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Guest Authors:
Dr Mikael Daouphars, Dr Mirjam Crul, Professor Shiro Hinotsu, Dr Naoyuki Kamatani, Dr Timothy L Ratliff, Dr Hideyuki Akaza, Dr András Süle, Dr Linda Krolop, Professor Ulrich Jaehde, Carole Chambers, Dr rer nat Thomas Klose, Dr rer nat Michael Putzker

EJOP Editorial Office:
Postbus 10001, BE-2400 Mol, Belgium
Tel.: +32 474 989572
Fax: +32 14 583048
editorial@ppme.eu - www.ejop.eu

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Production Assistant:
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Correspondents:
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Belgium: Isabelle Glorieux/Wilrijk
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New challenges for oncology pharmacy in Europe

Klaus Meier
Editor-in-Chief
EJOP

The European Commission recently appointed a new EU Commissioner for Health, Vytenis Andriukaitis from Lithuania, with responsibilities for consumer protection issues and pharmaceuticals and medical devices in the future. This is timely, as the potential amalgamation of industrial consumer protection affairs with the interests of the EU internal market would otherwise be detrimental to the interests of patients.

The outgoing Commissioner, Tonio Borg, who was thanked by ESOP for his involvement in ECOP in Krakow, Poland, remarked that strengthening the role of pharmacy in the overall process of patient care was a particular concern, and that he would ensure that the new Commissioner was given the appropriate information to continue the Commission's previous mission in support of ESOP.

Our work for oncology pharmacy has arrived in Brussels! This intermediate success gives us the strength and courage to place the needs of cancer patients high on the agenda of individual countries.

The activities of the *Deutsche Gesellschaft für Onkologische Pharma*zie (DGOP, German Oncology Pharmacy Society) relating to adherence of oral cancer therapy began in cooperation with all healthcare stakeholders five years ago. The progress in this case is not immediately visible to the uninitiated.

A well-known hospital pharmacist once said that he spent most of his time busy in his office trying to break stones and eliminate smoulder. But a house can only be built when a professional team are motivated to come together to achieve their vision.

Globalization is a noble goal for the purposes of increasing understanding among people. However, the language used, and people's thinking, needs to be transparent, in order to generate true understanding.

But what about the Transatlantic Trade and Investment Partnership (TTIP)? The content of the negotiations between the EU and the US remains elusive. Politicians from Berlin to Brussels do not like to talk about what shall stand in the desired contract for transatlantic free trade agreements. Should European citizens not learn early about the privileges of corporations and investors to be protected and even expanded by this Agreement?

The EU and the US want to unify their respective standards into 'trade' areas. But this targeted 'harmonization' is expected to take into account the interests of cash-rich corporations and to prioritize investors. Possible objections to the resolved delayed measures could lead to compensation payouts.

Now there are economies developed not only from the economic power of large corporations. For example, looking at the figures from the Federal Republic of Germany, including the middle class by quantitative definition:

- 99.7% of all VAT registered businesses in which almost,
- 65.9% of all social insurance contributions are made,
- approximately 38.3% of all revenues generated, and
- approximately 83.0% of all trainees are trained [1].

In considering these facts, social fabric is crucial for continued involvement of the entire population and social justice. Patients must be considered not only as consumers but as 'active decision-makers'.

The new EU Health Commissioner Andriukaitis seems to be the right man for the job, not only because he himself is a doctor, but because he has been Health Minister of Lithuania for over two years, and stands for health policy progress for the benefit of patients. Together with him, we want to work together to improve the pharmaceutical care of our cancer patients at a European level.

Reference

1. Diagnose Mittelstand 2012; Deutscher Mittelstand – stabil auch in schwierigen Zeiten. Deutscher Sparkassen- und Giroverband.

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ECOP 2014 Conference Report

The second ECOP took place in Krakow, Poland, in June 2014, with international attendance of over 500 people. Key themes included clinical and ward-based oncology pharmacy, and practical issues relating to compounding. Recent advances in research, patient management and practices were showcased in lectures, scientific symposia and poster sessions.

Mikael Daouphars PharmD, PhD

Mirjam Crul, PharmD, PhD

Following the successful first conference in Budapest, Hungary, in 2012, the 2nd European Conference of Oncology Pharmacy (ECOP 2) was held in Krakow, Poland, 26–28 June 2014. The meeting attracted around 500 participants, mainly from Europe, but also from other parts of the world. This conference received the patronage of Dr Tonio Borg, European Commissioner for Health, and has been accredited by the European Accreditation Council for Continuing Medical Education. The latest advances in research, patient management and practice were showcased in keynote lectures, scientific symposia and poster sessions. As with the first conference, the second comprised of two distinct tracks: the clinical track, focusing on pharmacotherapeutics and ward-based or bedside oncology pharmacy; and the practical track, in which the latest developments in different aspects of compounding were presented. In between sessions, there was ample opportunity for networking and exchanging practices with other participants, while enjoying treats from the abundant buffets filled with Polish delicacies. To choose highlights from ECOP 2 is a challenge, because there were many excellent speakers and the topics presented were diverse. We would like to stress that the selection of lectures summarized below is by no means a disqualification of the other sessions.

Keynote lecture

The opening keynote lecture was to be given by Professor Richard Sullivan from Kings College in London on future challenges in cancer care. Unfortunately, Professor Sullivan was prohibited to fly, for safety reasons, as he had just returned from working in an Ebola-endemic area in Western Africa. With grace, Professor Mariusz Ratajczak, the keynote lecturer who was scheduled to speak later in the programme, stood in for him and gave a highly educational presentation on advances in stem cell research. Although the ability to perform research with (embryonic) stem cells differs greatly between countries, owing to legislative restraints, advances have been made over the past decade. Pluripotent stem cells can now be derived from embryonic blastocysts, offering the possibility of growing multiple tissues and organs, which may, in the future, provide novel curative treatment options for transplant as well as cancer patients. In oncology, insulin growth factor 1 (IGF1) signalling is of particular interest, because low levels of IGF1 have been shown to correlate with longer life span and lower incidence of cancer in several mouse models. This effect seems to be mediated by the occurrence of higher levels of very small embryonic like stem cells in the bone marrow, as has also been shown in animal studies. Interestingly, a corresponding genetic variant resulting in low levels of IGF1, has recently been identified in a human population, the Laron Dwarfs. Laron Dwarfism is a form of dwarfism found in several South American families. Individuals who have Laron Dwarfism seem to have an extremely low possibility of developing cancer. Hence, further studies on the role of IGF1 in oncogenesis are eagerly awaited.

Highlights from the clinical track

The state-of-the-art of pharmacogenetics in oncology was presented, as this field is growing in importance. In recent years, chemotherapeutic options for treating cancer have expanded; however, overall benefit could be improved, both in efficacy and toxicity. Pharmacogenetics studies the association between heritable genetic variants in DNA (genotype) with outcome of therapy (phenotype). Pharmacogenetics in oncology will ideally allow oncologists to individualize therapy based on a genetic test result. Severe toxicity and clinically significant underdosing may be avoided, whereas predicted non-responders can be offered alternative therapy. Barriers for implementation in clinical practice still exist despite emerging evidence; however, pharmacogenetic testing is finding its way into routine patient care in some innovative cancer centres.

Also, the role of an oncology pharmacist on the ward as well as in multi-professional treatment teams was discussed. Studies of the

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clinical effects of basing a pharmacist on the oncology ward by Mr Shinya Suzuki from Japan showed a decrease in duration of hospital stay as well as a reduction in emergency re-admissions. Moreover, average drug costs decreased by almost 50% after including a pharmacist in the clinical team. Ms Fiona Fenech who performed medication reviews for all oncology inpatients in two clinical wards presented similar results from Malta. Drug-related problems were identified in all studied patients, followed by pharmacists' intervention. Afterwards, an independent panel rated almost 70% of the interventions as having a major or moderate clinical significance on patient care. These lectures demonstrate that a stronger involvement of the oncology pharmacist in the clinic improves patients' treatment outcomes.

Updates from clinical research on novel drug treatments in the field of breast cancer were presented by Dr Adrian Munilla Das in the form of results from two large trials into dual HER2 blockade in breast cancer with very appealing results, and by Dr Libby Hardy who summarized the latest developments in systemic melanoma treatment.

Highlights from the practical track

Preliminary results of the ESOP European Contamination Project were presented by Ms Ewelina Korczowska and Dr Jochen Türk who collaborated in performing this non-sponsored ESOP international trial. The main goal of this pilot study was to obtain an overview of the current situation in Europe on cytotoxic contamination in the workplace. Additionally, it will help to develop additional steps and programmes to improve working conditions and quality control. Knowledge is limited on levels of surface contamination with antineoplastic drugs in European hospitals in areas where these drugs are handled. The study was conducted in 19 European hospitals in which antineoplastic drugs are prepared and administered according to national guidelines. Assessment of surface contamination with antineoplastic drugs was carried out using wipe sampling and mass spectrometry. The study consisted of two parts: evaluation of surface contamination in preparation and administration areas; and after implementation of cleaning recommendations. The pilot study demonstrates the presence of surface contamination in preparation and administration areas in all investigated hospitals. The level of contamination was different in each hospital. Measurable amounts of at least one agent, however, were detected on sampled surfaces in each hospital. The extent of the contamination did not correlate with the number of preparations per year (in fact, hospitals with larger compounding volumes sometimes showed relatively low levels of contamination in the pharmacy), nor did the use of biohazard versus safety cabinets. Hospitals using needles showed relatively large amounts of surface contamination, but the use of closed systems did not improve outcomes when compared with the use of semi-closed systems (spikes). The results suggest that reviewing and implementing new cleaning procedures are still needed to help eliminate the presence of contamination in the workplace. Cytotoxic drug suppliers are also asked to take precautions to avoid breakage and external contamination.

Dedicated sessions

Special sessions included a debate on the pros and cons of the use of biosimilars. In the field of oncology, the first biosimilar monoclonal antibodies have yet to reach the market, but other pharmacotherapeutic areas, such as rheumatology and nephrology, already have experience in using biosimilars of infliximab and epoetin. Professor Alain Astier and Professor Arnold Vulto argued in favour of the use of biosimilars, based on the fact that therapeutic equivalence has to be demonstrated before a marketing authorization is granted, and because batch-to-batch variability is sometimes greater in the originator product than in the biosimilar. Professor Irene Krämer and Professor Atholl Johnston presented the case against the use of biosimilars. They emphasized that the risk of differences in immunogenicity, as well as the lack of clinical data on switching patients from originator to biosimilar, outweighs the financial benefit.

Another dedicated session dealt with the increasing worldwide drug shortages in oncology. An outline of the causes for this phenomenon was presented, including legislative reasons as well as lowered generic drug prices. This leads producers to withdraw non-profitable products from the market, thus increasing the vulnerability of the supply chain. A call for action to the European Medicines Agency was made, as well as the suggestion that oncology pharmacists can help to decrease the number and duration of drug shortages by forming strategic alliances with the drug suppliers. By acting intuitively – 'buy what you can' – the situation worsens. Pharmacists should try to move from discount buying to long-term supply chain partnership with reliable drug companies, and thus reward the good suppliers with more sales.

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Finally, an international roundtable on oral chemotherapy was organized with a panel of oncology pharmacists from Germany, Japan, South Africa, and the US. The debate was driven by questions related to how oral chemotherapy agents are handled, specifically in relation to the role of a community pharmacist, cancer facility, or both; how the communication is organized between the community setting and the cancer facility; what processes are used to ensure the safety of orders for oral and other non-parenteral dosage forms of chemotherapy and biotherapy; how patients receive education on oral cytotoxics and targeted therapies; and the educational needs and practice issues for healthcare professionals. This roundtable has identified many common issues worldwide in relation to patient safety and the educational needs of patients and healthcare professionals. Many innovative experiences to address these issues rely on a multi-professional, multidisciplinary approach involving the oncology pharmacists as they ensure economic use of resources and significantly improve patient safety.

Closing session

The best poster award was awarded to Ms Xiaoqing Liu, from Professor Graham Sewell's team, for her work on extended stability study of oxaliplatin infusions for dose banding.

The ESOP Yellow Hand Award was granted to several pharmaceutical companies, who fulfil the ESOP recommendations for safe transport of CMR-drugs.

Klaus Meier Award

In recognition of an ESOP member who has made a significant or sustained contribution to oncology pharmacy practice, the Klaus Meier Award was created at ECOP 2012.

The Klaus Meier Award was presented to Professor Alain Astier for his long-standing achievements in oncology pharmacy and his major involvement in ESOP.

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Special thanks go to all speakers and poster presenters for helping to make ECOP 2 an inspirational conference; the scientific committee for composing the programme; and Dr Annette Junker, Clinical Oncology Pharmacist, and Editor of ECOP 2 daily news.

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This short overview of ECOP 2014 will be covered more extensively in future issues of EJOP, as the editorial office will invite selective authors to present a report article, so that ESOP members who could not be present at this special event can nonetheless benefit from the information. ECOP Best Poster Award winners will present their work in future EJOP issues. Other ECOP authors are of course welcome to submit their results to EJOP editorial committee.

Do not miss ECOP 3 that will be held in Dubrovnik, Croatia, in May 2016.

Authors

Mikael Daouphars, PharmD, PhD
Pharmacy
Cancer Centre Henri Becquerel
1 rue d'Amiens
FR-76038 Rouen, France

Mirjam Crul, PharmD, PhD
Hospital Pharmacist
Division of Clinical Pharmacy
Onze Lieve Vrouwe Gasthuis
9 Oosterpark
NL-1090 HM Amsterdam, The Netherlands

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A systematic review and meta-analysis on the safety and efficacy of different strains of *Mycobacterium bovis* bacillus Calmette-Guérin for non-muscle invasive bladder cancer in Japan and US

Shiro Hinotsu[1], MD, PhD; Naoyuki Kamatani[2], MD, PhD; Timothy L Ratliff[3], PhD; Hideyuki Akaza[4], MD, PhD

Abstract

Objective: To compare efficacy and safety of different strains of *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) used in Japan and the US as intravesical therapeutics for non-muscle invasive bladder cancer.

Materials and methods: Papers for review were selected from PubMed and Igakuchuozasshi databases, and meta-analysis was performed using the data obtained.

Results: 352 papers from Japanese hospitals and 333 papers from US hospitals were reviewed. Strains used in Japan were Immunobladder® (Tokyo 172) and ImmuCyst® (Connaught (JP)), while those used in the US were TICE® (TICE) and TheraCys® (Connaught (US)). CR (complete remission) rates for patients with CIS (carcinoma *in situ*) were 0.824 (n = 380, 95% CI 0.782–0.861), 0.868 (n = 38, 95% CI 0.719–0.956), 0.714 (n = 35, 95% CI 0.537–0.854) and 0.574 (n = 385, 95% CI 0.523–0.624) for Tokyo 172, Connaught (JP), TICE and Connaught (US), respectively. Non-recurrence survival (NRS) rates for non-CIS patients were 0.754 (n = 429, 95% CI 0.714–0.794), 0.790 (n = 83, 95% CI 0.702–0.878), 0.673 (n = 250, 95% CI 0.615–0.731) and 0.598 (n = 255, 95% CI 0.538–0.658) for Tokyo 172, Connaught (JP), TICE and Connaught (US), respectively.

Conclusion: No significant differences were observed neither in efficacy nor in safety between two strains of BCG used Japan and the US. However, the rates of CR and NRS may be higher in Japan than the US, and the rates of severe adverse events may be higher in Japan than the US, although the data were not from controlled studies.

Keywords: Bacillus Calmette-Guérin (BCG), bladder cancer, ethnicity, strain

Introduction

Mycobacterium bovis Bacillus Calmette-Guérin (BCG) is used around the world as tuberculosis vaccines. It is also used as intravesical therapeutics for treating and prophylactic treatment of non-muscle invasive bladder cancer (NMIBC). All BCG products used in the world were derived from seed culture material at the Pasteur Institute in Paris. Although minor genetic differences among BCG strains are documented [1], they all appear to be clinically effective in the treatment of NMIBC as documented in published papers [2-6]. BCG treatment has been reported to be superior to transurethral tumour resection (TUR) alone [7], intravesical mitomycin C [8] and intravesical epirubicin [9] as reported by Cochrane's systematic review groups.

In the US, TICE® (Organon-Merck) and TheraCys® (Sanofi Pasteur) are currently marketed, while in Japan, both Immunobladder® (Japan BCG Laboratory, Tokyo) and TheraCys® (sold in Japan as ImmuCyst®) are clinically available. Immunobladder® is manufactured and sold by Japan BCG Laboratory using the BCG strain Tokyo 172 that was derived from the strain obtained from Pasteur Institute in 1924 [1]. TheraCys® was obtained by Connaught Laboratories in 1948 (Connaught strain) from the Institute Armand Frappier, which obtained a BCG strain from the Pasteur Institute in 1933. Throughout the manuscript, TICE® and TheraCys® used in the US are expressed as TICE and Connaught (US), respectively, while Immunobladder® and ImmuCyst® used in Japan are expressed as Tokyo 172 and Connaught (JP), respectively.

Although the efficacy and safety of each strain for the treatment of NMIBC have been published in many papers, comparison between different strains has been performed only in some studies with small sizes [10-12]. In the present manuscript, we extensively reviewed published papers and performed a meta-analysis to compare the differences in both efficacy and safety of BCG between different strains used for the treatment of NMIBC focusing on the results from Japan and the US.

In the meta-analysis, we focused on the separate comparison in each of the two countries, Japan and the US. This is because of the differences in both ethnic background and medical systems between both countries. However, since the same BCG strain is sold as Connaught (US) in the US and as Connaught (JP) in Japan, this strain can serve as a bridge to compare the efficacy and safety of different BCG strains used in the two countries. Therefore, we also tried to compare the efficacy and safety between two different countries.

Materials and methods

Data sources and search strategy

Data sources were PubMed and Igakuchuozasshi (literally means, in Japanese, Central Medical Journal). The latter database

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is the largest and the most popular database of medical papers published in Japanese journals.

The detailed strategies for the search for papers in databases, concepts of the meta-analysis, items extracted from each paper into the data-input format and the results of the selection of papers to be reviewed are in Appendix A, B, C and D, respectively, in Supplementary Materials. As a result, 352 papers describing the data from Japanese hospitals and 333 papers describing those from US hospitals were selected and reviewed, see Figure 1.

Statistical procedures

Statistical procedures were described in Supplementary Materials.

Results

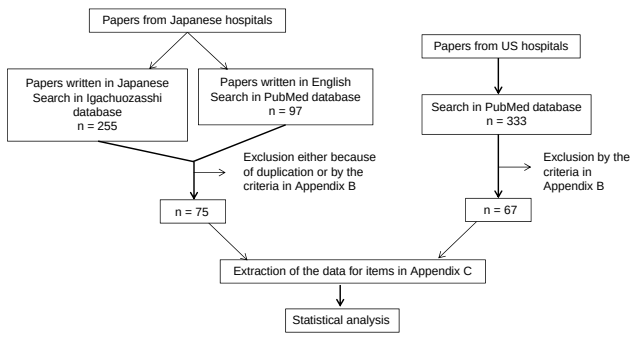
Direct comparison of the effects and safety between Tokyo 172 and Connaught (JP) used in Japan

Among the papers reported from Japanese hospitals, no prospective randomized study comparing Tokyo 172 and Connaught (JP) has been performed. There is one published report in which Tokyo 172 and Connaught (JP) were compared in a retrospective analysis of CIS (carcinoma *in situ*) patients treated at the same hospital [12]. The results showed no difference in the CR (complete remission) rates or dAE (daunorubicin, Ara-C, and etoposide) frequencies between the CIS patients treated with 80 mg Tokyo 172 and 81 mg Connaught (JP).

Comparison of CR rates for CIS patients between Tokyo 172 and Connaught (JP)

There were two papers for Connaught (JP) (81 mg) and six papers for Tokyo 172 (80 mg) that met the criteria for the inclusion in our analysis, see Supplementary Table 1. Calculated CR rate, estimated standard error (SE), and 95% CI of the rate for each paper were described in Figure 2 and Supplementary Table 1. The reported CR rates ranged from 0.84 to 0.92 for Connaught (JP), and from 0.67 to 0.86 for Tokyo 172. Since there was no significant heterogeneity between subgroups [Tokyo 172 group (p = 0.167); Connaught (JP) group (p = 0.404)] when analysed as described in the Statistical Procedures, we performed the meta-analysis using the fixed-effect model. We combined the data for each strain, and showed the data in Supplementary Table 1.

Figure 1: Data sources, number of manuscripts and search strategy was illustrated in detail



Supp Table 1: Comparison of the effects of BCG for CIS patients from Japanese hospitals

Strain and reference	Number of patients	Number of CR patients	CR rate	Lower[c]	Upper[c]
Connaught (JP)[a] [1]	25	21	0.840	0.639	0.955
Connaught (JP)[a] [2]	13	12	0.923	0.640	0.998
Tokyo[b] [3]	33	22	0.667	0.482	0.820
Tokyo[b] [4]	25	21	0.840	0.639	0.955
Tokyo[b] [5]	40	34	0.850	0.702	0.943
Tokyo[b] [6]	185	160	0.865	0.807	0.911
Tokyo[b] [7]	74	57	0.770	0.658	0.860
Tokyo[b] [8]	23	19	0.826	0.612	0.950
Combined data for:					
Tokyo[d]	380	313	0.824	0.782	0.861
Connaught (JP)[d]	38	33	0.868	0.719	0.956

Comparison of the effects of BCG (Bacilllus Calmette-Guerin) for CIS carcinoma *in situ* patients between Tokyo (80 mg) and Connaught (JP) (81 mg) strains in different papers by authors from Japanese hospitals. [a]Heterogeneity of Connaught (JP), p = 0.404; [b]Heterogeneity of Tokyo, p = 0.167; [c]Lower and Upper boundaries of 95% CI of CR rate; [d]p = 0.653 (Fisher's exact test), OR = 0.708 (95% CI 0.208–1.921). CR: complete remission; OR: odds ratio; Supp: supplementary.

The combined results revealed that the CR rate for Tokyo 172 was 0.824 (95% CI 0.782–0.861), while that for Connaught (JP) was 0.868 (95% CI 0.719–0.956). Statistical test by Fisher's exact test indicated that there is no significant difference in the CR rate between Connaught (JP) and Tokyo 172 by the meta-analysis (p = 0.653, Supplementary Table 1).

These results indicate that there is no evidence that the CR rates are different between the CIS patients in Japanese hospitals treated with Tokyo 172 and Connaught (JP) when the data from different papers are combined.

Comparison of non-recurrence survival (NRS) rates in the patients with NMIBC between Tokyo 172 and Connaught (JP)

There was only one paper in which the data about the NRS rates were described for Japanese patients with NMIBC in whom Connaught (JP) was used, see Supplementary Table 2. In contrast, the data of the NRS rates in the patients with NMIBC treated by 80 mg Tokyo 172 were obtained from nine different papers, see Supplementary Table 2. In different papers, 2-year, 3-year and 5-year NRS rates ranged between 64% and 85%, 46–82% and 49–80%, respectively. The 2-year and 3-year NRS rates of

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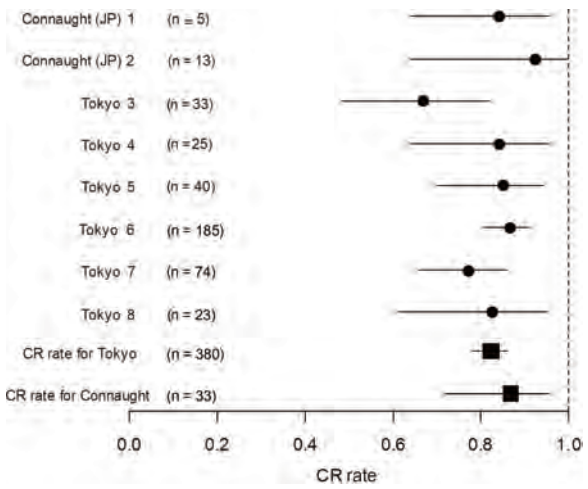
Figure 2: Comparison of the effects of BCG for CIS patients



Comparison of the effects of BCG (Bacilllus Calmette-Guerin) for CIS (Carcinoma *in situ*) patients between Tokyo 172 (80 mg) and Connaught (JP) (81 mg) strains in different papers from Japanese hospitals. The estimated CR (complete remission) rate and 95% CI are shown for each study (closed circle) and for each strain (closed square) obtained as the results of the meta-analysis. Number after the name of each strain indicates the reference number in Supplementary Materials.

Supp Table 2: NRS rates in papers from Japanese hospitals treated with Tokyo 172 BCG 80 mg or Connaught (JP) 81 mg

Strain and reference	n	3 years (%)	5 years (%)	2-year rate	SE[b] (2 years)	Lower[c] (2 years)	Upper[c] (2 years)
Tokyo[a] [9]	102	77.3	68.5	0.85	0.0354	0.781	0.919
Tokyo[a] [10]	64	70	67	0.74	0.0548	0.633	0.847
Tokyo[a] [11]	33	82	–	0.82	0.0669	0.689	0.951
Tokyo[a] [4]	19	64	64	0.64	0.110	0.424	0.856
Tokyo[a] [12]	147	72.4	69.1	–	–	–	–
Tokyo[a] [13]	85	68	65	0.70	0.0497	0.603	0.797
Tokyo[a] [14]	39	80	80	0.80	0.0641	0.674	0.926
Tokyo[a] [15]	50	46	–	0.68	0.0660	0.551	0.809
Tokyo[a] [16]	37	62	49.2	0.69	0.0760	0.541	0.839
Connaught (JP) [17]	83	75.3	–	0.79	0.0447	0.702	0.878
Combined data for:							
Tokyo	429	–	–	0.754[d]	0.0205	0.714	0.794
Connaught (JP)	83	–	–	0.790[d]	0.0447	0.702	0.878

[a]Heterogeneity of 2-year NRS rates between studies for Tokyo; p = 0.069; [b]SE: standard error; [c]Lower and Upper boundaries of 95%; [d]p = 0.465.
Supp: supplementary.

the patients treated with Connaught (JP) described in the available paper were 79% and 75.3%, respectively. We first tested the heterogeneity of the 2-year NRS rates between different studies for Tokyo 172 as described in the Statistical Procedures, but there was no significant heterogeneity (p = 0.069). We therefore used the fixed-effect model and calculated weighted average, estimated standard error (SE) and 95% CI for 2-year NRS rate for Tokyo 172, see Supplementary Table 2. Meta-analysis using the fixed effect model revealed that estimated 2-year NRS rate for Tokyo 172 was 0.75 (95% CI 0.71–0.79, n = 429), see Supplementary Table 2. In the available paper describing the NRS rates for Connaught (JP) from Japanese hospitals, the number of the patients who met our criteria was 83, and 2-year survival rate was 79%, see Supplementary Table 2. The 2-year NRS rates and 95% CIs for Tokyo 172 and Connaught (JP) are shown in Figure 2 and Supplementary Table 2. The difference between the weighted-average NRS rates at 2-year for Tokyo 172 and the NRS rate for Connaught (JP) is calculated to be 0.0359. Assuming the fixed-effect model, we tested the 2-year NRS rates between Tokyo 172 and Connaught (JP) as described in the Statistical Procedures. The result indicated that there is no significant difference (p = 0.465). 95% CI of the difference between the 2-year NRS rates for Tokyo 172 and Connaught (JP) was from -0.0605 to 0.132, and included 0.

AEs (adverse events) and dAE in the patients treated by Tokyo 172 or Connaught (JP)

The data about dAE were available from seven papers for Tokyo 172 and two papers for Connaught (JP), see Supplementary Table 3a. The frequencies of dAE described in the seven papers for Tokyo 172 ranged from 0–0.27, while those for Connaught (JP) ranged from 0.071–0.088 see Supplementary Table 3a. Meta-analysis using the fixed effect model revealed that the frequency of dAE for Tokyo 172 was 0.0561 (95% CI 0.0363–0.0823), while that for Connaught (JP) was 0.0789 (95% CI 0.0295–0.164), see Supplementary Table 3b. Fisher's exact test revealed that the *p* value was 0.438 see Supplementary Table 3b, thereby indicating that the difference in the frequencies are statistically not significant.

These results indicate that there is no evidence that the frequencies of dAE are different between Tokyo 172 and Connaught (JP) in the treatment of NMIBC when the data from different papers from Japanese hospitals are combined.

Comparison between CR rates for CIS patients treated with Connaught (US) and TICE

There were three papers for Connaught (US) and two papers for TICE that met the criteria for the inclusion in our analysis, see Supplementary Table 4. The doses used were 81 mg for Connaught (US) and 50 mg for TICE when they were written. A problem is that, in each group, significant heterogeneity was

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Supp Table 3a: AE and dAE in the papers by the authors in Japanese hospitals

Strain and reference	Number of cases	[a]dAE cases	Frequency of dAE	Pyrexia	Irritability	Macro-hematuria	Micturition pain	Pollakisuria	Dysuria	Arthralgia	Muscle pain	ALT, AST elevation	Bladder and pyuria	Tuberculosis
Tokyo [1]	25	2	0.0800											
Connaught (JP) [18]	34	3	0.0882											
Tokyo [10]	64	3	0.0469											
Tokyo [5]	40	1	0.0250	0.23		0.18							0.5	
Tokyo [19]	203	0	0											
Tokyo [20]	33	9	0.273											
Tokyo [14]	39	8	0.205	0.128	0.526	0.233								
Tokyo [15]	24	1	0.0420	0.14	0.4									0.04
Tokyo [4]	26													
Tokyo [7]	84			0.3		0.722	0.822	0.822	0.522	0.056	0.011	0.078		
Tokyo [8]	84				0.2	0.3								
Connaught (JP) [2]	42	3	0.0714	0.595		0.476	0.738	0.738	0.286					

[a]dAEs are defined here as the discontinuation of BCG treatment due to AEs. Supp: Supplementary.

Supp Table 3b: Comparison of dAE in papers from Japanese hospitals

Strain	Total number	Number of patients with dAE	Frequency	95% CI
Tokyo	428	24	0.0561	0.0363–0.0823
Connaught (JP)	76	6	0.0789	0.0295–0.164

Comparison of dAE between Tokyo 172 and Connaught (JP) in papers by authors from Japanese hospitals.
$p = 0.438$ (Fisher's exact Test); OR = 1.41 (95% CI 0.455 – 3.69).
Supp: supplementary.

shown, see Supplementary Table 4. Thus, the tests of heterogeneity were positive for both groups ($p = 1.83 \times 10^{-6}$ for Connaught (US) and $p = 0.023$ for TICE).

Especially, the heterogeneity of Connaught (US) was very high. This is attributed to the low CR rate (0.507) in the paper (Reference 21 in Supplementary Materials). This paper includes many patients (n = 278) and shows low CR rate for CIS patients. However, the CR rate data in this paper should be interpreted with care because, as stated in this paper by the authors, the purpose of the paper was to evaluate maintenance therapy, and the CR rate described was a by-product of the main study (Reference 21 in Supplementary Materials). We used the random effect model for the test of difference in CR rates by the method described in the Statistical Procedures. The results indicated that there was no significant difference between Connaught (US) and TICE ($p = 0.649$). The weighted averages of CR rates for different strains as well as the 95% CI were described, see Figure 3 and Supplementary Table 4.

These results indicate that there is no significant difference in the CR rates between Connaught (US) and TICE in the treatment of NMIBC CIS when the data from different papers from US hospitals are combined.

Comparison between NRS rates in the patients with NMIBC (non-CIS) treated by Connaught (US) and TICE

The strains of BCG used in US hospitals were Connaught (US) and TICE, see Supplementary Table 5. We focused on the 2-year NRS rates, and only the data from the papers including 2-year NRS are shown in Supplementary Table 6. The test of heterogeneity indicated that the subgroups in TICE were significantly heterogeneous ($p = 0.071$ for Connaught (US) and $p = 0.043$ for TICE), see Supplementary Table 6. The 2-year NRS rate and 95% CI for the data of each paper were shown in Figure 4 and Supplementary Table 6.

For Connaught (US), there were two papers that met the criteria for the inclusion in our analysis and contained the NRS rates at 2 years. The weighted average method has shown that the 2-year

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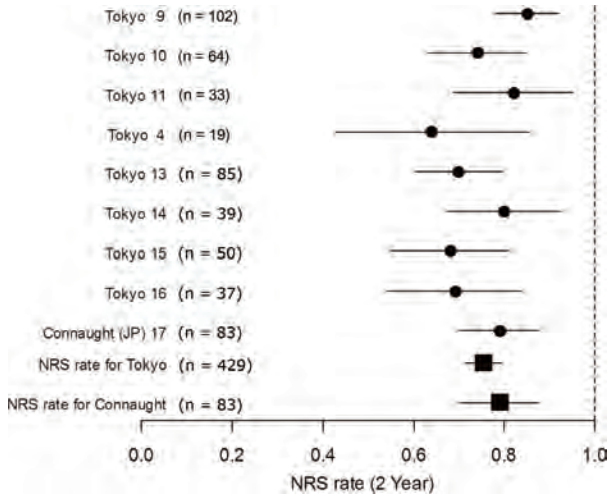
Figure 3: 2-year NRS rates in the papers from Japanese hospitals



2-year NRS rates in papers from Japanese hospitals for the patients treated with Tokyo 172 BCG 80 mg or Connaught (JP) 81 mg. The estimated 2-year NRS rate and 95% CI are shown for each study (closed circle) and for each strain (closed square) obtained as the results of the meta-analysis.
NRS: non-recurrence survival.

Supp Table 4: Comparison of CR rates for CIS cases treated with different strains of BCG reported by authors from US hospitals

Strain and reference	Number of cases	CR cases	CR rate	Dose	Lower[c)]	Upper[c)]
Connaught (US)[a)] [21]	278	141	0.507	81 mg	0.447	0.567
Connaught (US)[a)] [22]	64	45	0.703	–	0.576	0.811
Connaught (US)[a)] [23]	43	35	0.814	–	0.666	0.916
TICE[a)] [24]	16	14	0.875	50 mg	0.617	0.984
TICE[a)] [25]	19	11	0.579	–	0.335	0.797
Combined data for:						
Connaught (US)[b)]	385	221	0.574[d)]	–	0.523	0.624
TICE[b)]	35	25	0.714[d)]	–	0.537	0.854

[a)]Heterogeity of Connaught (US), $p = 1.83 \times 10^{-6}$, Heterogeneity of TICE, $p = 0.023$; [b)]Connaught versus TICE: $p = 0.649$ (random effect model); [c)]Lower and Upper boundaries of 95% CI; [d)]Weighted average of CR rate.
CIS: carcinoma *in situ*; CR: complete remission; Supp: supplementary.

survival rate from a total of 255 patients was 0.598 (95% CI 0.538–0.658), see Figure 4 and Supplementary Table 6.

For TICE, there were two papers that met the criteria for the inclusion in our analysis and the 2-year NRS rate was available (dosage was 50 mg). The weight average method has shown that the 2-year NRS rate from a total of 250 patients was 0.673 (95% CI 0.616–0.731), see Figure 4 and Supplementary Table 6.

Although the subgroups in TICE group were heterogeneous with marginal significance ($p = 0.043$), the test of difference was performed using the fixed effect model. The comparison between the 2-year NRS rates for Connaught (US) and TICE strains showed no significant difference ($p = 0.076$), see Supplementary Table 6.

These results suggest that there is no evidence for the difference in the 2-year NRS rates between Connaught (US) and TICE in the treatment of NMIBC (non-CIS).

Comparison between AEs in the patients treated by Connaught (US) and TICE

There were one paper for Connaught (US) and three papers for TICE including dAE data, see Supplementary Table 7. When the data from different papers were combined, the frequency of dAE for Connaught (US) and TICE were 0.0114 and 0.00341, respectively, see Supplementary Table 7. Fisher's exact test indicated that the difference in the frequencies between the two strains was not statistically significant ($p = 0.409$), see Supplementary Table 7.

These results indicate that there is no evidence that the frequencies of dAE are different between Connaught (US) and TICE.

Discussion

Table 1a displays the summarized CR rates (weighted averages) for different strains as well as *p* values for the tests of differences in CR rates between pairs of the strains. We should be careful to interpret the weighted average data for the strains used in the US because there were significant intra-group heterogeneities, especially the CR rate for Connaught (US).

The results of the analysis indicated that Tokyo 172 strain used in Japan may have higher CR rates than Connaught (US), see Table 1a.

Table 1b indicates the 2-year NRS rates (weighted averages) for different strains as well as the *p* values for the test of difference in 2-year NRS rates between different strains. The analysis has shown that Tokyo 172 strain used in Japan may have higher NRS rates than Connaught (US) and TICE, see Table 1b. In addition, Connaught (JP) may have higher NRS rates than Connaught (US) and TICE, see Table 1b. These data may indicate that BCG strains used in Japan tend to have higher effects than those used in US even for the same strain (Connaught (US) and Connaught (JP)). The differences in the effect of intravesical instillation of BCG as shown here should be re-evaluated by additional studies because,

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Supp Table 5: NRS rates in non-CIS patients in the papers reported from the US

Strain and reference	Number	1 year	2 years	3 years	5 years	Other period	Dose
Connaught (US) [21]	192		0.63	0.51	0.41		81 mg
Connaught (US) [22]	63		0.5	0.48	0.369		
Connaught (US) [23]	45	0.71					
TICE [27]	160	0.71	0.63				50 mg
TICE [24]	90		0.75				50 mg
TICE [28]	90					45/90 (about 4 years)	50 mg
TICE [26]	66					0.58 (1.5 years)	50 mg

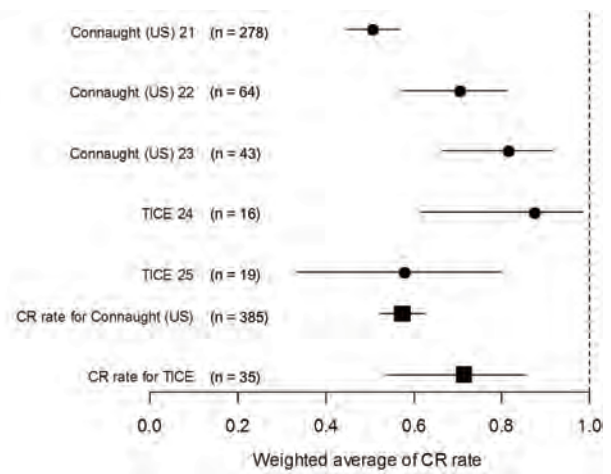
The data for 2-year rates are summarized in Supplementary Table 6.
CIS: carcinoma *in situ*; NRS: non-recurrence survival; Supp: supplementary.

Supp Table 6: NRS rates in non-CIS patients in the papers reported from the US

Strain and reference	n	2-year NRS	SE[b)]	95% CI
Connaught (US)[a)] [21]	192	0.63	0.0348	0.562–0.698
Connaught (US)[a)] [22]	63	0.50	0.063	0.377–0.623
TICE[a)] [27]	160	0.63	0.0382	0.555–0.705
TICE[a)] [24]	90	0.75	0.0456	0.661–0.839
Combined data for:				
Connaught (US)	255	0.598[c)]	0.0305	0.538–0.658
TICE	250	0.673[c)]	0.0294	0.615–0.731

[a)]Heterogeneity for Connaught (US), p = 0.071, Heterogeneity for TICE, p = 0.043; [b)]SE: standard error; [c)]Connaught (US) versus TICE: p = 0.076.
CIS: carcinoma *in situ*; NRS: non-recurrence survival; Supp: supplementary.

Figure 4: Comparison of CR rates for CIS cases



Comparison of CR rates for CIS cases treated with different strains of BCG reported by authors from US hospitals. The estimated CR rate and 95% CI are shown for each study (closed circle) and for each strain (closed square) obtained as the results of the meta-analysis.
CR: complete remission; CIS: carcinoma *in situ*.

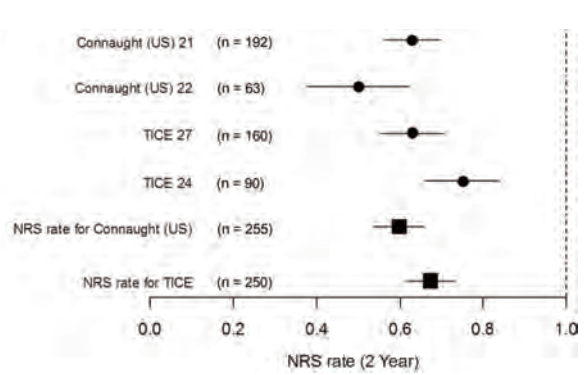
as stated above, the CR rate in one paper [6] may not be reliable and also because the data were not from randomized controlled studies.

Since there is no significant difference in CR rates either for CIS patients or NRS rates for non-CIS patients between Tokyo 172 and Connaught (JP), see Table 1a, b, used in Japan, the results are not likely to reflect the real differences of the effects between Tokyo 172 and Connaught strains.

If the difference in the effect between Japan and the US is real, one explanation may be the different recommended schedules of the treatments and the difference in the immunity to BCG between Japan and the US. Thus, the intravesical instillation of BCG is recommended to be performed once a week for eight consecutive weeks in Japan for both Connaught (JP) and Tokyo 172 (Product Information for ImmuCyst®, i.e. Connaught (JP), Product Information for Immunobladder, i.e. Tokyo 172), while TheraCys® (Connaught (US)) is recommended to be administered each week for 6 consecutive weeks (Product Information by Pasteur-Aventis). Therefore, the summed recommended dose of BCG is higher in Japan than in the US even for the same Connaught strain (JP vs US).

In addition, the difference in the immunological reaction to BCG may explain the difference in the effects Japan and the US. In this regard, prior to 2005, all Japanese infants were tested for an immunological reaction to tuberculosis by PPD (purified protein derivative) test, and BCG was inoculated when PPD test was negative. Therefore, Japanese are likely to have stronger

Figure 5: 2-year NRS rates in non-CIS patients of the US



2-year NRS rates in non-CIS patients in the papers reported from the US. The estimated 2-year NRS rate and 95% CI are shown for each study (closed circle) and for each strain (closed square) obtained as the results of the meta-analysis.
CIS: carcinoma *in situ*; NRS: non-recurrence survival.

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Supp Table 7: dAE and AE in US patients treated for different strains of BCG

Strain and reference	Number	dAE	Frequency	Pyrexia	Irritability	Macro-hematuria	Dysuria	Diarrhea	Nausea and Vomiting	Systemic BCG infection	95% CI
Connaught (US) [21]	353		–								–
Connaught (US) [22]	127		–	0.41	0.622	0.386		0.079	0.189		–
Connaught (US) [23]	88	1	0.0114								–
TICE [29]	27	1	0.037	0.22	1.00						–
TICE [27]	160	0	0								–
TICE [24]	106	0	0	0.16		0.27	0.64				–
TICE [30]	118		–	0.20	0.75	0.36					–
TICE [28]	153		–	0.076	0.60					0.01–0.02	–
Connaught (US)[a)]	88	1	0.0114								0.000288–0.0617
TICE[a)]	293	1	0.00341								8.64^{-5} – 1.89^{-2}

[a)]Connaught (US) versus TICE: p = 0.409, Fisher's exact test. Supp: supplementary.

Table 1a: Summary of weighted averages of the CR rates, and *p* values for the differences between two strains in CIS patients

CR rate (weighted average)		Tokyo	Connaught (JP)	Connaught (US)	TICE
		0.824	**0.868**	**0.574**	**0.714**
p value	Connaught (JP)	0.653			
	Connaught (US)	0.0241 (T > U)	0.0592		
	TICE	0.254	0.111	0.649	

Data were from Supplementary Table 1 and Supplementary Table 4, but some *p* values were calculated using the data in Supplementary Table 1 and Supplementary Table 4 as described in Statistical Procedures.
T: Tokyo; U: Connaught (US).

Table 1b: Summary of weighted averages of the 2-year NRS rates, and *p* values for the differences between two strains in non-CIS patients

NRS rate (weighted average)		Tokyo	Connaught (JP)	Connaught (US)	TICE
		0.754	**0.79**	**0.598**	**0.673**
p value	Connaught (JP)	0.465			
	Connaught (US)	2.14×10^{-5} (T > U)	0.00039 (J > U)		
	TICE	0.0242 (T > I)	0.0291 (J > I)	0.076	

Data were from Supplementary Table 2 and Supplementary Table 6, but some *p* values were calculated using the data in Supplementary Table 2 and Supplementary Table 6 as described in Statistical Procedures.
T: Tokyo; J: Connaught (JP); U: Connaught (US); I: TICE.

Table 2: Summary of weighted averages of the frequencies of dAE, and *p* values for the differences between two strains

dAE frequency (weighted average)		Tokyo	Connaught (JP)	Connaught (US)	TICE
		0.0561	**0.0789**	**0.0114**	**0.00341**
p value	Connaught (JP)	0.431			
	Connaught (US)	0.099	0.05 (J > U)		
	TICE	3.89×10^{-5} (T > I)	0.00038 (T > I)	0.409	

The data were from Supplementary Table 3b and Supplementary Table 7, but some *p* values were calculated using the data in Supplementary Table 3b and Supplementary Table 7 as described in Statistical Procedures.
dAE: daunorubicin, Ara-C, and etoposide; I: TICE; J: Connaught (JP); T: Tokyo; U: Connaught (US).

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immunity to BCG than Americans. It has been reported that the intravesical BCG treatment for bladder cancer patients is more effective when the patients have immunity to BCG [14, 15].

In any case, the differences in CR rates and NRS rates between Japan and the US are, if present at all, not likely to be attributed to the strain differences as clearly shown by the fact that CR and NRS rates between Tokyo 172 and Connaught (JP) strains are not different in the same ethnic group, see Table 1.

The data for the comparison of dAE between different strains of BCG used in Japan and the US were summarized in Table 2. The data indicate that the frequencies of dAE in Japan (Tokyo 172 and Connaught (JP)) may be generally higher than the strains used in the US. Thus, the differences were significant between Tokyo 172 and TICE ($p = 3.89 \times 10^{-5}$), between Connaugh (JP) and TICE ($p = 0.00038$), and between Connaught (JP) and Connaught (US) ($p = 0.05$). However, there was no significant difference between Tokyo 172 and Connaught (JP) ($P = 0.431$) nor between Connaught (US) in the US and Tokyo 172 in Japan ($p = 0.099$), see Table 2.

It is well known that Japanese doctors and patients are more sensitive to AEs than US doctors and patients, and it is likely that the discontinuation of BCG treatment may occur more often in Japan than in the US even when the AEs are similar. Alternatively, the different recommended schedules used for the treatment by BCG between the two countries may explain the difference in dAE. As stated in the efficacy section, the recommended treatment in Japan is more intense than in the US. Alternatively, the more robust immunity to BCG in Japan may explain in part the difference in AEs.

In conclusion, significant differences observed were neither in efficacy nor in safety between two strains of BCG used in each of Japan and the US. However, the rates of CR and NRS may be higher in Japan than in the US, and the rates of severe adverse events may be higher in Japan than the US, although the data were not from controlled studies.

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Authors

Professor Shiro Hinotsu[1], MD, PhD
Naoyuki Kamatani[2], MD, PhD
Timothy L Ratliff [3], PhD
Hideyuki Akaza[4], MD, PhD

[1]Center for Innovative Clinical Medicine, Okayama University Hospital
[2]Institute of Data Analysis, StaGen, Co Ltd
[3]Center for Cancer Research, Purdue University
[4]Department of Strategic Investigation on Comprehensive Cancer Network, Research Center for Advanced Science and Technology, The University of Tokyo

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Supplementary materials

Appendix A

Strategies for the search for papers in databases

Search criteria assessment for papers written in Japanese: Papers written in Japanese were collected using a Japanese medical literature database, Igakuchuozasshi (literally means, in Japanese, Central Medical Journal). In Igakuchuozasshi (the largest and the most popular database of medical papers written in Japanese), the key word 'BCG' includes a few different categories. The selection of 'BCG (Intravesical)' among them appears to be appropriate, and we used this category. 'Bladder and BCG (Intravesical)' appeared to be an appropriate phrase to select available papers for the meta-analysis. When 'therapy' was set as the Limit using the search phrase 'bladder and BCG (Intravesical)', many important papers were excluded. Thus, the Limit 'therapy' was not used. When the search phrase 'bladder and BCG (Intravesical)' was used, and the 'original paper' and 'meeting record' (papers are selected when they meet either of these two conditions) were used as Limits, most of the available papers were included. When the Limit was set only to 'original paper', many of the available papers were excluded. Therefore, the search phrase 'bladder and BCG (Intravesical)' and Limits, 'original paper' and 'meeting record' seem to be appropriate and were used to obtain the papers for the meta-analysis.

Search criteria assessment for PubMed paper selection: English papers were collected from the database PubMed. When the search phrase 'Bladder AND BCG' was used, most of the published papers describing BCG use for the treatment of non-muscle invasive bladder cancer (NMIBC) were identified. However, when 'Clinical Trial' was included in the Limits (Limits are the characters or concepts with which users select papers), many of the previously identified papers were excluded. As a result, 'clinical trial' limit was not used.

Procedures for selecting papers from PubMed and Igakuchuozasshi whose subject is intravesical BCG treatment performed by doctors in Japanese hospitals (written either in English or Japanese): English papers were collected using the database PubMed. We performed extensive examination regarding which conditions are appropriate for selecting papers for the present study. In conclusion, we decided to use the following search phrase and Limits in PubMed. The search phrase was 'Bladder AND BCG NOT Review AND Japan' and Limits were 'Human', 'Cancer', 'English' and 'Abstracts'.

Papers in Japanese journals were collected using the database Igakuchuozasshi. We performed extensive examination regarding which conditions are appropriate for selecting papers for the present study. In conclusion, we decided to use the following search phrase and Limits in Igakuchuozasshi. The search phrase was 'Bladder AND BCG (intravesical) NOT single case report AND original article AND abstracts'. The actual search phrase was in Japanese.

Procedures to select papers in PubMed written about the BCG treatment from doctors in US hospitals (two separate procedures were used): We considered various conditions in order to extract useful papers from PubMed for this study. We found that for the papers published before 1995, the country name USA or U.S.A. was not useful as a keyword. This is probably because the papers without any country names had been interpreted automatically as being from the US. We therefore used the following two procedures, one using the country name USA or U.S.A. and the other excluding the papers with the other country names.

(Condition 1)
Search phrase: Bladder AND BCG NOT Review AND (USA OR U.S.A.) Limits: Human Cancer English Abstracts

(Condition 2)
Limits: Human Cancer English Abstracts

Search phrase: Bladder AND BCG NOT Review AND (1995 [dp] OR 1994 [dp] OR 1993 [dp] OR 1992 [dp] OR 1991 [dp] OR 1990 [dp] OR 1989 [dp] OR 1988 [dp] OR 1987 [dp] OR 1986 [dp] OR 1985 [dp] OR 1984 [dp] OR 1983 [dp] OR 1982 [dp] OR 1981 [dp] OR 1980 [dp] OR 1979 [dp] OR 1978 [dp] OR 1977 [dp] OR 1976 [dp] OR 1975 [dp]) NOT Japan NOT USA NOT U.S.A. NOT Bulgaria NOT FRG NOT Hungary NOT Romania NOT Saudi NOT U.K. NOT Belgium NOT Egypt NOT Portugal NOT Denmark NOT Finland NOT Iran NOT Serbia NOT Austria NOT Russia NOT Norway NOT Argentina NOT Tunisia NOT Israel NOT Germany NOT India NOT Singapore NOT Malaysia NOT Philippines NOT Thailand NOT Taiwan NOT Korea NOT Poland NOT China NOT France NOT UK NOT Indonesia NOT England NOT Italy NOT Spain NOT Brazil NOT Mexico NOT Turkey NOT Greece NOT Sweden NOT Canada NOT Australia NOT Switzerland NOT United Kingdom NOT Netherlands

FRG: Federal Republic of Germany; Saudi: Saudi Arabia

Appendix B

Concepts of the meta-analysis of the BCG treatment for patients with NMIBC

Concepts for the present meta-analysis were fixed before the analysis as follows:

- Only the patients with bladder cancer on whom transurethral tumour resection (TURBT) followed by BCG instillation was performed, should be included.
- Patients with previous treatment (such as systemic chemotherapy for the bladder cancer; surgical bladder resection such as cystectomy) should be excluded.
- Patients with recurrent bladder cancer should not be excluded. If the number of patients with recurrent tumours is available, that should be noted.
- Patients with advanced cancer (involvement of other organs or invasion to muscular layer) should be excluded.
- If the patients with above 2–4 exclusion criteria are included in a paper, the data should be incorporated in our analysis when the data from the patients who should not be excluded are separately depicted in the paper.

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- The patients with carcinoma *in situ* (CIS) cases should be analysed separately from other cases. The data should be incorporated into our analysis only when the data from the patients with CIS are separately described in the paper.
- The data from a paper should be included only when not less than 10 cases meet the criteria shown here for the patients with CIS, while they should be included only when not less than 30 cases meet the criteria shown here for the cases with non-muscle invasive (superficial) bladder cancer treated by intravesical BCG instillation after TURBT.

Appendix C
Items extracted from each paper
The following items were extracted from each paper and entered into the data-input format tables for future analyses:

- Names of the facilities where the patients were hospitalized
- Interval during which the data were collected in years and months
- Prophylactic instillation after TURBT (Papillary) or Treatment for CIS
- Total number of the patients treated by intravesical BCG instillation after TURBT who meet the above inclusion criteria. Cases with CIS should be separately counted and analysed
- Strain of BCG; for example, Tokyo 172, Connaught (JP) or Connaught (US)
- For the patients with CIS, the rate of CR (complete response)
- Recurrence-free 2-year, 3-year, and 5-year survival rates after TURBT.
- Recurrence-free rate estimated from K-M plot (approximated value)
- T staging (Range); Ta, T1 and Tis
- G category (Grade) (Range or number); G1, G2 and G3 or Low grade/High grade
- Solitary or multiple (Number of tumours if data are available)
- Size of tumour (if available)
- Age (range and mean or median)
- Male/Female
- AE (names of the events and percentage)
- Number and percentage of the cases with dAE

Appendix D
Results of the selection of papers to be reviewed
To compare the efficacy and safety of different BCG strains for the treatment of NMIBC, two separate sets of papers were collected. The first set of papers were the papers written in either English or Japanese by the doctors in Japanese hospitals, and the second set of papers were those written in English by the doctors in US hospitals. This is because approved BCG strains, ethnicities of the patients and medical systems were different in both countries.

According to the criteria described in Appendix A, we selected papers for this study. For the first set of papers, we obtained 255 papers from Igakuchuozasshi (The search was performed on 6 September 2011) and 97 papers from PubMed (The search was performed on 23 January 2012). For the second set of papers, we obtained 114 papers under condition 1 and 219 papers under condition 2 as described in Appendix A (The search was performed on 13 September 2011).

Thus, the total numbers of papers selected from both Pubmed and Igakuchuozasshi databases were 352 (255 + 97) for the first set (Japanese hospitals) and 333 (114 + 219) for the second set (US hospitals). From a total of 352 papers reported by authors from Japanese hospitals, and 333 papers described by authors from US hospitals, we selected the papers that met the 'Concept' described in Appendix B by reading the abstracts. For example, the papers with fewer than 10 carcinoma *in situ* (CIS) patients, and the papers with fewer than 30 non-muscle invasive TCCa patients, were excluded. For the analysis of adverse reactions, however, the data from papers with 20–29 cases were included in some cases.

In addition, there was a problem in the first set of papers reported from Japanese hospitals. Thus, we read the abstracts of 255 Japanese and 97 English papers in the first data set carefully and found that the contents of some papers were very similar. Not all the names of the authors were the same, but the selected papers included the names of the same authors. By comparing the names of the hospitals of the authors as well as the abstracts, we concluded that some of the Japanese and English papers included essentially the same or similar sets of the patients. Only one paper using the same patient set was used in the analysis.

Using these criteria in Appendix B and removing the duplicated reports, 75 out of 352 papers by the doctors from Japanese hospitals were selected. From the second set of papers, 67 out of 333 papers described by the authors in US hospitals were selected. Those 142 papers are the final sets from which the data of efficacy and safety of BCG instillation in the bladder were extracted.

After the review of the final set of papers by two separate reviewers, the data were extracted into data-input format as described in Appendix C.

Statistical procedures
Heterogeneity of the frequencies between different subgroups in a group for complete response (CR) rate or non-recurrence survival (NRS) rate was tested by the x^2 method. The value $\Sigma_1^k n_i (p_i - \breve{p})2 / p_i(1-p_i)$ is expected to follow $x^2(k-1)$ distribution under the null hypothesis (p_is in different subgroups are the same), where n_i, p_i and k denote the size of the ith subgroup, frequency in the ith subgroup, and the number of the subgroups in the group and $\breve{p} = \Sigma_1^k n_i p_i / \Sigma_1^k n_i$. The group is judged to be heterogeneous when the cumulative distribution function of $x^2(k-1)$ at the calculated value exceeds 0.95. 95% CI for CR rate was calculated by Clopper-Person's method.[13]

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For the test of independence for a 2 × 2 contingency table, Fisher's exact test was used. In all the studies included in the analyses, the NRS rates had been calculated by the Kaplan-Meier's method. In some cases, the values of the NRS rates were described in the texts; however, only Kaplan-Meier's curves but not the values were shown in the others. In the latter cases, NRS rates were calculated by measuring the lengths between appropriate points in the figures.

First, the heterogeneity of each group was tested as described above, and when none of the groups in the analysis was judged to be significantly heterogeneous, the fixed effect model was used. The difference between the CR rate in CIS patients and the NRS rate in non-CIS patients is that, in the latter case, only the estimated rate of the patients with NRS compared to the all treated patients but not the exact number of the patients with NRS at a time point is available. Therefore, those two different types of studies were analysed in different methods in the present study.

For the *i*th study, the standard error of the NRS rate r_i was estimated as $SE = \sqrt{\check{r}_i(1-\check{r}_i)/n_i}$ where n_i denote the number of the patients initially enrolled in the study.

The estimate of the NRS rate at a time point after the BCG therapy (for example, two years) for a group (for example, the treatment using a BCG strain in either Japan or the US) in a meta-analysis was calculated by integrating the data from different studies. Thus, we calculated the weighted average $\check{r} = \Sigma_i^N n_i r / \Sigma_{i=1}^N n_i$ for the estimate of the NRS rate for the group. Standard error of $\check{r}$ was calculated as $SE = \sqrt{\Sigma_{i=1}^N n_i r_i (1-r_i) / \Sigma_{i=1}^N n_i}$. Here the NRS rates in different studies were assumed to be the same (fixed effect model).

For the test of the difference in the NRS rates between different categories (for example, Tokyo 172 in Japan and Connaught (JP) in Japan), $\check{r}_a - \check{r}_b$ was assumed to follow a normal distribution with the mean 0 and the standard error of $\sqrt{SE_a^2 + SE_b^2}$, where r_a and r_b denote NRS rates for groups *a* and *b*, respectively calculated by weighted average method, and SE_a and SE_b denote the standard errors calculated for $\check{r}_a$ and $\check{r}_b$ by the method described above. For the test of the difference between categories *a* and *b*, we tested by setting $r_a - r_b = 0$ as the null hypothesis assuming that it follows a normal distribution with the standard deviation of $\sqrt{SE_a^2 + SE_b^2}$.

When at least one of the groups in the analysis for CIS was judged to be significantly heterogeneous, random effect model was employed using the generalized linear mixed model assuming the binomial distribution. The analyses were performed using 'glmer' function in the 'lme4' package in the R environment. In case of NRS rate analysis, however, the exact integer numbers of the patients with NRS were not obtained. Fortunately, only the TICE data were significantly heterogeneous for NRS data and the *p* value for the test of heterogeneity was only 0.043. Considering the multiple-testing problem, this significance is only marginal. Therefore, the fixed effect model was used for all NRS analyses.

Safety assessment and revision of a central cytostatic unit based on ESOP guidelines

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Safety assessment and revision of a central cytostatic unit based on ESOP guidelines

András Süle, PharmD, PhD

Abstract

Introduction: The safety status of a central cytostatic unit in a major regional hospital was reviewed. Staff education, standard operating procedures, environmental concerns, and personal protective measures were assessed, based on the guidelines of the European Society of Oncology Pharmacy's Quality Standard for the Oncology Pharmacy Service (QuapoS).

Method: The assessment encompassed three main stages: SWOT analysis of the preceding conditions, analysis of the cytostatics workflow using the Ishikawa method, and risk assessment of the central cytostatic unit.

Results: The manual method used for cytotoxic drug preparation was found to be in need of comprehensive revision. Specifically, the following steps were taken: a comprehensive operating protocol was created containing specific and detailed standard operating procedures for every aspect of the unit's work; an in-house training programme was developed; the personal protective equipment set was revised; new devices and protective clothing were introduced; and workplace contamination was assessed by surface wipe tests. Upon evaluation of the results, a new laminar air flow safety cabinet was installed, and the cleaning standard operating procedures were also thoroughly revised; finally, to prevent accidental personal and environmental exposure, standardized spill kits were instituted, and the decontamination standard operating procedures were also updated accordingly.

Conclusion: The purpose of this work was to institute safe-handling practices and precisely regulated standard operating procedures, together with continuous staff education, thereby minimizing the risk of human and environmental exposure while maintaining the highest level of medication safety. In this case, the systematic revision of the central cytostatic unit provided a substantial leap forward in all of the areas stated above.

Keywords: Cytotoxics, exposure, personal protective equipment, production, risk assessment, safety

Introduction

The Szent György University Teaching Hospital in Székesfehérvár, Hungary, is a major regional institute, with more than 1,600 beds and a central cytostatic unit (CCU) that produces 80-110 infusions on a daily basis.

The CCU uses the traditional, manual volumetric method for cytotoxic drug preparation that bears a substantial inherent risk of both human and environmental exposure, as well as a reduced fault tolerance towards potential medication errors.

We aimed to assess the safety status of the existing CCU workflow and to revise the process accordingly. The assessment was based on the guidelines of the European Society of Oncology Pharmacy's (ESOP) QuapoS, and it encompassed staff regulations, education, standard operating procedures (SOPs), workplace environment, environmental concerns, and personal protective measures.

Study objectives

The systematic revision of the CCU followed a stepwise scheme of analysis, evaluation, planning, and realization. This included defining the key aspects of the workflow by analysing its exact causal structure using the Ishikawa method; assessing each fundamental feature thoroughly based on QuapoS, using the Ishikawa diagram; producing a SWOT analysis of the preceding conditions to obtain a clear and concise picture of the priorities; developing new operating and training protocols; and continuously evaluating the workflow.

Method

Ishikawa diagrams (also called cause and effect, or fishbone diagrams) show the causal structure of individual factors influencing an overall outcome [1]. Each cause is a source of variation and, as such, a source of imperfection too. Causes are usually grouped into major categories to identify these variabilities.

The arrangement of causes does not necessarily follow the stepwise or chronological nature of the workflow; they are rather to be considered as principal foundations of the desired outcome. It is, however, crucial for the analyst to have a broad understanding of the project in question, especially on a procedural level.

Central cytostatic units have a unique set of attributes that determine their productivity, safety and effectiveness, see Figure 1. It can be concluded that all of the determining factors fall into 4(+2) main categories (causes) that clearly resemble the genuine '6Ms' pattern of the Ishikawa method used in the manufacturing industry.

The components of the cytostatics workflow are described below.

Materials

Drugs and infusion solutions must only be purchased from certified vendors. Although drug counterfeiting is not a major issue in Hungary, procurement regulations should always ensure the reliable supply of materials.

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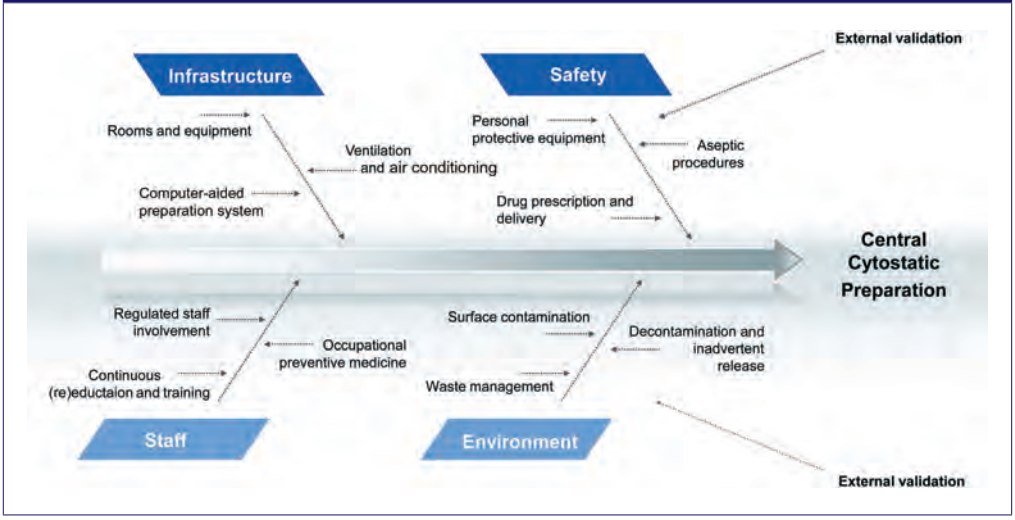
Figure 1: Key aspects of the cytostatics workflow



Infrastructure

Infrastructure includes machines and technology. Quality and safety of the produced infusions are greatly determined by the conditions of the preparation area, including the room(s), equipment and ventilation. The proper scheme of operation for CCU ventilation, including pressure differences, airborne particle filtering, and air quality is detailed in QuapoS [2].

Staff

Staff size, level of education and continuous training are major contributors in the accomplishment of the desired goal of a safe and effective CCU. Staff size for CCUs is regulated by national law. The required number of pharmacists and technicians is determined by the number of infusions prepared per day, see Table 1.

Table 1: Staff regulations for central cytostatic units [3]

	Preparations			
	1–25	**26–50**	**51–100**	**101–200**
Pharmacists	0.5	1	1.5	2
Pharmacy technicians	1	2	3	4

Safety (method)

The development of specific and detailed SOPs for every aspect of the unit's work is vital to ensure the proper use of aseptic procedures and certified personal protective equipment (PPE). Drug logistics should also be governed by SOPs, especially the safety of delivery. Cytostatics deliveries must be clearly labelled by the sender, and it is required that liquid-tight, re-sealable and durable containers are used for transporting ready-to-administer preparations.

Environment

Personal and environmental exposure is one of the main risks of working with cytotoxics. It is imperative that both of these threats are minimized and continuously monitored. Contaminated waste disposal and proper decontamination of the workspace should also be defined and governed by SOPs. The same is true for the emergency management of inadvertently released cytotoxics. The basic rule of waste and exposure management is to avoid unnecessary dangers to the staff and all personnel by collecting the waste, spill, or both as close to the point of origin as possible. All waste material contaminated with carcinogenic, mutagenic and reprotoxic (CMR) substances must be disposed of as hazardous toxic waste.

External validation

The technical and legal conformity of the workflow should be regularly monitored by authorities. Also, the institutional quality management system must be validated by external audits in a regular manner. Since the operating protocols governing the whole process of cytotoxic handling, preparation, and distribution are all integrated into the hospital-wide quality management system, external validation plays a vital role in ensuring their effectiveness.

Assessment of the fundamental workflow features

The next stage involved a careful analysis of the aforementioned key points. A SWOT analysis, see Figure 2, of the workflow was carried out, identifying the strengths and weaknesses of the pre-existing conditions and also finding the opportunities and threats that the *status quo ante* had been facing.

The main strength of the unit was found to be the staff itself. Their expertise and shared commitment towards constant improvement proved to be an invaluable asset. Also, the project gained substantial support from the hospital board of directors and the local authorities. These, combined with the hospital becoming a regional oncology centre, in turn, provided a much-needed momentum to deal with the challenges outlined by the analysis.

Most of the issues were infrastructure-related. The ageing equipment, local guidelines for personal protective measures, and the stressful work environment needed extensive improvement. External factors were also found to be unfavourable, especially in considering the financial background and state of the labour market, which made it impossible to find highly skilled, educated, and devoted staff members willing to work with cytotoxics in the public sector.

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Figure 2: SWOT analysis of the former central cytostatic unit workflow

Developing a new operating protocol

Under these circumstances, based on the findings of the previous analyses, the complete revision of the CCU's workflow began. Given the causal nature of the factors in question, it was beneficial to follow a systematic approach. The conclusions were also discussed with a highly experienced team of pharmacists at the *Sozialmedizinisches Zentrum Süd* – Kaiser-Franz-Josef-Spital in Vienna, Austria, as part of an international collaboration with ESOP.

Following the logical approach offered by QuapoS [2], a comprehensive operating protocol was developed, consisting of SOPs for each and every aspect of cytotoxics in the hospital.

Staff

Staff-related findings necessitated three main points of intervention: staff regulations, continuous education and occupational health.

Staff regulations

An SOP was created to govern who is involved in the CCU's workflow, when and how. As a main regulation, it was stated that all personnel involved in cytotoxic handling or production must be trained in working with cytostatics, and that they should receive plenty of information and be given enough time for proper comprehension.

Given the different skill requirements and risks, it proved viable, on an SOP level, to separate the job profiles of staff involved in the preparation from those who were not. This way, separate sets of rules and requirements could have been laid down for the two profiles throughout the whole operating protocol [4].

Basic rules set for staff involved in preparation: Preparation of cytostatic infusions is to be entrusted to pharmaceutical staff only. Pharmacists and pharmacy technicians must be proficient in handling CMR substances and also in aseptic preparation procedures. The staff must be instructed and trained continuously, and participation in further training is mandatory. Correct aseptic working techniques are tested regularly.

Basic rules set for non-pharmaceutical staff: These personnel may only be assigned to tasks supporting preparation. Proper and ongoing training is nonetheless crucial. Cleaning and maintenance staff are trained for clean room requirements and the special risks present in the preparation area. Compliance with the cleaning and disinfection plan is mandatory and documented.

Transport staff may accept infusion containers only if they are approved for delivery, properly packaged and labelled by the sender. Ready-to-administer preparations leaving the CCU must be signed by the pharmacist in charge beforehand. Transport staff are responsible for the correct and timely delivery to wards.

Education and training

A comprehensive training programme has been developed for the whole CCU team that focuses on theoretical knowledge and practical skills [5]. This in-house programme encompasses the training of new employees and the ongoing education of all personnel. The curriculum is based on Hungarian national directives and ESOP's guidelines.

All personnel must participate in training on a semi-annual basis. Participation in the ESOP Masterclass in oncology pharmacy series is also encouraged.

In-house training

Classroom lectures focus on the following subjects: chemical and biological properties of CMR substances; pharmacology, proceedings in pharmacotherapy; handling of hazardous substances, risk management, protective measures and PPE; decontamination, waste disposal, and dealing with the inadvertent release of cytotoxics; and quality assurance, documentation, accountability, and responsibilities.

Practical lessons include aseptic procedures, handling single-use and laboratory equipment; proper use of PPE; decontamination and emergency management, the spill kit; simulation of regular aseptic workflow and accidents, including ESOP's 'Clean Working' in-house course and certification scheme.

Occupational health and safety

The main risk presented by CMR drugs is based on their genotoxic effect, which bears a stochastic dose–effect principle: chronic and subchronic exposure only increases the probability at which an unwanted side effect might occur in the future. Consequently, it is almost impossible to quantify that risk precisely for the staff exposed. It is possible, however, to

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perform a hazard evaluation to determine the dangers associated with each part of the workflow [6].

From an occupational health and safety viewpoint, therefore, prevention is crucial. Hazard evaluation also helps to define the appropriate protective measures, including training, personal protective equipment, laboratory gear, and infrastructure.

Hazard evaluation for the CCU comprised the following steps:
Definition: The workflow was defined by the appropriate work areas, reception of shipments, preparation laboratory, administrative room, storage, transport, and cleaning.
Ascertainment: Risks and dangers were assessed for each work area. A list of hazardous substances was created and mechanical hazards were also defined.
Evaluation: Hazard analysis was carried out on the basis of national legislative regulations.
Decision: As stated above, to avoid unnecessary dangers, risks should be dealt with as close to their places of origin as possible. Technical and personal preventive measures were defined accordingly.
Control of efficacy: Protective measures were set to be re-evaluated on a regular basis to determine their effectiveness. Semi-annual validation of laboratory equipment (including physical, chemical and microbiological testing) as well as regular medical control of the staff has been determined necessary.
Documentation: Hazard evaluation has been documented in writing and signed by the staff working in each area.

Table 2: The Institute of Energy and Environmental Technology surface contamination test results

Sampled substance	Safety cabinet workspace	Dispensing table	Preparation bench	Laboratory floor
5-Fluorouracil	+++	+	D	–
Gemcitabine	++	D	D	D
Methotrexate	–	–	–	–
Cyclophosphamide	+	D	D	+
Ifosphamide	+	D	–	–
Etoposide	+	D	–	–
Docetaxel	–	–	–	–
Paclitaxel	D	D	–	–

+++: > 100x reference limit; ++: 10–100x reference limit; +: < 10x reference limit; D: detectable, below reference limit; –: below detection level. Institute of Energy and Environmental Technology reference limit: 0.1ng/cm^2.

Environment and infrastructure
Berner International GmbH and the Institute of Energy and Environmental Technology (IUTA) PharmaMonitor surface contamination test, introduced as an efficacy control measure by the hazard analysis plan, was one of the major driving forces behind this work [7], see photo below.

Although the initial contamination levels, see Table 2, proved to be more favourable than expected, some areas needed immediate attention.

Decontamination procedures
The decontamination, cleaning and disinfection SOPs needed complete revision because of the high level of CMR drug residue inside the safety cabinet and throughout the preparation area. Surface contamination outside the safety cabinet suggested a less than adequate filtering and isolation efficacy of the appliance.

Reorganization of the workflow
The replacement of the old safety cabinet with a Berner FlowSafe C-[MaxPro]^3, DIN 12980:2005 and EN 12469:2000 compliant unit has been one of the most substantial developments in this project. Laboratory fittings, including the previous dispensing tables were removed, and new furniture and workflow orientation was introduced for better ergonomics and handling.

In consultation with IUTA and ESOP, a new chemical decontamination SOP was created based around the 'alcohol-hydroxide'—0.1M sodium-hydroxide in 70% ethanol—solvent. Cleaning and disinfection SOPs, as well as the training guides for the cleaning personnel were also revised accordingly.

Safety and exposure
Personal protective equipment
Personal protective equipment requirements were updated to match or supersede QuapoS guidelines. Personal protective equipment of the following specifications was made mandatory.
Protective coat: Single-use, water and CMR-impermeable gown with tight fitting cuffs, sealed seams and a breathable back.
Gloves: Latex-free, hypoallergenic, sterile nitrile gloves, compliant with the 89/686/EEC, EN 374:2003:1-3, EN 388:2003 and EN 420:2001 regulations and standards. For additional safety and easy visual detection of physical damage, double gloving with different coloured gloves is mandatory [8].

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Shoes: Impermeable shoes with anti-slip soles must be worn. Their usage is exclusive to the cytostatic unit only.
Respiratory masks: Particle filtering FFP3D class half masks with EN 149:2001 compliance must be worn at all times in the preparation area.

Technical equipment for preparation
In order to provide the maximum standard of safety, a new range of technical equipment was introduced into the production workflow [9, 10].
Preparation mats: Spill-proof, three-layered preparation mats were specifically designed for cytostatic agents.
Syringes: The previously used single-use syringes with traditional 'Luer-Slip' fittings were replaced in favour of 'Luer-Lock' systems with double-sealed, siliconized pistons. As the preparation method is volumetric, dosage accuracy is crucial. It was vital that the preparation SOP explicitly stated the imperative to choose syringe sizes closely matched to the volume of individual measurements.
Pressure release systems: To effectively compensate pressure differences arising throughout the dissolution process, transfer spikes with double filters were introduced (0.2 µm hydrophobic air filter, 6 µm liquid particulate filter).
Self-contained systems: PhaSeal and Tevadaptor needleless self-contained systems were put into use for selected substances to prevent aerosol formation and release during dissolution, see photo below.


Infusion preparation using the revised set of equipment

Waste containers: Single-use, bright yellow, hermetically sealable, appropriately labelled plastic containers were introduced. The institutional hazardous waste handling policy was updated according to the SOP governing cytotoxic waste disposal.

Inadvertent release of cytostatics
Previously, institutional directives were lacking the proper and unified handling directives for inadvertently released CMR substances. The inclusion of ESOP's standardized 'Spill Kit' into the appropriate SOPs has remedied this shortcoming.

Along with the Spill Kits, the CCU provides general counselling on the usage of CMR substances and handling unexpected situations for the wards.

Conclusion

The main goal of this work was to systematically revise the operating protocols and the practical workflow of the CCU. On the basis of the SWOT analysis of the preceding setting, the local facilities and ESOP's current guidelines, the precise agenda could have been narrowed down to how to institute safe-handling practices and precisely regulated SOPs, together with continuous staff education, thus minimizing the risk of human and environmental exposure, while maintaining the highest level of medication safety.

ESOP guidelines, the QuapoS, and the effective international networking, made it possible to incorporate the most recent proceedings in CCU safety with respect to local possibilities.

The whole set of detailed SOPs governing the workflow of cytotoxics was revised and integrated into a comprehensive CCU operating protocol that became an integral part of the institutional quality management system.

According to the new protocol, the central pharmacy and the CCU assume an integrative and supportive role in the area of cytostatics handling and safety.

In the future, additional steps are to be taken to further improve on the areas discussed above. A major milestone is set for fourth quarter of 2014, when the new building for the central pharmacy is due to be opened, along with a newly designed cytostatic unit, based on the approach detailed in this work.

Author

András Süle, PharmD, PhD
Péterfy Hospital and Trauma Centre
Central Pharmacy
8-20 Péterfy Sándor utca
HU-1076 Budapest, Hungary

Szent György University Teaching Hospital
Central Pharmacy
3 Seregélyesi út
HU-8000 Székesfehérvár, Hungary

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References 5–10 can be found on page 18.

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Enhancing adherence to oral anticancer medication

Linda Krolop, PhD; Professor Dr Ulrich Jaehde, PhD

Abstract

Introduction: The efficacy of orally administered anticancer drugs depends on a high level of patient adherence. Therefore, the development of an adherence monitoring and enhancing infrastructure is a necessary prerequisite to exploit their full potential. We evaluated an adherence-enhancing intervention for cancer patients treated with capecitabine, a prodrug of fluorouracil.

Method: Adherence was measured in two prospective observational cohort studies using an electronic medication event monitoring system (MEMS®). In the first study, one group of patients received standard care (control group), while the other group received multidisciplinary pharmaceutical care consisting of written and spoken information (intervention group). To use the limited resources in health care most efficiently we designed a second study dividing the patients into two groups based on measured adherence during the first cycle. According to their daily adherence, patients were identified as initially non-adherent (< 90% adherence) or adherent (≥ 90%). Initially non-adherent patients received additional adherence support.

Results: In the first study, patients in the intervention group exhibited a significantly higher daily adherence to capecitabine. Variability of adherence was considerably reduced when pharmaceutical care was provided. In the second study, about 80% of the patients were initially adherent and 20% non-adherent. Daily adherence of initially non-adherent patients increased when specific adherence support was provided. Daily adherence of initially adherent patients was 100% throughout all cycles.

Discussion/Conclusion: The provision of multidisciplinary pharmaceutical care can enhance adherence to oral anticancer medication. An early adherence screening effectively identifies patients who benefit from specific adherence support.

Keywords: Adherence, capecitabine, oral chemotherapy, pharmaceutical care

Cancer therapy has traditionally been dominated by intravenously administered agents [1]. However, during the previous decade many orally administered anticancer drugs have been developed [2]. Convenience is the most important advantage of oral anticancer therapy among patients. Medicines can be taken at home without the need for time-consuming appointments at treatment sites [2, 3]. Further benefits are the avoidance of venipuncture and extravasation as well as a greater patient autonomy. Patients appreciate the decrease of the daily presence of this psychologically distressing disease [4]. Reduced contact between patient and healthcare providers means, however, that responsibilities in terms of managing the course of treatment, such as monitoring of doses and toxicity, are transferred to the patient [2, 5]. One example of an oral chemotherapeutic agent is capecitabine, a prodrug of fluorouracil (5FU), which is indicated for the treatment of patients suffering from colorectal cancer, gastric cancer or breast cancer. The recommended starting dose for capecitabine is 1,250 mg/m^2 administered twice daily for two weeks, followed by a one-week medication-free interval. Usually capecitabine is given in three-week cycles. In contrast to intravenously administered anticancer treatments, healthcare providers cannot always assume that the patients are adherent to their treatment, which is a key prerequisite for treatment success.

Causes of non-adherence

The World Health Organization (WHO) defines adherence as 'the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider' [6]. About 200 factors have been suggested to influence patient adherence. According to the WHO, adherence is a 'multidimensional phenomenon determined by the interplay of five sets of factors' [6]:

- Examples for *social and economic factors* known to negatively influence adherence are higher age, greater distance from the treatment setting, financially weak situation, e.g. unemployment, low level of education and family dysfunctions.
- *System-related factors* might also affect patient adherence. These include a poor patient–physician relationship, lack of knowledge and training for healthcare providers, overworked healthcare providers, short consultations and insufficient delivery of patient education.
- *Therapy-related factors* that most notably affect adherence are those related to the complexity of the medication treatment, such as duration of treatment, previous treatment failures, frequent changes in treatment and adverse drug reactions. The adherence to a once- or twice-daily intake is significantly higher than to a three or four times daily intake [7, 8].
- Examples of *patient-related factors* that might decrease adherence are a lack of self-perceived need for treatment, forgetfulness, anxieties about possible adverse effects, low motivation and inadequate knowledge and skills in managing the disease symptoms and treatment.
- *Condition-related factors* that strongly determine adherence include severity of symptoms, level of disability, progression rate and availability of effective treatments. These factors influence patients' risk perception, the importance of following the treatment, and the priority placed on adherence. Co-morbidity, e.g. depression in HIV/AIDS or diabetes, as well as alcohol abuse are major modifiers of medication-taking behaviour.

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Adherence measurement

The detection of extent, pattern and cause of low adherence is very important for the selection of an appropriate adherence-enhancing strategy. Thus, detailed information on the exact nature of patient medication behaviour is required.

Adherence-measuring methods can be divided into direct and indirect methods as summarized in Table 1 [7, 9].

In adherence studies electronic medication monitors are frequently used such as the medication event monitoring system (MEMS®) consisting of medication bottles with a screw cap containing a microprocessor. The bottles can be filled with orally administered dosage forms and are capable of recording and displaying date and time of bottle openings [10]. Thus, special behavioural patterns can be tracked, e.g. if a patient mostly forgets their evening dosage or does not take their medication mostly on the weekends. A disadvantage of these devices is the non-documentation of the actual ingestion of the drug. The patient might have opened the bottle without taking his drug, taken his medication from another source (other medication container, medication package), or taken multiple doses at the same time. Furthermore, the execution of this method is relatively complex. Patients need to visit their therapy site more often than normally required and the healthcare provider needs to read data from medication vials using special software. Thus, electronic monitoring of adherence is not used in daily routine so far. But despite existing disadvantages, this measure provides the most accurate and valuable data on patient medication intake behaviour [7, 9].

Adherence support

Adherence-enhancing interventions are complex and require a combination of different measures [11]. Basically, four different categories can be distinguished [7, 11]:

- *Educational interventions* imply patient education, counselling and written information material and contribute to a better understanding of the disease and therapy. These interventions are appropriate for the improvement of intentional non-adherence. Patients who better understand their disease and pharmacotherapy are more likely to follow their treatment plan.
- *Behavioural interventions* are treatment diaries, medication dosette boxes, reminder cards pinned at a distinctive spot, alarm clocks, and/or the inclusion of family members into the process of care. Behavioural interventions aim to improve unintentional non-adherence and remind forgetful patients of their medication intake. 'Cue-dosing' is also a behavioural

Table 1: Direct and indirect methods for measuring patient adherence including advantages and disadvantages [7, 9]

	Advantages	Disadvantages
Direct methods		
Direct supervision of the intake	+ Most precise	– Impractical for routine use – Prone to 'Hawthorne effect' – Patients can hide tablets in the mouth and discard them
Measurement of drug or metabolite concentration in plasma	+ Objective	– Variations in metabolism and white-coat adherence can give a false impression of adherence – Expensive – Blood samples required
Indirect methods		
Patient questionnaires, patient self-reports	+ Generally easy to perform + Inexpensive + Most useful method in the clinical setting	– Susceptible to errors with increases in time between visits – Easily altered by the patient
Patient diaries	+ Help to correct for poor recall	– Easily altered by the patient
Pill counts	+ Objective + Quantifiable + Easy to perform	– Easily altered by the patient, e.g. pill dumping
Rates of prescription refills	+ Objective + Easy to obtain data	– A prescription refill is not equivalent to ingestion of medication – Requires a closed pharmacy system
Electronic medication monitors	+ Precise + Quantifiable + Tracks patterns of taking medication	– Expensive – Requires return visits and reading data from medication vials – No proof of actual intake
Assessment of the patient's clinical or pharmacodynamic response, e.g. blood pressure in hypertensive patients	+ Simple + Generally easy to perform	– Factors other than medication adherence can affect clinical response – Often no appropriate marker available

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intervention. It is the linking of drug intake with a certain activity in daily life.

- *Monitoring interventions*, e.g. the regular monitoring of patients' blood pressure or other health outcomes, increase the patients' motivation to take their medication as prescribed. Furthermore, measurement of adherence itself may have an effect on the medication taking behaviour and improve adherence. This beneficial effect of the observation itself on the outcome is termed the 'Hawthorne effect' [9].
- *Pharmacotherapeutic interventions* comprise the simplification of treatment regimens such as the prescription of extended release or combination formulations. Faith in treatment and adherence can decrease in patients who are instructed to split their tablets [12, 13]. Thus, half or quartered tablets should be prescribed as rarely as possible.

Adherence of cancer patients to capecitabine

Long-term adherence in patients with chronic, non-oncologic conditions is estimated at 50% [6, 14]. Since cancer is a distressing and life-threatening disease, cancer patients' medication-taking behaviour is presumed to be particularly precise and adherent [7, 15-18]. For oral anticancer agents, adherence rates from 16% to 100% have been reported. The variability can be explained by the different anticancer agents, the definition of adherence and the method of measurement [16, 19]. The adherence to oral capecitabine treatment has been explored by several recent studies.

Partridge et al. used MEMS® for adherence assessment in 161 older women (aged from 65 to 89 years) with early-stage breast cancer. Adherence was defined as the number of doses taken divided by doses expected. Patients were considered adherent if ≥ 80% of the expected doses were recorded by MEMS®. One hundred and twenty-four patients (83%) persisted with capecitabine up to the completion of the planned protocol – six cycles. Seventy-five per cent of participants performed more than 80% of expected openings and were regarded as adherent. Average adherence was 78% across all cycles, and adherence did not vary by cycle. This study was part of a clinical trial and might not reflect usual care [20, 21].

Patient self-reports were used to assess adherence to capecitabine of 143 gastrointestinal and 34 breast cancer patients. Patients recorded their capecitabine intake each day in patient diaries. 91% of the participants were found to be fully adherent, whereas only 9% participants reported some kind of adherence error, which was defined as any violation of the recommended regimen. Reasons for non-adherence included forgetfulness, adverse drug reactions and misunderstanding of instructions [15].

Mayer et al. explored adherence among metastatic breast cancer patients by means of MEMS® vials (n = 13) as well as self-reports using a daily drug diary completed by each patient (n = 12). Adherence was defined as observed divided by expected doses. An adherence of > 80% was used to define acceptable adherence. Adherence measured by MEMS® ranged from 75% to 100% and both median and mean adherence accounted for 96%. Self-reported adherence ranged from 89% to 100% and median adherence was 97% – mean adherence: 99% [22].

The authors of another study recruited breast and colorectal cancer patients treated with capecitabine in a UK teaching hospital and assessed self-reported patient non-adherence using the Medication Adherence Report Scale (MARS). Respondents were asked to report whether any divergence from treatment originates from dose alteration, omission, intentional termination, or forgetting. Non-adherence was stated by 10 of the 43 patients (23%). Four patients reported several types of deviation. Forgetting to take a capecitabine dose was the most commonly stated reason for a deviation [23].

Adherence to capecitabine was also assessed using a qualitative approach in 42 patients. The results of group and individual interviews did not suggest deliberate non-adherence but poor observance of the dosing schedule. Most frequently, patients deviated from the instruction to take capecitabine after a meal [24].

A Canadian study in 2007 surveyed 25 patients treated with capecitabine. Adherence was measured using pill counts and patient self-reports and defined as any indication of not having 100% adherence. Patients were randomly assigned to either receive capecitabine provided in convention pill bottles or prefilled per patient's prescription into daily pillboxes. After the completion of one cycle the patients switched over to the alternate packaging method. It could not be demonstrated that daily pillboxes improved adherence to capecitabine. Adherence rates were similar when using daily (81%) and conventional pill bottles (86%) [25].

Pharmaceutical care as adherence-enhancing intervention

Multidisciplinary patient care and specific patient education regarding all aspects of the treatment regimen are crucial to maintain adherence [4, 5, 26-28]. Continuous pharmaceutical care has been shown to be particularly suitable to enhance medication adherence. Several studies have provided evidence that the integration of a pharmacist in patient care has a beneficial effect on adherence [29-32].

The effect of an intensified multidisciplinary pharmaceutical care programme on the adherence of cancer patients treated with capecitabine was investigated by two consecutive studies at the University of Bonn, Germany. In both studies, adherence was measured using MEMS® and daily adherence was defined as the percentage of days with correct medication-taking behaviour. Prospective multi-centre observational cohort study designs were used. 24 colorectal and 24 breast cancer patients participated in the first study. Patients of the control group (n = 24) received standard care, patients of the intervention group (n = 24) received pharmaceutical care comprising patient education on drug treatment, adverse events management and the importance of adherence. Moreover, medication

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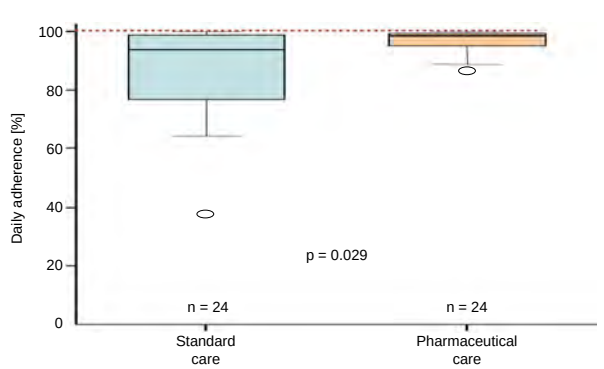
reviews, interaction checks and written dosing schedules were provided. Patients in the intervention group exhibited a significantly higher daily adherence compared with the control group – p = 0.029, see Figure 1.

Variability of this adherence parameter was considerably reduced when pharmaceutical care was provided. At the end of the observation period of 126 days, the probability of still being treated with capecitabine was found to be 48% in the control group and 83% in the intervention group (p = 0.019) [33].

Although adherence of patients treated with capecitabine is relatively high compared with non-oncologic oral drugs it can still be increased by specific measures. However, since only some patients treated with capecitabine are in need of an adherence-enhancing intervention, limited resources could be used more efficiently. Most patients manage their oral treatment regimen independently and do not benefit from specialized patient care. Since lack of time is a restricting factor in daily practice, it is important to know which patients benefit from an adherence supporting intervention and which patients do not.

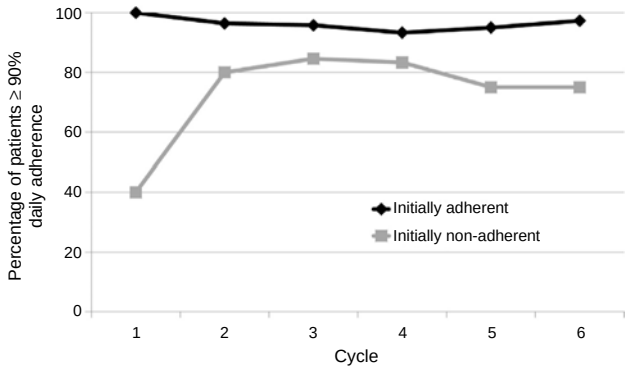
In the second study, cancer patients were screened for their initial adherence to capecitabine treatment in order to detect potential non-adherers. According to their daily adherence during the first cycle, patients were identified as initially non-adherent (< 90% adherence) or adherent (≥ 90% adherence). Both adherence groups received two pharmaceutical care modules consisting of oral and written information. Module 1 (basic pharmaceutical care) comprised medication reviews, patient education on drug treatment, interaction checks and an individual medication plan. Module 2 (specific toxicity management) comprised patient education on possible adverse events and their appropriate management. Initially, non-adherent patients received additional adherence support comprising detailed discussions of adherence results with the patient as well as specific patient education

Figure 1: Daily adherence to the prescribed capecitabine regimen* [33]



*In patients with standard care (control group) and pharmaceutical care (intervention group) shown as box plot. The bottom and top of the box are the first and third quartiles, the line inside the box is the median, O indicates an outlier.

Figure 2: Percentage of patients exhibiting a daily adherence to capecitabine ≥ 90%§ [34]



§Initially adherent patients without specific adherence support; initially non-adherent patients with specific adherence support after completion of cycle 1.

concerning adherence. A total of 73 patients with various tumour entities were enrolled, 58 were initially adherent and 15 non-adherent. Median daily adherence of initially non-adherent patients increased from 85.7% to 97.6% during the observation period of six cycles. Throughout all cycles, median daily adherence of initially adherent patients was 100%, see Figure 2.

There was not any significant association between daily adherence and socio-demographic and disease-related characteristics [34].

Conclusion

Pharmaceutical care can enhance adherence to oral anticancer drug therapy as shown for capecitabine. An early adherence screening effectively distinguishes between patients adhering and non-adhering to the prescribed regimen. The provision of specific adherence support can enhance adherence of initially non-adherent patients, whereas initially adherent patients remain adherent without specific support. The early identification of potential non-adherers followed by needs-based adherence-enhancing measures may help to use available resources for adherence management efficiently and may contribute to the effectiveness of oral anticancer drug therapy. These results underline the importance of multidisciplinary care to assure the effectiveness of oral anticancer drug therapy.

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Authors

Linda Krolop, PhD
Professor Dr Ulrich Jaehde, PhD
Institute of Pharmacy
Clinical Pharmacy
University of Bonn
4 An der Immenburg
DE-53121 Bonn, Germany

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Oncology medication safety: what steps can you take proactively to risk proof your practice?

The concept of robust and fragile points in our medication system is highlighted. A recent oncology medication safety self assessment is available through the Institute for Safe Medication Practice at https://mssa.ismp-canada.org/oncology and will assist all of us at examining our oncology medication system to address risk points.

Carole Chambers, BSc(Pharm) MBA, FCSHP, FISOPP

Oncology medication safety has been a priority for many years with numerous reviews written and recommendations made [1, 2]. The ultimate goal of these recommendations is to have a medication system in place for oncology agents that is robust. Robust means that should a human error happen at any step, our medication system would be able to detect and correct it prior to the mistake, with its potential for harm, reaching our cancer patient. Alternately, a fragile stage in our medication system is a point at which, if an error was inserted, harm would reach the cancer patient. For those of you able to have attended the 2014 NZW (German Oncology Pharmacy Congress), this paper presents the highlight of the oncology medication safety session held in Hamburg, Germany.

Elements of our medication system that we know about from the literature and professional practice standards have seen practices improve over the last several decades, and some feel are now robust points would be included, but not limited to, the following [3]:

a) Physician ordering of medication – no trailing zeros on medication doses, e.g.15 mg rather than l5.0 mg, decimals framed by a zero, e.g. 0.l rather than .1, no verbal orders for chemotherapy, use of preprinted order templates or computerized physician order entry systems.
b) Pharmacy medication handling – the strategies around look-alike sound-alike drugs such as TALLman lettering [4], the use of generic nomenclature, and no abbreviations.
c) Patient identification – the use of two identifiers to ensure health provider has the correct patient.
d) Vincristine administration in minibags following the WHO Alert 115 [5].

However, there are still ongoing reports of patient harm where these same risk points appear in the review [6-8]. Thus, the learning to take from this is that you need to remain vigilant at maintaining system improvements that we have already got the evidence of harm if they are not in place. I believe the idiom is that those who do not learn from history are bound to repeat it.

A few decades ago, though, these robust stages in our medication system were unknown or unappreciated fragile stages. In the continuing growth of this area of practice, due to both an increased number of cancer patients and the drugs used to treat their conditions, are there still more or new fragile stages that we should be considering? Some potential fragile stages from the literature may be:

a) height and weight of our patients [9]
b) pharmacy compounding hood set up [10]
c) pharmacy checking method [11]
d) actual drug in the bag for administration [12, 13]
e) point of RN about to begin administration to the patient (oncology medication safety self assessment – MSSA).

Have you ever had the height and weight of your patient transposed in your system? This particular example focused on an electronic ordering system where the height was placed in the weight and the weight placed in the height section. The electronic system did not have alerts to warn the practitioners that this was unlikely an adult human being, and none of the involved health professionals noted this either prior to the patient receiving the incorrect dose of chemotherapy. That electronic system, as well as many other systems, does not provide a pictogram showing what those entries would look like beside a 'normal' adult measurement. The recommendation for that side by side comparison was to quickly alert the health professionals of the mismatch in the height and weight entries.

Our pharmacy compounding hoods offer another point to examine how safe our practices are. The International Society of Oncology Pharmacy Practitioners (ISOPP) recommends that only one drug at a time is within the hood for production. This would be a forcing function that eliminates any possibility of a drug mix up happening within the hood. Practices range though from this one drug in the hood at a time through a number of combinations, such as one patient's medications together, one drug for many patients together, to multiple patients with multiple drugs at the same time.

If you have a person checking the drug that is being prepared by a second person the actual checking process itself could be a fragile point to exam. The Institute for Safe Medication Practice (ISMP) recommends that for at least any high alert medication, which chemotherapy definitely is, should employ an independent check of the vials, prepared syringes, and container labels (drug and diluent) prior to adding it to the solution. A post-production type of checking called 'pull-back' method is less than ideal as

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it relies on human memory versus actual in process checking prior to final admixture. This article does note that newer technologies that allow the post-production option with robotics, bar code scanning with video technology or stored digital images reduce the post-production checking process risks.

Technology is appearing that will actually deal with a fragile point of identifying what drug is in the admixture bag that is being administered to the patient. This takes that step beyond a human check or even surrogates such as bar coding technology. For high hazard agents there is now the emerging technology to test your IV admixture to determine both the drug and its concentration.

An interesting item in the oncology MSSA is the suggested practice that just prior to the nurse starting to administer the chemotherapy to the patient there be a full stop. Everything has been gathered and you are sitting in front of the patient and after this point in time administration has started. Full stop is to confirm you have the right patient, the right drug, the right dose, the right route, and all those other key elements one final time. It is an interesting concept as our cancer patients are being dealt with in very busy environments where this immediate re-focus is considered a best practice recommendation.

Recently, an international oncology MSSA tool was developed and made available during 2012 [14]. All medication systems have some key elements and with a focus on oncology some interesting early results have been shared [7, 15]. This oncology MSSA is available through the ISMP website: https://mssa.ismp-canada.org/oncology and will assist all of us in examining our oncology medication system to address risk points. The few mentioned above are teasers from the literature. If you were to take your practice through the oncology MSSA you would have an individualized risk assessment for your practice or in other words the fragile points in your system that would benefit from attention prior to any patient harm occurring.

Ultimately if we can proactively find those fragile stages in our oncology medication system and take steps to enhance them to a robust level, without patient harm as the teacher, our cancer patients will benefit.

Author

Carole R Chambers, BSc(Pharm) MBA, FCSHP, FISOPP
Director of Pharmacy
Cancer Services
Alberta Health Services Pharmacy
Tom Baker Cancer Clinic Pharmacy
1331-29th Street NW
Calgary, Alberta T2N 4N2, Canada

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Global validated cold chain transport (2°C–8°C) of clinical trials and drugs: challenge for the novel GDP guideline from 2013

Abstract

Many drugs have to be distributed by cold chain. In a climate chamber 3 packaging designs were assayed. The container RCW 25 (Dometic) with thermocouples (delta T) kept test drugs for 56 hours ≤ 8°C at 40°C outside and for 66 h ≥ 2°C at -10°C. Insulation systems are capable to fulfil the GDP (good distribution practice) guideline.

Background

In Germany, there are currently about 6,500 different proprietary medicinal products according to the 'Red List' from 2013. Most of them are stored and transported in temperatures between 15°C to 25°C; about a third are subject to eventual cooling, and an estimated 250 products are subject to a cold chain at 2°C–8°C throughout their entire existence from industrial production until administration to a patient. Based upon the 'Physicochemical stability of parenteral cytostatic, virustatic and supporting drugs' most of these have to be stored and therefore also distributed according to this temperature interval in order to maintain maximum therapeutic effect [1]. For the whole pharmaceutical supply chain composed of the pharmaceutical industry, wholesale trade, as well as hospital or public pharmacies, the revised good distribution practice (GDP) policy [2] creates technical and logistical challenges. The surveillance authorities are additionally concerned since they have to supervise the realization of the novel guideline.

Dr rer nat Thomas Klose, PhD

Dr rer nat Michael Putzker, PhD

Methods

Three different passive cooling transport systems were treated with +4°C WHO-approved thermocouples of 200/400/1,000/3,000 mL volume:

(i) RCW25; Dometic Medical Systems, Hosingen, Luxembourg, see Figure 1a
(ii) BlueLine 30 L; delta T GmbH, Fernwald, Germany, see Figure 1b
(iii) PharmaCase 23 L; delta T GmbH, Fernwald, Germany, see Figure 1c

As test pharmaceuticals, 20 vials filled with water for infusion were used in the PharmaCase box; in the other two boxes (BlueLine and RCW25), 20 or 30 bags each filled with 250 mL of physiological NaCl were used. In each box, three calibrated temperature loggers (ThermoScan Messsonde -40 bis +80°C, delta T, see above) were placed: at the bottom left, in the centre, and in the upper right corner among the pre-cooled 5°C packaged goods. The boxes were incubated in parallel for 72 h at -10°C, +20°C, and +40°C, respectively, in a climate chamber (Beck-Messtechnik, Flein, Germany; accredited to EN ISO 17025:2005), see Figure 2; followed by an evaluation of the logger data (ThermoScan USB-Kit, delta T, see above).

Results

The differences between the logger positions were clearly detectable but not very large (after 72 h, Δ ≤ 2°C each). As expected, coldness had the most impact at the bottom measuring point (worst case), heat at the upper point (worst case), optimum buffering was given in the centre due to the most efficient insulation. The significantly shortest time to exceed or fall below the temperature limits for cold-chain active compounds were observed for the BlueLine box (~ 5 h and ~ 6 h). This outcome is dependent on the limited insulation with only two thermocouples placed above and below the drugs due to the construction of the container. PharmaCase and RCW25 box with cubic arrangement of the thermoelements kept the drugs for 35 and 56 h ≤ 8°C (at +40°C outside incubation temperature), and

Figure 1: Passive insulation-based systems for the quality-assured transport of clinical trials and drugs

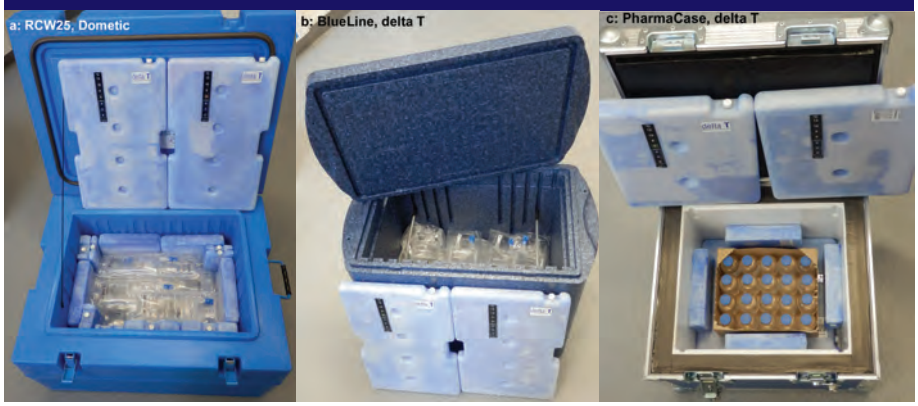

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Table 1: Examination results of the three investigated tranportation systems with respect to the different outside incubation temperatures (–10°C, +20°C, +40°C)

Box	Surrounding temperature	Position of data logger	< 2°C after ~ [h]	> 8°C after ~ [h]
BlueLine	-10°C	bottom left corner	5.50	n.o.
BlueLine	-10°C	centre of goods	6.50	n.o.
BlueLine	-10°C	upper right corner	5.75*	n.o.
BlueLine	+20°C	bottom left corner	n.o.	10.50*
BlueLine	+20°C	centre of goods	n.o.	11.25
BlueLine	+20°C	upper right corner	n.o.	10.75
BlueLine	+40°C	bottom left corner	n.o.	4.75*
BlueLine	+40°C	centre of goods	n.o.	5.50
BlueLine	+40°C	upper right corner	n.o.	5.25
PharmaCase	-10°C	bottom left corner	41.50	n.o.
PharmaCase	-10°C	centre of goods	43.00	n.o.
PharmaCase	-10°C	upper right corner	40.75*	n.o.
PharmaCase	+20°C	bottom left corner	n.o.	> 72
PharmaCase	+20°C	centre of goods	n.o.	> 72
PharmaCase	+20°C	upper right corner	n.o.	> 72
PharmaCase	+40°C	bottom left corner	n.o.	35.25*
PharmaCase	+40°C	centre of goods	n.o.	37.25
PharmaCase	+40°C	upper right corner	n.o.	35.75
RCW25	-10°C	bottom left corner	66.75	n.o.
RCW25	-10°C	centre of goods	68.00	n.o.
RCW25	-10°C	upper right corner	65.75*	n.o.
RCW25	+20°C	bottom left corner	n.o.	> 72
RCW25	+20°C	centre of goods	n.o.	> 72
RCW25	+20°C	upper right corner	n.o.	> 72
RCW25	+40°C	bottom left corner	n.o.	56.25*
RCW25	+40°C	centre of goods	n.o.	58.50
RCW25	+40°C	upper right corner	n.o.	58.00

n.o.: not observed; *worst case.

for 41 and 66 h ≥ 2°C (at -10°C outside incubation temperature). At +20°C the maximum transport time increased both > 72 h, the end of the experimental incubation period, and even BlueLine achieved > 10 h.

Conclusion

Valid insulation-based systems are available for up to 2–3 days of cold chain transport of drugs and clinical trials, without the need of connectivity to a power supply [2–6]. Two of the investigated arrangements provided excellent results, which might be improvable by pre-cooling the box. Based upon these data, concerned substances, such as cytostatic drugs for infusion should be globally transportable in best quality by any part of the supply chain. Further studies should reveal whether parameters such as air pressure (e.g. below atmospheric pressure in the cargo space of an aircraft), humidity, shock (e.g. during the loading process), and vibration (e.g. caused by the engine of the car or van) could negatively affect the quality during transport and have to be taken into consideration in future. Influence has been demonstrated for low atmospheric pressure and vibration concerning red blood cell concentrates during the supply of military field hospitals as well as during humanitarian help in natural disaster scenarios [7].

Figure 2: Incubation design in order to store the three transport systems at –10°C, +20°C and +40°C, respectively, simulating transportation conditions in the climate chamber

Authors

Dr rer nat Thomas Klose, PhD
Pharmacist, Owner and Head of Pharmacy
Dr rer nat Michael Putzker, PhD
Biologist, Head of Quality Management
Sonnenschein Apotheke EK
5 Neversstrasse
DE-56068 Koblenz, Germany

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References 5–7 can be found on page 18.

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