank of Cyprus Oncology Centre

Stavroula Theophanous-Kitiri, MSc

Spreading the word about oncology pharmacy: a leading centre in Cyprus invited influential Greek colleagues to look round and meet a senior politician.

Representatives of the Pan-Hellenic Association of Hospital Pharmacists (PEFNI), Despina Makridaki (Vice President), Irene Tsikalaki (Secretary), Zoe Dede (Treasurer) and other members visited the Bank of Cyprus Oncology Centre on 10-11 May 2007 for a study day on the functioning of the pharmacy department, featuring in particular the operation of the central unit for preparing cytotoxic drugs. The aim of the visit was for the society to be informed of the whole procedure that is followed including the development and modification of a chemotherapy protocol, checking chemotherapy protocols by the pharmacist, reconstitution of cytotoxic drugs, administration of the drugs to the patient. The association had the chance to see the development of a working unit based on QuapoS (Quality Standards for the Oncology Pharmacy Practice).

Stavroula Theophanous-Kiti chaired an informative exchange of views

The first day the members had the chance to visit the outpatient pharmacy, the main pharmacy and also to discuss the isolators, the clean room and other important issues with the Head of Pharmacy Department and other Centre staff.

In the evening a dinner was held with the Chief Executive of the Oncology Centre, Mr Alecos Stamatis, at a traditional tavern in Nicosia, Cyprus.

The next day members divided their time in between the chemotherapy pharmacy, preparatory room and preparation room. In the evening they seized the opportunity to dance to traditional Greek music.

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