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Guest Authors:

Dr Marta P Trojaniak, Dr Klaus Geissler, Sherif Kamal, Dr Maggie Abbassi, Professor Sherif Abouelnaga, Professor Azza Agha, Sinead Nic Suibhne, Fionnuala King, Veronica Treacy, John Kennedy, Ian Collins, Dr Anita E Weidmann, Heba Farouk El Nokoudy, Professor Mohamed Hany Hussein, Dr Jochem Potenberg, Dr Gisela Sproßmann-Günther, Stacey van den Aardweg, Dr Panos Kanavos

EJOP Editorial Office:

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

EJOP Editorial Board:

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Dr Mikael Daouphars, France
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Professor Dr Günther J Wiedemann, Germany
Dr Bogumila Julia Sobkowiak, Poland
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Publisher:

Lasia Tang - Ltang@ejop.eu

Editor-in-Chief:

Klaus Meier - kmeier@ejop.eu

Senior Executive Editor:

Associate Professor Esra Kurt, PhD, Turkey
ek@ppme.eu

Editors:

Maysoun Delahunty, BA
Bea Perks, PhD

Marketing Assistant/Subscriptions:

Jessica Knopp - info@ppme.eu

Editorial Production Team:

support@ppme.eu

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Cancer declaration 2013 must be constantly brought into consciousness

Since 1990 in Germany, the number of people diagnosed with cancer and requiring treatment has significantly increased. According to 2011 data from The Robert Koch Institute this has been caused by an increase in the proportion of older people in the population, an increase in people requiring long-term treatment, increased incidence rates in some locations, and improved survival prospects for many cancers.

The pronounced demographic changes in Germany have resulted in a marked increase in men diagnosed with cancer (about 80%) compared with women (35%), with the trend reversing in 2010 for the first time since 1990: men (60%); women (40%); projected 5-year prevalence: men (731,000); women (721,000). This trend, however, is not exclusive to Germany. It applies to most European countries with similar standards of living.

On the basis of these and other worldwide data, the Union for International Cancer Control published a declaration in 2013 calling upon government leaders and health policymakers to significantly reduce the global cancer burden, promote greater equity, and integrate cancer control into the world health and development agenda.

The global cancer community has built on the 'global non-communicable diseases action plan' (2013–20) agreed by Member States at the World Health Assembly in May 2013. A set of immediate actions for all stakeholders has been identified, in particular governments, to advance towards the nine World Cancer Declaration targets, and achieve the overarching goal of significantly reducing premature deaths from cancer and improving quality of life and cancer survival rates by 2025.

Target 1 – Health systems will be strengthened to ensure sustained delivery of effective and comprehensive, patient-centred cancer-control programmes across the life-course.

Target 2 – Population-based cancer registries and surveillance systems will be established in all countries to measure the global cancer burden and the effect of national cancer control programmes.

Target 3 – Global tobacco consumption, overweight and obesity, unhealthy diet, alcohol intake, and levels of physical inactivity, as well as exposure to other known cancer risk factors, will have fallen significantly.

Target 4 – The cancer-causing infections, human papilloma virus and hepatitis B, will be covered by universal vaccination programmes.



Klaus Meier
Editor-in-Chief



Target 5 – Stigma associated with cancer will be reduced, and damaging myths and misconceptions about the disease will be dispelled.

Target 6 – Population-based screening and early detection programmes will be universally implemented, and levels of public and professional awareness about important cancer warning signs and symptoms will have improved.

Target 7 – Access to accurate cancer diagnosis, quality multimodal treatment, rehabilitation, supportive and palliative care services, including the availability of affordable essential medicines and technologies, will have improved.

Target 8 – Effective pain control and distress management services will be universally available.

Target 9 – Innovative education and training opportunities for healthcare professionals in all disciplines of cancer control will have improved significantly, particularly in low- and middle-income countries.

The European Society of Oncology Pharmacy (ESOP) has now published this Declaration on its social media platform, Facebook, and has also asked its members to support these goals. We, as oncology pharmacists, must actively ensure that people with cancer are properly and safely cared for, with particular emphasis on pharmacology of anticancer drugs and correct preparation and handling. We must also cooperate with other healthcare professionals in the provision of cancer treatment, which includes pharmacological care of cancer patients, provision of pharmacological advice to doctors and nurses working in oncology, and handling of oncological data.

ESOP has been a member of the European CanCER Organisation (ECCO) since 2003, which became a full member of the Union for International Cancer Control in 2008.

Through its 24 Member Organisations, representing over 50,000 professionals, ECCO is the only multidisciplinary and multi-professional organisation that connects and responds to all stakeholders in oncology Europe-wide. As a non-profit association that exists to uphold the right of all European cancer patients to the best possible treatment and care, ECCO promotes interaction between all organizations involved in cancer research, education, treatment, and care at the European level.

It does this by creating awareness of patients' needs and wishes, encouraging progressive thinking in cancer policy, training and education, and promoting European cancer research through the all organizations of international multidisciplinary meetings.

Metastatic breast cancer—traditional and novel treatment options

Breast cancer is the main cause of death from cancer among women globally. Outcomes have improved as a result of progress in multidisciplinary care, but few patients with metastatic disease are cured. The advent of targeted therapies gives more strategic options for these patients.

Introduction

Breast cancer is the most common malignancy in women [1]. As such, it accounts for more than 20% of the global burden of cancers worldwide. Approximately 6% of breast cancers are metastatic at diagnosis with a 5-year survival rate of 21%. The average 10-year distant recurrence rate in early breast cancer is estimated at between 20% and 30% [2]. It is also the principle cause of death from cancer among women globally. The crude incidence in the European Union is 109.8/100,000 and the mortality is 38.4/100,000 women/year. Since 1990 the incidence rate has increased 1.5% annually [3].

The prevalence of breast cancer is increasing as more women are living with the disease. Outcomes have improved as a result of progress in all major aspects of multidisciplinary care. These include surgery, radiotherapy, hormonal therapy, chemotherapy and newer targeted drugs. Although objective responses to some chemotherapy regimens are common, few patients with metastatic disease are cured and treatments cause substantial adverse events [4]. The advent of targeted therapies, anti-*HER2* and antiangiogenic therapies, gives more strategic options in metastatic breast cancer (mBC) management. These agents are not necessarily less toxic than traditional cytotoxics since potentially they are associated with serious adverse events. Actual research focuses on the development of biological markers of disease; consequently, targeted strategies will continue to become more individualized.

Breast cancer occurs more frequently in older women, but one in four breast cancers is diagnosed in women under the age of 50. In most Western countries, fewer women have died of breast cancer in recent years, especially in younger age groups because of improved treatment and earlier detection.

Treatment options in mBC

Metastatic breast cancer remains essentially incurable, and the main treatment goal is palliation, with the aim of prolongation of overall survival time without negatively impacting quality of life. It is represented, based on the TNM (Tumour, Node, Metastasis) cancer staging system, by stage IV with any T, any N and with M1, indicating the presence of distant recurrences—the TNM staging system is based on the size and/or extent (reach) of the primary tumour (T), whether cancer cells have spread to nearby (regional)



Marta P Trojnik
PharmD

lymph nodes (N), and whether metastasis (M), or the spread of the cancer to other parts of the body, has occurred. The most common sites of distant metastasis are: lymph nodes, bone, lung, liver, brain and skin. Approximately one quarter of patients with lymph node-negative disease, and one half of patients with lymph node-positive tumours will ultimately develop distant recurrent breast cancer. Mortality rates from breast cancer have been decreasing due to advances both in early detection and in treatment option, but it is still the leading cause of cancer mortality in women worldwide [5, 6].

The approach to mBC should consider both patient-related and disease-related factors, when choosing the optimal type of systemic treatment, optimal timing and individualized therapeutic approaches. It is very important to balance between efficacy and toxicity, considering more aggressive and stressful therapy for symptomatic patients in order to relieve their tumour-related symptoms.

Currently, the treatment of patients with mBC involves the use of individualised agents to allow specific targeting, including endocrine therapies for hormone receptor-positive (estrogen receptor (ER)/progesterone receptor (PR) positive) disease, cytotoxic chemotherapy, therapies targeting human epidermal growth factor receptor 2 (*HER2*) and vascular endothelial growth factor (VEGF) pathways. *HER2* has been identified as an important target for breast cancer [7, 8].

In practice, whilst many clinical trials in women with mBC have shown higher response rates and/or progression-free survival (PFS), very few have demonstrated prolonged overall survival.

Increasing availability of improved therapies has contributed to improved trends in survival in the last two decades. The major shift was observed during the 1990s following the introduction of new agents effective in the metastatic setting: taxanes (paclitaxel, docetaxel), the aromatase inhibitors (anastrozole, exemestane, letrozole), the *HER2* targeted agents (trastuzumab), and anthracyclines, vinorelbine, gemcitabine and capecitabine. More recently, albumin-bound paclitaxel (abraxane) and the *HER2*-targeted agent lapatinib have been added, alongside the epothilone B analogue ixabepilone, and



the anti-VEGF targeted antibody bevacizumab, although its ability to prolong overall survival has recently been called into question. This availability of effective treatment agents for mBC has played an important role in expanding the number of agents able to control the spread of the disease, prolong PFS or even prolong survival.

Patients with mBC can be stratified according to the molecular characteristics (ER, PR and *HER2* status) and the presence or absence of bone metastasis, and then further stratified.

For patients with ER/PR-positive cancers, unless there has been a short disease-free interval or they have rapidly progressive visceral disease; endocrine therapy should be the first option, with the choice of agent based upon the patient's menopausal status and prior adjuvant therapy. In postmenopausal women first-line hormonal therapy consists of tamoxifen or the 3rd generation aromatase inhibitors daily oral treatment [9]. Randomized controlled trials (RCTs) have shown that aromatase inhibitors are superior to tamoxifen as a first-line treatment [10-13]. In premenopausal women, the first-line option is luteinizing-hormone-releasing hormone analogues as a monthly intramuscular injection. The decision of the type of endocrine therapy should take into account the differences in side effects profiles among these agents [14]. If and when these women relapse, they may receive subsequent lines of endocrine therapy, such as fulvestrant monthly intramuscular injection, until they become refractory to such treatments or their disease becomes more aggressive [15]. At that point they should start chemotherapy. The chemotherapy may consist of a single agent, especially in the case of aggressive and symptomatic disease. Polyagent chemotherapy is used for visceral crisis or disease requiring rapid response.

For those patients with *HER2*-positive cancers, the majority of which are ER/PR- negative, treatment choices include the *HER2*-targeted agents such as trastuzumab and lapatinib, usually in combination with cytotoxic chemotherapy, i.e. paclitaxel and capecitabine. Women with breast cancers that over-express *HER2* have an aggressive form of the disease with significantly shortened disease-free survival and overall survival [16]. *HER2* is over expressed in 25–30% of breast

cancers. The overexpression of *HER2* is measured by immunohistochemistry, and graded as 0, 1+, 2+ and 3+ based on staining characteristics. Negative results are represented by 0 and 1+, while 2+ is an equivocal or borderline result, which should be followed with fluorescent *in situ* hybridization (FISH) to determine status (amplified or not amplified). A grading of 3+ represents a positive result and does not need further FISH confirmation. A better response rate is achievable when trastuzumab is combined with standard chemotherapy, such as paclitaxel, docetaxel, vinorelbine, gemcitabine, capecitabine or taxane and platinum based protocol. As compared with chemotherapy alone, treatment with chemotherapy plus trastuzumab was associated with a significantly higher rate of overall response (50% vs 32%, $p < 0.001$), a longer duration of response (median, 9.1 vs 6.1 months; $p < 0.001$), and a longer time to treatment failure (median, 6.9 vs 4.5 months; $p < 0.001$). When adding trastuzumab to the standard chemotherapy, the median survival was 25.1 months in the group given chemotherapy plus trastuzumab and 20.3 months in the group that received chemotherapy alone ($p = 0.046$) [17]. A phase III randomised clinical trial comparing lapatinib and capecitabine versus capecitabine alone revealed that the median time to progression was 8.4 months with lapatinib and capecitabine and 4.4 months with capecitabine alone [18]. These data indicate that lapatinib in combination with capecitabine is superior to capecitabine alone in women with *HER2*-positive breast cancer that has progressed after treatment regimens that included trastuzumab. It is still not clear if lapatinib is superior to trastuzumab in mBC patients with cerebral metastasis.

For those patients with triple negative breast cancer, the majority of which are ER/PR/*HER2*- negative, cytotoxic chemotherapy is a mainstay of treatment [19]. The triple negative breast cancer is characterized by an aggressive biology with increased early recurrence risk and significantly inferior survival. The sites of metastasis are preferentially visceral, with a high rate of central nervous system metastasis. The emerging targeted agents, such as poly (ADP)-ribose polymerase inhibitor (iniparib) [20, 21], EGFR (epidermal growth factor receptor) and angiogenesis inhibitors (bevacizumab), were found to increase progression-free survival but are rarely able to improve overall survival.

For all patients, other considerations regarding disease stratification include their performance status, co-morbidities, disease-free interval and prior therapy as well as their personal preferences.

In addition to the specific biomarkers, such as ER, PR or *HER2*, the genetic type may also be important when choosing the optimal treatment.

The combination of the results regarding hormone receptor status, *HER2* status and Ki-67 labelling index (determines the level of cell proliferation) is used to classify breast cancer in four subtypes: luminal A, luminal B, *HER2* type, and triple

negative. This is also important in order to know which therapies are most likely to be effective because each of these subtypes respond differently to treatment. Overall, clinical challenges in mBC consist of individualizing treatment to specific biology, reducing and managing toxicity of therapy, overcoming resistance to chemotherapy and hormone therapy, and increasing disease control and survival. The impact of recent advances has been modest and there remain many challenges [22].

A great deal of effort has been expended in recent years on the development of new cytotoxic and targeted therapies for mBC. Such agents include albumin-bound paclitaxel (Abraxane), the *HER2*-targeted agent lapatinib, trastuzumab-DM1, non taxane micro-tubule inhibitors such as the epothilone B analogue ixabepilone and erbulin, anti-VEGF targeted antibody bevacizumab and tyrosine kinase inhibitors (sunitinib, axitinib), poly ADP ribose polymerase inhibitors (iniparib, olaparib), and the mechanistic target of rapamycin (mTOR) inhibitor everolimus [23-28]. This ever-increasing availability of effective treatment agents for mBC has played an important role in controlling the spread of the disease. New agents are often added to the standard treatment in order to enhance the clinical outcomes. A common characteristic among these therapies is their ability to target cancer cells, enhancing the potency and reducing toxicity compared with the standard cytotoxics.

Discussion

Treatment options for metastatic breast cancer range from chemotherapy, endocrine therapy, and psychosocial interventions to supportive care. Women with advanced breast cancer have an average survival of about two years, although some of them may live for many years beyond this. Therefore, it is important to investigate different systemic treatment options that can improve survival outcomes taking into account possible side effects and quality of life. The sites of the metastases influence decisions regarding the timing and aggressiveness of therapy. There are many chemotherapeutic agents that have reasonable activity against breast cancer. There is no evidence, however, that any specific sequence of chemotherapy is superior and that use of combination chemotherapy rather than single cytotoxic drugs improves overall survival. Anthracycline and taxane-based therapies have traditionally shown the highest degree of activity in mBC. Hormonal therapy is the preferred systemic treatment for patients with ER/PR-positive mBC with an indolent course or with asymptomatic visceral disease allowing for delayed cytotoxic therapy. As for chemotherapy, optimal sequencing of various endocrine agents and their role in combination regimens has not yet been resolved.

The advent of 'targeted' therapies, anti-*HER2* and antiangiogenic therapies, gives more strategic options in mBC management. These agents are not necessarily less toxic than traditional cytotoxics since potentially they are associated with serious adverse events. Actual research focuses on the development of

biological markers of disease; consequently targeted strategies will continue to become more individualised.

The requirement for every new drug approval is a demonstration of net clinical benefit, but even randomised clinical trials could fail to show relevance in modifying the natural history of a disease in clinical practice. As demonstrated for bevacizumab in mBC, after 'accelerated approval' intended to get novel treatments to patients sooner, follow-up trials indicated no improvement in overall survival, according to US FDA. There are increasing questions about the use of antiangiogenic therapy in this setting. Performing the same treatment in the general population may yield considerable differences from a RCT because the treatment conditions are less well defined (patients, diagnosis and treatment variations) and more patients are involved.

Conclusion

While providing life-extending treatments with chemotherapy, hormonal therapy, and targeted therapies, supportive care is also very important in order to optimize the management of fatigue and pain. Patients' preferences should always be taken into account regarding both treatment options and methods of treatment administration. Post-marketing studies are essential in order to verify both effectiveness and safety in the general population, testing the external validity of the randomized trials. This kind of assessment is lacking in randomized clinical trials, further emphasizing the importance of multicentre observational investigations of clinical practice. When a drug enters the market after approval, clinical trials may leave residual but important questions from the prescriber's and payer's point of view: the effectiveness may differ from that seen in an experimental setting, as may the frequency and nature of adverse events. The national health systems worldwide need new tools to determine the price of new drugs and health technologies.

Author

Marta P Trojaniak, PharmD
Pharmacist
Oncology Pharmacy Department
Venetian Oncology Institute (Istituto Oncologico Veneto, IRCCS)
64 via Gattamelata
IT-35128 Padova, Italy

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What is the right timing for chemotherapy

Few studies have investigated the right timing for chemotherapy, so the best moment to start and to stop cytotoxic treatment remains an important issue for scientific discussion. Here, we summarize the latest findings from clinical trials in order to give some answers to open questions.

Introduction

An enormous number of clinical studies are demonstrating the efficacy and toxicity of antineoplastic therapy in cancer patients; however, the number of studies investigating the right timing of chemotherapy (CT) is limited. Therefore, the question with regard to the right moment to start and to stop cytotoxic treatment remains an important issue for scientific discussion. Timing of CT is important for several practical and theoretical reasons. Diagnosis of cancer is a life-threatening event that patients, and sometimes physicians, may react hastily to because of their intuitive beliefs that immediate treatment will result in improved outcome. Immediate treatment, however, may compromise a patient's opportunity to address several issues that are important to them. For example, young patients who are supposed to receive CT that might cause infertility may not have sufficient time to donate eggs or sperms. In other patients there may be different personal matters to attend to before initiating treatment, including work or insurance issues. From a theoretical point of view, cell biological issues also have to be considered. Thus, the emergence of resistant cell clones may be affected by the temporal design of chemotherapy, which may be an important variable with respect to outcome. Basic questions with regard to the right moment to stop chemotherapy are also important. For instance, longer than needed treatment will expose the patient to chemotherapy toxicity without providing benefit in terms of superior survival. It is therefore fundamental to determine the optimal timing for the administration of currently used CTs. Here, information from clinical trials is summarized in order to give some answers to open questions.

When to start chemotherapy in operable cancer

In the preclinical mouse model, studies trying to find out the optimal timing of CT in relation to surgery have given conflicting results. In an osteosarcoma tumour model that investigated the efficacy of preoperative, perioperative and postoperative CT on the development of pulmonary metastases, a significant advantage in preventing relapse by perioperative CT was demonstrated [1]. In another study, marginally effective adjuvant therapy was found to become effective when started preoperatively, and in the second model effective adjuvant therapy was found to be less effective when started preoperatively [2]. Summarizing these data it becomes clear that it is not justified to generalise statements regarding the benefit or harm, respectively, of preoperative CT, but it is necessary to address this question in every specific entity separately. Such clinical trials have been



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performed in entities including breast and bladder tumours. One major trial on this topic is the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18 that was initiated in 1988 to determine whether four cycles of doxorubicin/cyclophosphamide given preoperatively improve overall survival (OS) and disease-free survival (DFS) when compared with the same CT given postoperatively. An update of this study through nine years of follow-up showed no statistically significant differences in OS or DFS between

the two treatment groups [3]. Survival at nine years was 70% in the postoperative group and 69% in the preoperative group ($p = 0.80$). DFS was 53% in postoperative patients and 55% in preoperative patients ($p = 0.50$). In patients with bladder cancer, there is only evidence from retrospective studies. In one of these studies 146 patients who received systemic perioperative CT (73 neoadjuvant, 73 adjuvant) were analyzed [4]. Of these, 84% (122/146) received cisplatin-based CT compared with carboplatin-based CT (24/146, 16.4%). In multivariable analysis, there was no significant difference in disease-specific survival (DSS) ($p = 0.46$) or OS ($p = 0.76$) between neoadjuvant or adjuvant CT groups. There was statistically significant improvement in DSS, however, when patients received neoadjuvant gemcitabine/cisplatin (GC) rather than adjuvant GC— $p = 0.049$; hazard ratio (HR): 10.6; 95% confidence interval (CI): 1.01–112.2.

When to start adjuvant chemotherapy in cancer

In colon cancer patients who are candidates for adjuvant antineoplastic therapy, delay of CT for more than three months is consistently associated with worse outcome in retrospective analyses. Among 4,382 patients with colon cancer, 1,122 patients (26%) began adjuvant CT within one month, 2,391 patients (55%) began adjuvant CT in one to two months, 454 patients (10%) began adjuvant CT in two to three months, and 415 patients (9%) began adjuvant CT > 3 months after surgery [5]. Intervals of > 3 months (delay) were associated with older age, increased comorbid conditions, well/moderately differentiated grade, and being unmarried. Also colon cancer-specific mortality was associated with a delay > 3 months in the initiation of CT (HR: 1.48; CI: 1.15–1.92). In a meta-analysis comparing delayed CT with standard care, eight studies could be used for analysis, including 13,158 patients (5,576 colon cancers, 6,677 rectal, 1,265 missing data) [6]. Delaying CT more than eight weeks was associated with worse OS (RR: 1.20; CI: 1.15–1.26). In the meta-analysis including all studies whatever their cut off, longer delay was similarly

associated with a worse OS but not a worse relapse-free survival (RFS) (five studies).

In breast cancer patients, delay of adjuvant CT was generally not associated with worse outcome in the majority of retrospective studies. In the nation-wide clinical trials of the Danish Breast Cancer Cooperative Group, 7,501 breast cancer patients received CT within three months of surgery between 1977 and 1999: 352 with classical cyclophosphamide, methotrexate and 5FU (CMF), 6,065 with intravenous CMF and 1,084 with cyclophosphamide, epirubicin and 5FU [7]. For the analysis, the time between surgery and the start of CT was divided into four strata (1–3, 4, 5 and 6–13 weeks). There was no pattern indicating a benefit from early start of CT. In one study it was shown, however, that among patients with ER-absent tumours, the 10-year DFS was 60% for the early initiation group (within 20 days) compared with 34% for the conventional initiation group (226 patients; HR: 0.49; CI: 0.33–0.72; $p = 0.0003$) [8].

When to stop adjuvant chemotherapy

To evaluate the optimal duration of adjuvant treatment, a meta-analysis of all randomised controlled trials (RCTs) between 1998 and 2009 comparing two durations of adjuvant treatment—six months versus nine to 12 months in patients with surgically resected colorectal cancer with high risk of recurrence—was performed [9]. Several RCTs compared shorter versus longer durations of CT, 6 studies for OS and 7 studies for RFS, for a total of 10,326 patients, mean age 63.1 years, including 9,826 colon and 500 rectum cancers. Treatments were always based on 5FU. Shorter duration of CT (3–6 months) compared with longer duration (9–12 months) was not associated with poorer RFS (RR = 0.96; CI: 0.90–1.02) and OS (RR = 0.96; 95% CI: 0.91–1.02). Thus, this meta-analysis confirmed that adjuvant CT of CRC should not last for more than six months. Prolonged duration would result in lower benefit to risk ratio. However, based on these results it was not possible to favour either 3- or 6-month durations. In a retrospective study including 1,722 patients ≥ 65 years who received one to seven months of FU-based CT, older age, being unmarried, and having comorbid conditions were associated with receiving less than five months of treatment [10]. Among the 1,579 patients who survived ≥ 8 months, the 1,091 (69.1%) who received five to seven months of treatment had lower overall (HR: 0.59; CI: 0.49–0.71) and colon cancer-specific (HR: 0.53; CI: 0.43–0.66) mortality than the 488 (30.9%) who received one to four months of treatment.

When to start palliative chemotherapy in cancer

A seminal study in patients with chronic lymphocytic leukaemia (CLL) was one of the first trials addressing the question if CT benefits asymptomatic patients with incurable malignant disease.

In the first trial, 609 patients with stage A CLL were randomly assigned to receive either daily chlorambucil or no treatment; in the second trial, 926 patients were randomly assigned to receive either intermittent chlorambucil plus prednisone or no treatment. Treatment of indolent CLL did not increase survival in either

trial [11]. In the treated group, as compared with the untreated group, the relative risk of death was 1.14 (CI: 0.92–1.41; $p = 0.23$) in the first trial and 0.96 (CI: 0.75–1.23; $p = 0.74$) in the second trial, with 76% and 69% of patients, respectively, having a response to therapy. Since deferring therapy until the disease progresses to stage B or C does not compromise survival, treatment of indolent CLL is unnecessary.

In solid tumours, a prospectively planned meta-analysis combining two almost identical trials undertaken in Australasia and Canada to study the effect of starting chemotherapy immediately in asymptomatic patients with metastatic colorectal cancer was reported [12]. Patients ($n = 168$) were randomised to receive either immediate or delayed treatment (at onset of predefined symptoms). Median survival was not significantly better with immediate treatment (median 13 vs 11 months; HR: 1.15; CI: 0.79–1.72; $p = 0.49$). There was no statistically significant difference in PFS (time from randomization until first evidence of progression after chemotherapy, 10.2 vs 10.8 months; HR: 1.08; CI 0.71–1.64; $p = 0.73$). There was no difference in overall quality of life (QoL) or its individual domains between the two treatment strategies at baseline or at any subsequent time point. Early treatment of asymptomatic patients with metastatic colorectal cancer did not provide a survival benefit or improve QoL compared to withholding treatment until symptoms occurred.

A meta-analysis including 3,811 asymptomatic patients from 10 randomised trials was performed in order to address this question also in other advanced malignancies [13]. The review analysed three studies each in prostate cancer and multiple myeloma, two in CLL, and one each in lung cancer, and follicular lymphoma. The treatment studied in these trials was endocrine treatment in all three prostate cancer trials, radiation in the lung cancer trial, and chemotherapy in all other tumour entities. The analyses showed no survival benefit with early treatment except in prostate cancer—HR: 1.23, 95% CI: 1.11–1.37; $p < 0.001$. In trials using chemotherapy there was no survival difference in multiple myeloma, CLL, or follicular lymphoma. No statistically significant difference in response rate between early and late treatment was detected in any cancer type. Data shows that delaying cancer treatments does not necessarily compromise therapeutic outcomes except possibly in locally advanced prostate cancer using endocrine treatment.

When to stop palliative chemotherapy in cancer

This question has been addressed in randomised trials in breast cancer and colon cancer. The first trial, which addressed this fundamental question, was a trial that included 250 women with metastatic breast cancer who received six courses of cyclophosphamide (CY), doxorubicin, and FU given every three weeks [14]. Women whose disease either regressed or remained stable were randomly assigned to receive either continued treatment with CY, methotrexate, and FU or no further treatment. The median time to progression was 9.4 months for patients in the maintenance-therapy group and 3.2 months for patients in the observation group ($p > 0.001$) but the median

length of survival from the time of initial therapy was not significantly different (21.1 vs 19.6 months). Regarding toxicity, nausea, vomiting and mucositis were more frequent in the maintenance group. Following trials on this topic using modern CTs basically confirmed these results leading to the conclusion that in breast cancer patients' maintenance chemotherapy following induction chemotherapy does not improve OS but increases toxicity in the palliative setting.

Colorectal cancer is another entity where trials like this have been performed in a large cohort of patients. In one of these trials, patients with metastatic colorectal cancer received continuous oxaliplatin and fluoropyrimidine combination (arm A), continuous CT plus cetuximab (arm B), or intermittent (arm C) CT [15]. Whereas treatment continued until development of progressive disease, cumulative toxic effects, or the patient chose to stop in arms A and B, patients in arm C, who had not progressed at their 12-week scan, started a CT-free interval until evidence of disease progression, when the same treatment was restarted. Median survival in the 'intent to treat' population (n = 815 in both groups) was 15.8 months in arm A and 14.4 months in arm C (HR: 1.084). Pre-planned subgroup analyses in the per-protocol population showed that a raised baseline platelet count, defined as ≥ 400.000 per μL was associated with poor survival with intermittent CT. Thus, stopping CT after 12 weeks and restarting treatment on progress may be a reasonable and less toxic option in patients with metastatic colorectal cancer without increased platelet counts.

Recently, a provocative study questioned the role of uncritical administration of CT in advanced cancer in general. Patients with newly diagnosed metastatic non-small-cell lung cancer were randomly assigned to receive either early palliative care integrated with standard oncologic care or standard oncologic care alone [16]. Patients assigned to early palliative care had a better QoL than did patients assigned to standard care—mean score on the FACT-L scale—in which scores range from 0 to 136, with higher scores indicating better QoL, 98.0 vs 91.5; $p = 0.03$. In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs 38%, $p = 0.01$). Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care (33% vs 54%, $p = 0.05$), median survival was longer among patients receiving early palliative care (11.6 months vs 8.9 months, $p = 0.02$).

Author

Klaus Geissler, MD
Ludwig Boltzmann Institute for Clinical Oncology
1 Wolkersbergenstraße
AT-1130 Vienna, Austria

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Valproic acid use in paediatric oncology in Egypt

— Sherif Kamal, BSc, RPh; Maggie Abbassi, PhD; Professor Sherif A Abouelnaga, MD, PhD; Professor Azza Agha, PhD

Abstract

Introduction: Valproic acid (VPA) is a broad-spectrum anticonvulsant drug. The risk of seizures varies by tumour type and its location in the brain. Post-operative seizure prophylaxis after brain tumour resection is still controversial.

Methods: A prospective study of paediatric brain tumour patients was performed to evaluate the effect of VPA on post-operative seizure prophylaxis. The patients were monitored for a period of 3 months post-operatively to determine whether VPA was effective in prophylaxis from seizures.

Results: Eligible patients were 120 and for the retrospective arm were 62. Post-operatively, a total of 15 patients had seizures, 3 patients in the VPA group with an onset of 12, 15 and 60 days, and 12 patients in the non-VPA group with an average onset of 23 days. Comparing the incidence of seizures post-operatively using Fisher's exact test, the difference between the two groups was not statistically significantly different ($p = 0.0714$).

Conclusion: Although VPA tended to reduce the incidence of seizure events and to delay the onset of seizures post-operatively in brain tumour patients, the difference did not reach statistical significance. Further studies are needed to investigate this difference on a larger number of patients to examine whether the difference observed is real, to investigate the anticancer effect of VPA and to investigate the prophylactic potential of other new generation antiepileptic drugs (AEDs). On the other hand, effort needs to be done to routinely monitor the side effects and seizure severity scale. Further studies need to validate the scales to be used.

Keywords: AED, epilepsy, post-operative, prophylaxis, side effects

Introduction

Patients with brain tumours have a complex therapeutic profile. Antiepileptic drugs (AEDs), chemotherapy, and supportive care should be considered for patients with epilepsy associated with brain tumours [1]. Around 3% of all children younger than 15 years with a brain tumour have seizures [2]. Four per cent of patients with brain tumours who suffer from seizures are epileptic [3]. An epileptic seizure is the presenting clinical sign of a tumour in 25% of the patients, and 10-30% will develop seizures later in their disease progression [4-10].

The risk of epileptogenesis depends on histological type of brain tumour, grade, location, and the individual's genetic susceptibility [11-13]. Patients with tumours are at an increased risk of developing recurrent seizures when seizures are the presenting symptom of a tumour regardless of tumour type and antiepileptic treatment [14].

The routine use of post-operative anticonvulsants is not recommended in patients with newly diagnosed primary or secondary brain tumours who do not experience seizures [15].

On the basis of a meta-analysis of four randomized-controlled clinical trials [10-12, 16], the Quality Standards Subcommittee of the American Academy of Neurology does not recommend the routine use of prophylactic antiepileptics in patients with newly diagnosed brain tumours [17]. It has been shown, however, that many physicians (33% of radiation oncologists, 53% of neurologists, and 81% of neurosurgeons) routinely use AED to prevent new onset seizures in patients with cerebral tumours [18]; in particular, neurosurgeons still prescribe AED

for patients with brain tumours who have no history of seizures [19-22].

Methods

Study design

We conducted a prospective study at the Children's Cancer Hospital Egypt to evaluate the effect of VPA on post-operative seizure prophylaxis between May 2011 and September 2012.

Children eligible for inclusion were interviewed at week 1, and at months 1, 2 and 3 after surgery. The children were followed in the intensive care unit and in the inpatient ward, and the laboratory values included in the study were recorded. Data collected included: age, sex, weight, prescribed antiepileptic drugs, platelet count, albumin and liver enzymes, duration of VPA treatment, serum VPA concentration, and any other medications the child was receiving. Any clinical intervention and drug interactions were recorded in the designed patient sheet.

Participants

The children were selected from the Cerner power chart patient list, as they were admitted to the neuro-oncology clinic of the hospital after May 2011.

Inclusion criteria

The following criteria were used for patients selection: hospitalized children (aged 0–18 years) diagnosed with a brain tumour and undergoing brain tumour resection; and children either receiving a constant dose of VPA for at least five days after surgery (VPA group) or no antiepileptic medication other than phenytoin peri-operatively (non-VPA group).

Exclusion criteria

Children were excluded from the study on the following basis: those with underlying disorders or medication that predisposes them to thrombocytopaenia; severe hepatic, renal impairment, or both; and children taking AED other than VPA.

Patient data needed to be complete for the 3-month period of study, and patients who died or missed follow-up were excluded from the study.

Valproic acid therapeutic drug monitoring

We followed our patient list and obtained results at weeks 1, and months 1, 2, and 3 after surgery. The assay was measured in the Pharmacokinetic Laboratory, Department of Pharmaceutical Services at the Children's Cancer Hospital Egypt. Serum samples were taken before the morning dose was administered at the scheduled time at week 1, and months 1, 2 and 3. Enzyme multiplied immunoassay method (Viva E) was used for determining the serum VPA concentration.

Outcomes measurements

Onset of seizures after starting VPA treatment was calculated by measuring the number of days between the date of surgery and the start of the first seizure. The number of patients having seizures from the different groups was established from the neurologist's records. Serum albumin, platelets, liver enzymes and VPA levels were determined as markers of VPA adverse effects.

The data for the onset of seizure were then analyzed by Fisher's exact method using GraphPad online statistical calculator (www.graphpad.com/quickcalcs/contingency2). The data for the laboratory results were then analyzed by ANOVA method using online software (www.danielsoper.com/statcalc3).

Correlation studies

Vaproic acid and weight gain

We investigated the possible causal link between treatment and weight gain in children with epilepsy, patients were categorized by age and weight during week 1, and months 1, 2 and 3, and statistically analysed for significant differences in weight increases in the VPA group compared with the non-VPA group.

Valproic acid and thrombocytopaenia

Correlation between VPA level and thrombocytopaenia was measured by comparing VPA groups and non-VPA groups at week 1, and months 1, 2 and 3, using the online Spearman's rank test calculator (www.maccery.com/math).

Effect of clinical pharmacy services on patient satisfaction

The children, parents, or both, were interviewed at the Multi-specialty Clinic at the Children's Cancer Hospital Egypt, where

the clinical pharmacy service was provided for the neurology clinic.

Physicians and nurses were also interviewed by questionnaire to evaluate their satisfaction about the service provided by the pharmacy.

Results

All patients were recruited from the Children's Cancer Hospital Egypt. The total number eligible for inclusion was 120. Four patients from the VPA group had a history of seizures compared with only one patient in the non-VPA group. Post-operatively, a total of 15 patients had seizures (24%), three in the VPA group (11.5%) with an onset of 12, 15 and 60 days, and 12 in the non-VPA group (33%), with an average onset of 23 days. The incidence of seizures post-operatively was compared using Fisher's exact test (two tails); the difference between the two groups was not statistically significantly different ($p = 0.0714$).

Slow-growing tumours, such as oligodendrogliomas, are associated with a high risk for occurrence of seizures. Tumour surgery cures many cases of seizures associated with paediatric tumour, and some children are controlled with AED medication; however, additional epilepsy surgery may be needed for refractory cases.

The student's t-test was used to measure statistically significant differences between platelet counts in the VPA group and the non-VPA group only after the third month: $p = 0.006$, mean values were 235 ± 143 in the VPA group and 359 ± 105 in the non-VPA group. The t-test was used to measure changes in weight liver enzymes, and kidney function in the 3-month study period; however, no statistically significant differences were found between the two groups.

The Spearman correlation was used to measure VPA level and platelet count. Linear correlation ranged from strong correlation in week 1 (Spearman rank [SR] = 0.72) then moderate correlation in month 1 (SR = 0.56), 2 (SR = 0.58) and 3 (SR = 0.64).

Linear regression VPA level and platelet count showed $R^2 = 0.002$ with Y (platelet count) = $403.16337958067 - 1.5603807627699x$.

In the VPA group, one patient with temporal region brain tumour had a seizure, and two patients with supratentorial peripheral neuroectodermal tumour had a seizure.

In the non-VPA group, children with the following conditions had seizures: temporal region brain ($n = 3$; 25%); craniopharngioma ($n = 2$; 16%) ependymoma ($n = 1$; 7.6%), ganglioglioma ($n = 1$; 7.6%), gliosarcoma ($n = 1$; 7.6%), peripheral neuroectodermal tumour ($n = 1$; 7.6%), cerebral tumours ($n = 1$; 7.6%), atypical teratoid rhabdoid tumour ($n = 1$; 7.6%), and subependymal giant cell astrocytoma ($n = 1$; 7.6%).

Effect of pharmacy services in paediatric neuro-oncology

One hundred and eighty-three children visiting the neurology clinic were interviewed: 113 boys and 70 girls. Seventy-six children aged between 0 and 3 years; 74 children aged between 3 and 6 years; and 33 children aged between 6 and 9 years.

Parent's educational backgrounds were high school (38%) and diploma education (62%). Only 8.9% of parents were in healthcare-related jobs.

Out of the 183 patients surveyed for their satisfaction of neuro-oncology pharmacy services, the following ratings between 1 and 10 were obtained: 1 (n = 1; 2%); 2 (n = 2; 4%); 3 (n = 3; 5%); 4 (n = 4; 7%); 5 (n = 5; 9%); 6 (n = 15; 11%); 7 (n = 35; 13%); 8 (n = 30; 16%); 9 (n = 29; 16%); 10 (n = 30; 16%).

Physician and nurse views about pharmacy services were as follows: 4.5% of respondents felt that clinical pharmacists could be replaced by doctors or nurses, whereas 95.5% disagreed.

A total of 62.5% of physicians and nurses were satisfied with the services provided by the pharmacy; 6.2% were not satisfied; and 31.2% were somewhat satisfied. A total of 72.7% of physicians and nurses said that they were satisfied by the level of care provided by the pharmacy; 18.1% of respondents were not satisfied; and 9.2% of respondents said that they were somewhat satisfied. A total of 75% of respondents agreed that management supported the pharmacist staff in the hospital; 18.5% of respondents disagreed; and 6.5% of respondents said that this support was somewhat present.

Physicians and nurses evaluated the behaviour of pharmacists at work: 12.5% of respondents rated their behavior as excellent; 37.5% agreed that it was very good, 31.3% of responders rated it as good; and 18.7% rated it as acceptable.

The efficiency of the pharmacy in dealing directly with staff was rated as follows: excellent (13.3%); very good (53%); good (13.3%); and acceptable (20.4%).

A total of 75% of respondents agreed that the pharmacy had sufficient stock, and 81% agreed that the products stocked in the pharmacy were of high quality.

Respondents were asked to rate the ideal way of running a pharmacy, and the following results were obtained: organization (37%); efficiency (30%); attention to detail (10%); use of high-tech equipment (6%); and access to pharmaceutical care (17%).

Conclusion and discussion

Valproic acid tended to reduce the incidence of seizures and delay the onset of seizures post-operatively in children with brain tumours; however, the difference did not reach statistical significance. Further studies are needed to investigate this

difference on a larger number of patients to examine whether the observed difference is real. Future research is also needed to establish the anticancer effect of VPA.

In our study, four children from the VPA group had a history of seizures compared with only one child in the non-VPA group. Post-operatively, a total of 15 children had seizures (24%), three in the VPA group (11.5%), with an onset of 12, 15 and 60 days, and 12 in the non-VPA group (33%), with an average onset of 23 days. The incidence of post-operative seizures, measured by Fisher's exact test (two tails), was not statistically significantly different between the two groups ($p = 0.0714$).

In our study we aimed to establish whether children with newly diagnosed brain tumours should receive prophylactic VPA to reduce seizure risk.

The average and standard deviation of VPA levels were as follows: in week 1 (58 ± 27); month 1 (52.9 ± 20); month 2 (54 ± 17.8); and month 3 (55 ± 18.97).

The service provided by our laboratory, and the added value of the provision and follow up of recommendations made by the clinical pharmacy service, reduced failure of treatment as a result of sub-therapeutic levels.

In our study, 30% of children receiving anticonvulsant prophylaxis who experienced a seizure had sub-therapeutic levels of that drug. Compared with a later study [6], 23% of patients receiving anticonvulsant prophylaxis who experienced a seizure had sub-therapeutic levels of the drug, and the author concluded that this might be one explanation for the ineffectiveness of anticonvulsant prophylaxis in some patients [6].

When analyzing the albumin laboratory results, levels in all age groups in both study groups were low. The two-tailed t-test p value was less than 0.0001 in both study groups; this difference is considered to be extremely statistically significant. This is indicative of protein energy malnutrition according to Deeb [22].

Vecht and Breemen [11] stated that AED are ineffective seizure prophylaxis in some patients, and increase the risk of complications in other patients. In our population using VPA, no increased clinical toxicity was observed.

Schaller and Ruegg [23] postulated three reasons for the failure of AED to prevent seizures in patients with brain tumours. First, the AED mechanism of action does not cover the mechanism of cancer-mediated seizures. Second, seizures may occur because of tumour progression, which is not affected by AED. Third, AED have insufficient serum concentration owing to drug interactions or reduced plasma protein levels.

Glantz et al. [6] found that 33% of radiation oncologists, 53% of neurologists, and 81% of neurosurgeons routinely

used AEDs to prevent new-onset seizures in patients with cerebral tumours. Other studies have shown that physicians often administer anticonvulsant medication prophylactically to patients with brain tumours without evidence that prophylactic anticonvulsant therapy is effective in preventing first seizures [24-27]. In 2000, The American Academy of Neurology devised a practice parameter against the use of prophylaxis; however, controversy still persists. In 2004, Sirven et al. [28] summarized the convincing body of literature showing lack of efficacy of prophylactic AED treatment in this context. More double-blind randomized-controlled trials are needed to determine whether newer AEDs can prevent seizures resulting from brain tumours.

In clinical practice, the clinical decision to start a patient on an AED should be based on the judgement that the risk of seizure occurrence is higher than the risk of AEDs toxic effects.

Author for correspondence

Sherif Kamal, BSc, RPh
Director, Department of Pharmaceutical Services
Children's Cancer Hospital Egypt 57357
Seket Al-Emam Street
El-Madbah El-Kadeem Yard
El-Saida Zenab
Cairo, Egypt

Co-authors

Maggie Abbassi, PhD
Clinical Pharmacy Department
Cairo University

Professor Sherif Abouelnaga Abouelnaga, MD, PhD
Vice President, Academic Affairs, Training and Outreach
Children's Cancer Hospital Egypt 57357

Professor Azza Agha, PhD
Dean, Faculty of Pharmacy
Cairo University

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References 23–28 can be found on page 6.

Toxicity and dose intensity of FOLFOX in patients with increased body mass index

This study was conducted at St James's Hospital, Dublin, Ireland, in 2010. It evaluated the dose intensity and toxicities experienced by patients of normal and increased body mass index treated with FOLFOX chemotherapy, and demonstrated that overweight patients may tolerate doses based on actual body weight.

Introduction

Obesity is an escalating problem. In 2008, the World Health Organization (WHO) estimated more than 1.4 billion adults, 20 years and older, were overweight. Overall, more than one in ten of the world's adult population was obese [1]. In Ireland, obesity is a major public health concern, where in 2001 it was estimated that 39% of adults were overweight and 18% were obese [2]. Evidence suggests that colorectal cancer risk increases with increasing body mass index (BMI). In the highest BMI categories, the relative risks were found to be 1.6 for men and 1.3 for women [3]. Obesity has been shown to increase the risk of colorectal cancer and it may also impact on the dosing of chemotherapy for the treatment of colorectal cancer.

Chemotherapy dosing in the overweight

Pharmacokinetic parameters for consideration in the obese patient include the volume of drug distribution (Vd), metabolism and excretion [4]. The Vd is dependent upon physiochemical properties of the drug, the degree of plasma protein binding and tissue blood flow [5]. Increased adipose tissue may indirectly alter the Vd by impairing regional blood flow to tissue and affecting plasma protein binding. Obesity does not appear to have an impact on drug binding to albumin, however, the reduction in tissue blood flow and alterations in cardiac structure and function noted in obese individuals may limit the ability of a drug to bind to albumin [6]. Drug clearance is controlled by hepatic and renal physiology. Increases in cytochrome p450 activity have been observed in obese people [5]. Adipose tissue also infiltrates into the liver affecting liver blood flow and hepatic metabolism. The effects of obesity on renal tubular secretion, tubular resorption and glomerular filtration have not been completely established yet. The Cockcroft-Gault formula overestimates renal function in the obese when actual body weight is used and underestimates it when ideal body weight is used [6]. As with the Vd, a single validated size metric to characterise drug clearance in the obese does not exist.

The body surface area (BSA) has been used to calculate doses of chemotherapy but may result in inappropriate dosing as the calculation does not consider whether the kilogram of fat is the same as a kilogram of muscle or oedema. A 2006 study compared the many different formulae for calculating BSA to the Mosteller version in patients of different BMI groups [7].



Sinead Nic Suibhne
MSc (Pharm), MPharm (Hons)

It was noted that the BSA prediction with the commonly used DuBois formula underestimated BSA in obese patients by as much as 3% (male) and 5% (female).

Sparreboom et al. highlighted that 'in clinical practice, a diverse range of empiric dosing regimens is widely employed to calculate drug doses for the obese', and that 'most of these practices have not been evaluated in the context of a controlled clinical trial and in many cases will likely result in significant under

treatment' [8].

Toxicity of chemotherapy

A study by Meyerhardt et al. in 2003 found that there was no association between obesity and any increase in chemotherapy-related toxicity showing that there is room for tolerability of full doses. It was found that patients who were overweight and obese experienced significantly lower rates of any toxicity compared to patients with a normal BMI [9].

The Common Terminology Criteria for Adverse Events (CTCAE) is a validated assessment tool, which utilises a grading (severity) scale for each adverse event. These adverse events include any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporarily associated with the use of a medical treatment that may or may not be related to the medical treatment [10].

Another study by Meyerhardt et al. in 2004, a retrospective investigation, examined the influence of BMI on the rates of treatment-related toxicity amongst other outcomes in colorectal cancer patients. A total of 1,688 patients were assessed and obesity was classified according to WHO classification. Actual body weight was used to calculate the doses and there was no significant difference in the under dosing of chemotherapy in the BMI groups. The obese group were found to experience less grade 3 and 4 toxicities and lower overall grades of neutropenia and stomatitis. This study concluded with the recommendation that obese and overweight individuals can tolerate full doses of fluorouracil [11].

Relative dose intensity

Differences in dosing between patients can be quantified by calculating the relative dose intensity (RDI). RDI is the

relationship between the actual dose and duration of the delivered chemotherapy to the intended dose and duration of the standard chemotherapy regimen [12]. RDI is affected by patient visit cancellations, dose reductions, under- or non-use of haematopoietic growth factors and deviation from original chemotherapy treatment plan [13]. According to practice surveys, at least half of the dose reductions in chemotherapy dose intensity are planned at initiation of treatment and most commonly occur in overweight and obese patients [13].

Due to the association of less toxicities being experienced by the obese group, they may be receiving a sub-therapeutic dose of chemotherapy [14]. Therefore, the aim of this study was to establish whether there is a difference in the severity of toxicity experienced by patients with an increased BMI compared to a group of patients of normal BMI treated with FOLFOX chemotherapy in adjuvant and metastatic colorectal cancer.

Method

This study was approved by the Ethical Review Panel of the School of Pharmacy and Life Sciences at Robert Gordon University (RGU), Aberdeen, UK; and the local Ethics Committee of St James's Hospital (SJH), Ireland.

Setting

The retrospective study was carried out within the Medical Oncology Department of SJH in 2010. SJH is a large teaching hospital in Dublin, Ireland, with approximately 1,000 beds. According to hospital enquiry data collected for an audit within SJH in 2006, the colorectal service manages approximately 8% of the national workload [15]. In 2010, the outpatient clinic of the Medical Oncology Department treated, on average, 30 patients per day with a wide range of chemotherapy regimens.

Sampling strategy

All patients who received FOLFOX 6 (+/- bevacizumab) between January 2006 and March 2010 were identified using Clinichemo. Clinichemo is the computerized system used for dispensing chemotherapy. It allows selection of patients who are on a specific regimen during a particular time period and has a record of each patient's height and weight facilitating the calculation of BMI. All patients which fitted into either the normal BMI group or the increased BMI group were stratified for age and gender. Randomised selection from each stratified group was employed. A sample size of $n = 17$ was calculated to be sufficient by the nQuery Advisor software package (Statistical Solutions) to detect a significant difference between the two groups (CI 95%). Initially, 38 patients were included in each group to allow for loss to follow up.

Inclusion criteria

Patients who had initiated treatment for adjuvant and/or metastatic colorectal cancer between January 2006 and March 2010, with the regimen FOLFOX-6 (+/- bevacizumab), in SJH with:

- BMI $> 25 \text{ kg/m}^2$ were allocated to the increased BMI group

- BMI $18.5\text{--}24.99 \text{ kg/m}^2$ were allocated to the control (normal BMI) group

Exclusion criteria

- Patients treated with FOLFOX 4 (a reduced dosage regimen of FOLFOX)
- Patients with a BMI $< 18.5 \text{ kg/m}^2$

Data collection

The data collection spreadsheet recorded the severity of each toxicity experienced based on the CTCAE toxicity grading system version 3.0. It also allowed for inclusion of information on doses of chemotherapy given and intervals between each cycle as required for calculation of RDI. The data collection tool was checked for face and content validity by conducting a pilot study in a sample of 10 patients, representative of twenty nine percent of the final sample size. The main study was conducted in 34 patients, because of the 76 charts sought, only 35 were retrievable. The date of cycle 1 chemotherapy was known from Clinichemo. Individual entries in their medical notes and on the electronic patient record system, at the date of cycle 1, were considered and their treatment followed for six cycles of FOLFOX.

All relevant information for each individual patient was captured on the data collection spreadsheet including ethnicity, stage of disease, co-morbidities, concurrent medication, treatment dates and doses of each chemotherapy agent, whether a dose reduction or dose delay occurred due to toxicity, CTCAE grade of toxicity and duration of hospital admission due to toxicity. Only the data required for the purpose of this study was collected and kept in accordance with the data protection act [16].

Data analysis

All statistics were analyzed using a power of 80% and significance level of 5% with SPSS version 17. An independent t-test was used to:

- investigate the difference in the severity of toxicities between the groups
- investigate whether or not there was a difference in the RDI percentage given to patients of normal and increased BMI across the study, as well as the final dose intensity
- assess the differences between patients of normal and increased BMI completing treatment
- investigate any difference between groups in the number of days spent in hospital due to toxicity.

Results

There were 17 patients in each group. The patient characteristics are presented in Table 1.

Toxicities

There were no significant differences in the severity of toxicities (p values > 0.05 , 2-tailed t test). The normal BMI group experienced equal or more severe toxicity than the increased

Table 1: Demographic data between the two study groups at cycle 1 day 1

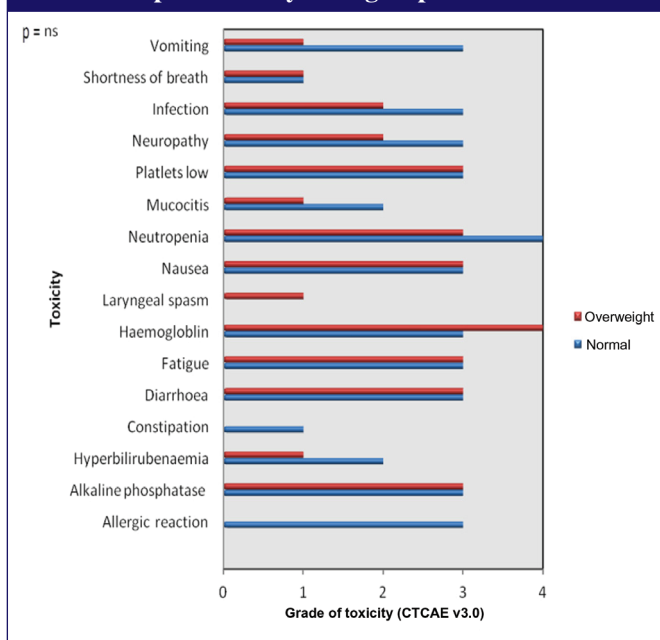
Patient demographics/ characteristics	Normal BMI group (BMI 18.5–24.99 Kg/m ²)	Increased BMI group (BMI > 25 Kg/m ²)
Patient information		
Age ranges (years)	36–72	28–80
Mean age (years)	54.88235	61.64706
Number of patients	n = 17	n = 17
Female	6	2
Male	11	15
Ethnicity	Irish (17)	Irish (15); Polish (1); Unknown (1)
BSA range	1.34–2.6 m ²	1.68–2.3 m ²
Mean BSA	1.72 m ²	1.96 m ²
BMI range	20.68–24.19 kg/m ²	25.01–31.93 kg/m ²
Mean BMI	22.83 kg/m ²	28.15 kg/m ²
Other co-morbidities (severity in brackets)		
Diabetes (Type 2)	1	1
Anaemia	5	12
Arthritis	0	1
Chronic obstructive pulmonary disease	0	1
Hepatic impairment at cycle 1	3 (mild) 1 (moderate)	2 (mild)
Hypertension	1	3
Renal impairment at cycle 1	1 (moderate)	0
Interacting medicines at cycle 1	0	0
Stage of disease at cycle 1		
Adjuvant	9	12
Metastatic disease	7	5
Information unavailable	1	0

BMI: body mass index.

BMI group for all toxicities, other than laryngeal spasm (n = 17, CTCAE grade 0) or low haemoglobin (n = 17, CTCAE grade 3), see Figure 1. The most severe grade of toxicity experienced by the normal BMI group was neutropenia (n = 17, CTCAE grade 4), and the most severe toxicity experienced by the increased BMI group was low haemoglobin (n = 17, CTCAE grade 4).

Table 2 shows the severity grades of the toxicities experienced by the two study groups over the six cycles of FOLFOX. Only the most severe toxicity experienced by each patient is

Figure 1: Severity grade of toxicity (CTCAE v3.0) experienced by each group



presented. The increased BMI group suffered less grade 3/4 toxicities, n = 7(41%) than the normal BMI study group, n = 11 (65%).

Dose intensities between the two groups over the six cycles

The average percentage dose intensity of all three agents (oxaliplatin, fluorouracil pump and fluorouracil push) combined at each dosing stage is shown in Figure 2. The normal BMI group had higher dose intensity at cycle 1 day 1 but for the remainder of treatment this group received lower dose intensity than the increased BMI group.

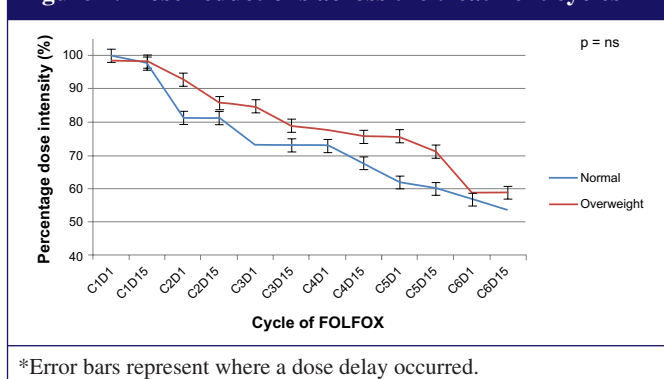
Relative dose intensity of each agent

There was no significant difference in the average dose intensity of any of the drugs given at the end of the study (p values > 0.05, 2-tailed t test) and there was no difference in the average per cent relative dose intensity of all three drugs given in tandem between groups, with the normal BMI group receiving 64.78 +/- 7.39%, and the increased BMI group receiving 67.05 +/- 6.84% (p = 0.824, 2-tailed t test). These results indicate

Table 2: The number of patients and percentage within each group who experienced each grade of toxicity

Group (n = 17)	Common terminology criteria for adverse events			
	Grade 1	Grade 2	Grade 3	Grade 4
Increased BMI	5 (29.4%)	2 (11.8%)	6 (35.2%)	1 (5.9%)
Normal BMI	2 (11.8%)	2 (11.8%)	10 (58.8%)	1 (5.9%)

BMI: body mass index.

Figure 2: Dose reductions across the treatment cycles*

that both groups received similar levels of all three drugs across the study.

Factors which contributed to low RDI percentage

Dose reduction at cycle 1 day 1

At cycle 1 day 1 the BSA was calculated using actual body weight rather than ideal body weight in all of the normal BMI group and the increased BMI group. Three patients from the increased BMI group had their BSA capped at 2.0 m².

Dose reductions due to toxicity

Two patients from each group remained on a hundred RDI percentage of the three drugs throughout the treatment course, with reductions due to toxicity occurring in 11 (n = 11, 65%) of the normal BMI group, and 9 (n = 9, 53%) of the increased BMI group.

Dose delays due to toxicity

There was no association between BMI group and the incidence of a dose delay during the study. In fact, n = 11 (65%) patients from each group experienced a dose delay due to toxicity at some point during the study.

The occurrence of dose reductions and dose delays due to toxicities at each of the 12 dosing intervals (six cycles) is presented in Figure 2.

Number of cycles completed by each group

An independent test revealed no significant difference between the number of cycles completed by either group. Normal BMI patients (n = 17) completed an average of 4.65 +/- 0.53 cycles, while patients of increased BMI (n = 17) completed an average of 5.12 +/- 0.41 cycles, (p = 0.49, 2-tailed t test).

Hospital admissions due to toxicity

The normal BMI group spent a mean of 4.41 +/- 2.7 days in hospital, while the increased BMI group spent a mean of 0.12 +/- 0.11 days in hospital. This test revealed no significant difference (p = 0.123, 2-tailed t test).

Discussion

The main findings from this study were that there was no statistically significant difference in the RDI percentage with which

the patients of normal BMI and those with increased BMI were treated. The severity of toxicities between the groups also proved non-significant. However, a trend can be seen whereby the normal BMI group experienced more severe toxicities despite being treated with lower dose intensity than the increased BMI group.

The method used in this study was straightforward, robust and non-expensive. The patients were easily identified from pharmacy records. The WHO classification for BMI is well known and clearly defined the inclusion and exclusion criteria. The CTCAE toxicity grading tool is used in clinical trials and by many researchers, therefore, it is a well-established method of measuring the severity of toxicity. The RDI is quoted by numerous authors in their studies and is a validated method of comparing doses received with that of a protocol.

There have been many articles questioning the methods used to calculate doses in obese patients and where the balance lies between overdosing and under treating a patient. The method identified in this study for intentional dose reduction pre-treatment was capping the BSA at 2 m² and this was used in three of the increased BMI patients. The dose intensity with which each group was treated was low but similar in both groups by the end of treatment. The increased BMI group were able to tolerate the doses given throughout treatment and received a higher dose intensity throughout the six cycles compared to the normal BMI group. If the sample of obese patients had been greater, more than three patients may have been dose reduced at cycle 1. However, it may be reassuring to know that despite these initial dose reductions, the individuals in the increased BMI group were treated with a similar overall RDI to normal BMI individuals and can tolerate treatment as good, if not better than patients of normal BMI.

The reduction in dose intensity as treatment progressed was due to dose delays and dose reductions. A phase II trial by Ghosn et al. showed that delays in treatment only occurred in n = 5 (17%) patients [17]. In this study the number of dose delays in both groups due to toxicity was greater, n = 11 (65%). Therefore, it is clear that both study groups were treated equally with regards dose to delays due to toxicity. In a study to evaluate the FOLFOX 4 regimen as first-line therapy for patients with inoperable metastatic colorectal cancer in Cuba, Lami et al. found that dose reductions occurred in thirteen (n = 13, 23.2%) patients [18]. In this study eleven patients (n = 11, 65%) of the normal BMI group, and only nine (n = 9, 53%) of the increased BMI group had dose reductions due to toxicity. This shows that the prescriber dose reduced more patients in the normal BMI group than in the increased BMI group, adding to the argument that patients in the increased BMI group tolerated treatment better. This is complemented by the fact that authors found more severe toxicities being experienced by the normal BMI group. FOLFOX 4 is a regimen of lower dosing and this may explain the reason why Lami et al. found a lower percentage of patients being dose-reduced due to toxicity. Even with this in mind, patients in both groups of this study still received a lower than ideal RDI. However, patients with metastatic disease and

those with adjuvant disease were not distinguished so this may be masking the results. If the study was to be conducted again this would need to be taken into account.

The other piece of information found in this study was the lack of statistically significant differences in the severity of toxicities experienced by patients who are of normal BMI and those who were of increased BMI. However, the presence of CTCAE grade 3/4 was $n = 11$ (65%) in the normal BMI group and $n = 7$ (41%) in the increased BMI group. Meyerhardt et al. conducted a study looking across BMI groups and part of the investigation was to see what the influence of BMI was on treatment-related toxicity in patients with colorectal cancer [9]. It demonstrated that obesity was not associated with any increase in treatment-related toxicity. He also saw that with increasing BMI, patients experienced lower rates of grade 3 and 4 toxicity. In the obese category 46% of patients experienced grade 3–4 toxicity, whereas in patients of normal BMI he found that 53% experienced grade 3–4 toxicity. The risk factors for nausea, vomiting and other adverse effects can vary from one individual to the next. This will have had an impact on the validity of the results. However, it is not possible to prevent this confounding factor. Maximum control of toxicities is needed to ensure patients tolerate as much chemotherapy as possible and that optimum RDI percentage is achieved. Appropriate prescribing of supportive medications and compliance with such may have had an impact on the severity of toxicities experienced.

From an economic viewpoint, the number of days an inpatient bed is occupied is relevant. The normal BMI group spent a mean of 4.41 ± 2.7 days in hospital, while the increased BMI group spent a mean of 0.12 ± 0.11 days in hospital. Although not a statistically significant result there is a noticeable difference. Goldstein et al. found that of 62 patients studied, 15 % required hospital admission for toxicity. This study found that there was a greater percentage of hospitalisation due to toxicity with $n = 5$ (29%) in the normal BMI group and $n = 2$ (12%) in the increased BMI group [19].

To prevent the validity of this study being compromised by co-morbidities, details on such were collected so the results could be viewed in light of the background co-morbidities. The severity of low haemoglobin was grade 4 in the increased BMI group. This may be due to the fact that $n = 12$ (71%) increased BMI patients as opposed to $n = 5$ (29%) in the normal group were anaemic prior to initiation of chemotherapy. Patients were stratified by age and gender prior to seeking medical notes in an attempt to match the patient cohorts as best as possible. Since some of the medical notes were not retrievable this resulted in the balance of males and females being disturbed. In hindsight, it would have been better to stratify after medical notes were sourced so that loss to follow-up did not impact on the matching of the patient cohorts.

The main confounding factor in this study was that some patients treated with 5FU push and infusions were changed to Xeloda.

Since compliance or prescribing/dispensing of Xeloda was not recorded, it was decided to exclude Xeloda when patients switched from 5FU. As a result, some of the toxicities are contributable to Xeloda where the dose intensities of 5FU are low.

This study has shown that there is no significant difference in the RDI percentage or in the severity of treatment induced toxicities between patients of normal BMI and those with an increased BMI.

Conclusion

Although the results seen in this study were not statistically significant, it can be seen that the increased BMI group suffered less grade 3 and 4 toxicities, completed more cycles on average than the normal BMI group, had less frequent dose reductions due to toxicity, spent less days in hospital due to toxicity and tolerated a higher RDI percentage. The increased BMI group were initiated on a lower dose intensity percentage due to capping of the BSA at 2 m^2 , but after cycle 1 day 1 they were tolerating a higher dose intensity percentage than the normal BMI group throughout treatment. This suggests, in line with the recent ASCO Guidelines, that patients with an increased BMI can tolerate doses of FOLFOX based on actual body weight. In the future, clinical trials will need to address the impact of obesity on drug therapy.

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Authors

Sinead Nic Suibhne, MScPharm, MPharm (Hons)
Fionnuala King, MRPharmS, MSc
Veronica Treacy, BScPharm, MBA
John Kennedy, MB FRCPI
Ian Collins, MB BCh BAO, MSc

St James's Hospital
PO Box 580
James's Street
Dublin 8, Ireland

Anita E Weidmann, MPharm (Hons), MRPharmS, PhD,
PgCert, HELT, FHEA
School of Pharmacy and Life Sciences
Robert Gordon University
Schoolhill

AB10 1FR Aberdeen, Scotland, UK

References 1–19 can be found on page 26.

Assessing the quality of patient counselling at the Children's Cancer Hospital in Egypt

The authors assessed the quality of the patient counselling service at the outpatient department of the Children's Cancer Hospital Egypt. Two hundred patients completed a written questionnaire while waiting for their prescriptions to be dispensed. This helped formulate an action plan to develop this service.

Introduction

Patient knowledge about medication and disease is reasonably good. A patient's ability to remember instructions given by their physician is insufficient, as 50% of information given will be forgotten immediately. Lack of communication and lack of patient uptake of information may account for up to 55% of patient deviation from prescribed drugs [1, 2].

Patients should be educated about their disease state and medication to improve knowledge, encourage active participation in treatment, and improve medication adherence. This will ultimately improve patient outcomes. Informed patients are more likely to comply with drug-treatment programmes, feel less anxious and better able to take charge of their own medication and treatment schedule [3, 4].

For rational use of drugs, patients should receive medications appropriate to their specific clinical needs, e.g. effective, safe, and suitable in doses that meet their own individual requirements for a sufficient length of time, with the lowest cost to them and their community [5].

Lack of knowledge about medications contributes to non-compliance with medication regimens. Patients who fail to know what medications they are taking and when to take them also are unlikely to know about their side effects and what to do about them [6].

Studies show that compliance with drug regimens can be increased through patient counselling. Written information leaflets, however, have been shown to be most beneficial when used in conjunction with verbal reinforcement [7, 8]. With more medications increasingly becoming available, many with similar names, patients can no longer refer to their drugs.

In February 2012, the authors conducted a study at the Children's Cancer Hospital in Egypt to assess the quality of the patient counselling service.

Method

The authors conducted a pilot study among the first 50 patients, and adjusted the questionnaire according to patient feedback.



Heba Farouk El Nokoudy
BSc

Two hundred patients visiting the outpatient department were surveyed directly by written questionnaire, see appendix. They were asked to complete the questionnaire while waiting for their prescriptions to be dispensed in the Department of Pharmaceutical Services.

Results

Positive feedback was received from patients and their families. Out of 200 patients involved in the study, 118 (59%) were boys and 82 (41%) were girls, aged between one day and 16 years. The education level of the patients

varied from proprietary (39%), secondary (18%), university degree (33%), and non-educated (10%). Only 8% of the study groups had health-related jobs.

The study found that 90% of patients knew their exact diagnosis, and that this figure reduced to 32.5% in patients using five drugs or more. The numbers of patients taking one drug or more are presented in Table 1. Most were taking five or more drugs.

Only 10% of patients did not know the diagnosis of their diseases. A total of 32.5% were taking five drugs or more, and only 65.5% were able to recall the names of their medications.

The methods by which patients were able to recognize their medications are presented in Table 2. Most patients (65.5%) were able to recognize their medications by name. Colour was one of the least recognizable methods of identifying medications.

Table 1: Number of drugs taken by participants

Number of drugs	Number of patients	Patients (%)
1	32	16
2	45	22.5
3	35	17.5
4	23	11.5
More than 5	65	32.5
Total	200	100

Table 2: How patients recognize their medications

Method	Number of patients	Patient (%)
Name	131	65.5
Shape	41	20.5
Colour	17	8.5
Others	11	5.5
Total	200	100

The questionnaire

- Sex: a) Male b) Female
- Age:
- Education: a) Proprietary b) Secondary c) University
- Job Type: a) Health related b) Non-health related
- Do you know your diagnosis: a) Yes b) No
- How many drugs are you taking regularly:
 - a) 1 b) 2 c) 3 d) 4 e) 5 or more
- Can you remember the name(s) of your medications:
 - a) Yes b) No c) Some of them
- Do you know the exact strength and the dose of your medications: a) Yes b) No c) Some of them
- Do you know the most common side effects of your medications: a) Yes b) No
- How can you recognize your medications:
 - a) Colour b) Shape c) Name d) Others
- Have you been informed about special drug instructions:
 - a) Yes b) No
- If yes by whom: a) Doctor b) Pharmacist c) Both
- Do you prefer drug instructions to be:
 - a) Verbal b) Written c) Both
- Do you take your medications:
 - a) By yourself b) Under supervision of someone else
- Once you feel yourself in a good condition:
 - a) Do you stop taking your medication on your own?
 - b) Continue until next doctor appointment
- Can you evaluate the pharmacist performance
 - a) Excellent performance b) Good c) Need to be better
- Are you satisfied with the answers to your questions:
 - a) Yes b) No
- Do you rate the pharmacist care about your medical problems as:
 - a) Excellent performance b) Good c) Need to be better

The authors found that about 91% of patients were informed about special drug instructions; of these, 16% were provided by the doctor, 41% by the pharmacist and 43% by both. Twenty-three per cent of patients preferred verbal, 35% written, and 42% preferred both verbal and written instructions by doctors and pharmacists.

A total of 9.5% of respondents revealed that they would stop their medications if they felt well enough, without consulting their doctors compared with 90.5% of respondents who would not stop their medications without consulting their doctors.

Ninety per cent of patients were aware of the exact diagnosis. Thirty per cent did not know the side effects of their medications. Forty-six per cent of patients were able to recall their medication names, and 21.5% of the patients were taking more than five drugs.

When asked about the health of their children after receiving treatment in hospital, 41% of parents said that their children's health was excellent, 42% good and 17% as needing to be better.

About 68% of parents were totally satisfied with the performance of the healthcare professionals involved in the care of their children. About 96% of patients were totally satisfied with the answers to their questions. Pharmacist performance was rated by 68% as excellent, 24% as good and 8% as needing to be better. Pharmacist care about the patient's medical problem was rated as good by 72% of patients, and this reflects the importance of the patient counselling service offered by the pharmacists.

Discussion

In this study, the authors attempted to assess the quality of the patient counselling service in the Children's Cancer Hospital, the only specialized paediatric cancer hospital in Egypt.

Compared with the study by Al-Nsour et al. [9], the authors found that only 10% of the patients did not know their exact diagnosis. In the field of cancer, it is most important that parents of children with cancer know the exact diagnosis.

In this study, a high proportion of patients (32.5%) were taking five or more drugs. This is because the study was conducted among patients with cancer holding a medication card, and most of those were being treated for more than one condition, e.g. using one or more chemotherapy, diuretic, or oral mouth care medication.

On the basis of these results, the authors devised and implemented a plan to improve the patient counselling service in the Children's Cancer Hospital Egypt. This was achieved by providing training to the inpatient clinical pharmacists, and making available an Arabic patient education resource for each disease and each medication.

Many other important points were taken into consideration:

- Specially designed multidisciplinary medication education programmes with repeated written and verbal reinforcement for patients may improve patient's knowledge about their medications.
- The importance of drug information should be stressed and the counselling role of the pharmacist should be activated, especially for newly diagnosed patients.
- Co-operation of the medical team should be intensified for the benefit of patients.

Conclusion

Results of the survey showed that the patient education counselling service at the Children's Cancer Hospital Egypt was

rated highly for having a good knowledge of medications and providing an effective service. Levels of patient satisfaction with the service were also high. This study will help us action a plan to cascade this service throughout the hospital.

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Authors

Heba Farouk El Nokoudy, BSc
Clinical Pharmacist/Patient Education Coordinator
Department of Pharmaceutical Services

Sherif Kamal, BSc, RPh
Director, Department of Pharmaceutical Services

Professor Mohamed Hany Hussein, MD
Professor of Pediatric Oncology

Children's Cancer Hospital Egypt 57357
Seket Al-Emam Street
El-Madbah El-Kadeem Yard
El-Saida Zenab
Cairo, Egypt

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Toxicity and dose intensity of FOLFOX in patients with increased body mass index

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Treatment of malignant ascites

The treatment of malignant ascites or peritoneal carcinomatosis is improving thanks to the involvement of an interdisciplinary tumour board comprising surgeons, gynaecologists, internal oncologists, pathologists, pharmacists, radiologists and radiotherapists.

Introduction

Ascites is fluid in the peritoneum. The main reason for the appearance of fluid in the peritoneal cavity is an increase in pressure in the portal system of the liver, frequently as a result of cirrhosis of the liver. Ascites can also result from inflammation or neoplasia in the abdomen.

The diagnosis of ascites is made either clinically, by sonography, or by computed tomography (CT) scan. Taking a sample of the fluid by inserting a needle or catheter into the peritoneal cavity, and processing the sample by cytocentrifugation followed by Papanheim staining, distinguishes between several causes of peritoneal fluid, see Table 1.



Jochem Potenberg, MD

- Surgery with intention of a R0-resection followed by chemotherapy—standard therapy [ECOG 0/2]
- Local chemotherapy
- Hyperthermic intraperitoneal chemotherapy (HIPEC)
- Local therapy with antibodies

In a certified cancer centre, this is selected by an interdisciplinary tumour board. Malignant ascites is frequently a sign of peritoneal carcinomatosis, or more rarely a sign of malignant lymphoma. Chemotherapy is often the only treatment for malignant lymphoma.

Condition	Number of patients	Percentage (%)
Without inflammation or neoplasia	30	50.8
Inflammation	12	20.3
Neoplasia	17	28.9
Total	59	100

*Data from the Evangelisches Waldkrankenhaus Laboratory, Berlin, Germany.

The presence of malignant cells in the ascites proves the existence of neoplasia. Malignant cells are observed in ascites as a result of ovarian cancer, stomach cancer, pancreatic cancer, colorectal cancer and malignant mesothelioma.

Clinical presentation

Ascites causes an increase in the circumference of the abdomen, often accompanied by an increase in weight. Sonography or CT scan can lead to the diagnosis.

The diagnosis of the fluid in Figure 1 is unknown. A puncture is needed to prove the nature of the condition. Cytology shows ascites without inflammation or cancer cells, see Figure 2A, ascites with inflammation, see Figure 2B or cancer cells representing peritoneal adenocarcinomatosis, see Figure 2C.

Therapy

Once 'malignant ascites' has been diagnosed, the most appropriate therapy is selected, and the treatment options are:

The tumour board comprises surgeons, gynaecologists, internal oncologists, pathologists, pharmacists, radiologists and radiotherapists. The surgeon is often the first specialist involved in the therapy, but this must be in accord with the other members in the tumour board in order to assure optimal oncological results.

The importance of surgery is determined by the entity of the tumour. If ovarian or colorectal cancer is present, the surgical approach has to be radical. In contrast, in the case of a locally advanced cervical cancer, the surgical de-bulking is a patient-centred decision.

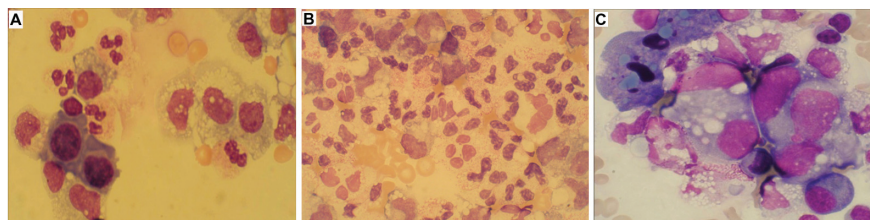
Ovarian cancer therapy—intravenous, intra-peritoneal

The treatment of ovarian cancer is the most efficient surgical approach followed by six cycles of platin- and taxane-containing chemotherapy. This leads to an optimal overall survival and is the worldwide standard of care.

Several trials were conducted to improve the results of his approach. One possible improvement is the local application of cytotoxic agents in the peritoneal area itself. This could lead to a higher concentration of a drug, with a potentially greater effect.

The American Gynaecology Oncology Group conducted a phase III study comparing two different application schemes – intravenous (IV) versus IV + intraperitoneal (IP) – for treatment of an International Federation of Obstetricians and Gynaecologists (FIGO) stage III tumour [1], see Table 2.

The increase of progression free survival and overall survival was associated with the presence of a higher rate of severe or life-threatening (grade 3 or 4) adverse events, see Table 3.

Figure 1: CT image of ascites surrounding the liver**Figure 2: (A) Cytology: ascites without inflammation or neoplasia. (B) with inflammation. (C) with peritoneal carcinomatosis**

It was of scientific interest that patients with and without residual tumour benefitted by the IP treatment, see Table 4.

Because of the large number of adverse events, this regimen would not be accepted as a new standard of care in ovarian cancer.

Treatment of advanced colorectal cancer—surgery, IV chemotherapy, HIPEC

Cancer centres in Germany treat colorectal cancer according to the S3-guidelines stipulated by the German Cancer Society [2]. Metastasis in the lung, the liver and the peritoneum are described as stage IV by Union for International Cancer

Table 2: Comparison of application schemes for ovarian cancer treatment

	IV regimen (n = 210)	IV + IP regimen (n = 205)
FIGO III, remaining tumour after surgery < 10 mm	135 mg/qm paclitaxel IV d1 75 mg/qm cisplatin IV d2	135 mg/qm paclitaxel IV 100 mg/qm cisplatin IP d2 60 mg/qm paclitaxel IP d8
Progression-free survival	18.3 months	23.5 months (P = 0.05)
Overall survival	49.7 months	65.6 months (P = 0.03)

Table 3: Adverse events (grade 3 or 4) by application scheme

Adverse event	IV regimen (n = 210)	IV + IP regimen (n = 205)
Leucopenia	64%	76% (P < 0.001)
GI symptoms	24%	46% (P < 0.001)
Neurological symptoms	9%	19% (P = 0.001)
Infection	6%	16% (P = 0.02)
Fatigue	4%	18% (P < 0.001)
Metabolic problems	7%	27% (P < 0.001)
Pain	1%	11% (P < 0.01)

Table 4: Difference in survival against presence of residual tumour

	IV regimen (n = 210)	IV + IP regimen (n = 205)
Residual tumour after surgery	15.4 months PFS	18.3 months (CI 0.62–1.05)
Without residual tumour	35.2 months PFS	37.6 months (CI 0.54–1.21)
Residual tumour after surgery	39.1 months OS	52.6 months (CI 0.57–1.04)
Without residual tumour	78.2 months OS	Not reached (CI 0.41–1.17)

PFS: progression free survival; OS: overall survival; CI: confidence interval.

Control. Generally this is a negative prognostic factor with a median 5-year survival under 5%.

Isolated metastases in the liver are described in detail in the S3-guidelines because of an increase in the 5-year survival up to 57% if treated by an experienced surgeon [3]. Resection of lung metastases could lead to an improvement in the 5-year survival up to 22% [4].

Once peritoneal metastasis is present, the condition is generally incurable. Specialized surgeons have worked on an approach to peritoneal carcinomatosis, and now propose new therapeutic methods. But the term peritoneal carcinomatosis can mean many different clinical conditions. One case presents as a very severe disease, e.g. frozen pelvis. Another case could be

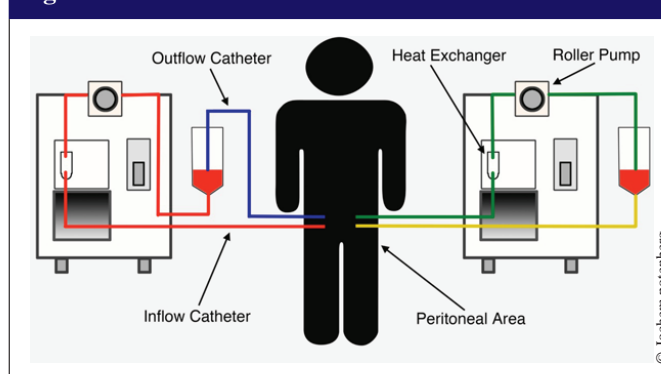
Figure 3: HIPEC chart

Figure 4: Temperature graph with HIPEC

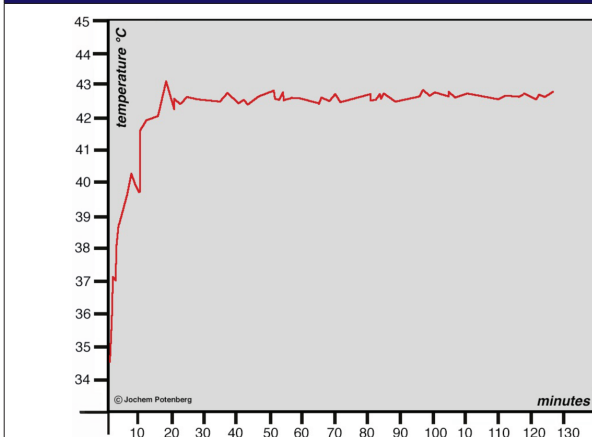
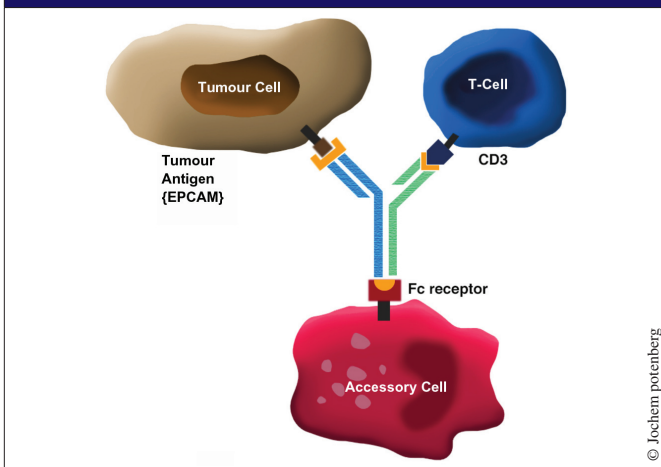


Figure 5: Structure of catumaxomab



minimal infiltration of the tumour, which is treated successfully by a surgeon. Any comparison between these different types of neoplasia must be made by a surgeon who performs laparotomy and inspects the abdomen [5].

One new approach is HIPEC. Tubes are placed in the abdomen surgically and rinsed by cytotoxic agents such as mitomycin C. Figure 3 depicts such an approach with two inlet tubes with heated fluid and two outlet tubes. The patient has to be in a good or very good performance status (PS 0 or 1) to endure such a procedure. The heating process of the fluid is shown in Figure 4. Usually these procedures are performed in teaching hospitals with a specialized team guided by a surgeon who puts the tubes in place.

Therapy of malignant ascites with topically applied antibodies

Catumaxomab is a trifunctionally active antibody, see Figure 5. The Fc region binds to accessory cells such as macrophages. Another binding site interacts with the CD3 epitope of T-cells, while the other arm of the antibody binds to the epithelial cell adhesion molecule (EpCAM) epitope of neoplastic cells. The

Table 5: The efficacy of catumaxomab

Patient category		Catumaxomab		Control	
		n = 170	Puncture-free days	n = 88	Puncture-free days
Advanced primary tumour	Ovarian cancer	85	52	44	11
	Non-ovarian cancer	85	37	44	14
	Stomach cancer	46	44	20	15
Distant metastasis	No	70	48	32	11
	Yes	99	44	56	13
Presence of liver metastasis	No	133	49	68	14
	Yes	36	27	20	9
Age group	Older than the median	84	44	44	11
	Younger than the median	86	48	44	13

presence of the EpCAM structure is widespread in malignant epithelial tumours.

The data in Table 5 show the efficacy of catumaxomab in patients with malignant ascites, with locally advanced disease, and with distant metastasis. Neither the presence of liver metastasis nor age was contraindications for the procedure [6]. The antibody was given intraperitoneally four times in two weeks in increased doses and the puncture-free days were recorded.

Conclusion

The treatment of malignant ascites or peritoneal carcinomatosis has improved in recent years as a result of an interdisciplinary approach. The survival of patients with locally advanced ovarian and colorectal cancer has increased thanks to the combined techniques of surgery and chemotherapy. HIPEC and locally applied antibodies given by surgeons, oncologists and pharmacists working closely together have improved survival for a subgroup of patients.

Authors

Jochem Potenberg, MD
Oncologist
Gisela Sproßmann-Günther, MD
Oncology Pharmacist

Evangelisches Waldkrankenhaus Spandau
555 Stadtrandstrasse
DE-13589 Berlin-Spandau, Germany

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Assessing the cost-effectiveness of orphan drugs

Streamlining health technology assessment (HTA) processes will increase the efficiency and effectiveness in orphan drug appraisal and reduce discrepancies in access to orphan drugs. This paper demonstrates the use of cost-effectiveness evidence, reasons for HTA recommendations and the policy implications.

Objectives and methods

The unique constraints in designing and undertaking robust clinical trials for orphan drugs present difficulties for accurately assessing the effectiveness and cost-effectiveness of such treatments [1]. Where orphan drugs are assessed using standard health technology assessment (HTA) processes that include economic evaluation, they are unlikely to prove cost-effective and hence receive limited coverage [2]. Such methods give little consideration to the unique nature of these treatments, the level of need, severity of disease and extent of individual health gains from such drugs [3]. When measured against standard cost-effectiveness thresholds utilised by HTA agencies, substantial uncertainty regarding the long-term value and level of innovation of novel technologies combined with the high treatment cost results in restricted and inequitable access to much needed new technologies.

EU defines orphan drugs as pharmaceuticals that are directed towards the treatment of life-threatening or severely debilitating conditions with very low prevalence, affecting up to five in 10,000 patients in the EU, for which there are no alternative therapies or that offer 'significant benefits' over existing treatments where these exist [4]. These criteria are utilised in isolating orphan drugs within the marketing authorisation process, however, marketing authorisation by no means predicts or dictates reimbursement in the case of orphan drugs. This discrepancy makes them a particularly interesting case to examine.

Drugs with EU orphan indications, based on EMA register of designated orphan medicinal products [5], were identified and selected for study and cross-referenced against a database of 292 drugs appraised by six leading HTA agenciesⁱ between January 2007 and December 2009. To enable comparison, only compounds that were assessed by at least two of the six agencies were included in the final detailed analysis, resulting in a set of 23 recommendations for different compound-indication



Stacey van den
Aardweg



Panos Kanavos
PhD

pairs of orphan drugs, including 17 drugs with cancer-related indicationsⁱⁱ. Recommendations were categorized as either 'positive' (Recommend List/List with Criteria/*Amélioration du service médical rendu* (ASMR) I-IVⁱⁱⁱ) or 'negative' (Reject/Do not list/ASMR V) based on the final recommendation of the agency in question. A detailed analysis of HTA process and qualitative and quantitative endpoints considered as part of each drug appraisal was undertaken.

Use of cost-effectiveness evidence for HTA

The number and final outcomes of recommendations pertaining to treatment for rare diseases varied across countries. In making recommendations regarding individual orphan drugs, cost-effectiveness is clearly a focus, with the exception of *Haute Autorité de Santé* (HAS) that does not examine economic evidence.

For a number of drugs, manufacturers provided incremental cost-effectiveness ratio (ICER) estimates to all agencies except HAS. The common outcome measure used by National Institute for Clinical Excellence (NICE), *Tandvårds-och läkemedelsförmånsverket* (TLV) and Scottish Medicines Consortium (SMC) was cost/quality-adjusted life years (QALY). ICER values were calculated in a variety of units in submissions to Pharmaceutical Benefits Advisory Committee (PBAC) and Common Drug Review (CDR). PBAC and NICE both considered ICERs in the majority of appraisals (86% and 79% respectively), while CDR/Ontario Committee to Evaluate Drugs (CED) occasionally published them explicitly (23%).

Directly comparing ICER estimates in US dollars across countries it is evident that there is significant variation in cost/measure estimates, see Figure 1. For example, levodopa/carbidopa for Parkinson's disease, the base case cost/QALY submitted to PBAC was US\$665,650, but only US\$68,395.45 – US\$74,757.82 for TLV and US\$142,232.89 for SMC.^{iv}

Surprisingly, the base case cost/QALY estimates submitted to NICE are consistently higher (by up to double) than those submitted to SMC. For similar ICER estimates, SMC frequently rejected orphan drugs that other agencies listed with criteria. For some rejections, e.g. eculizumab and levodopa/carbidopa monohydrate, the economic case for recommending a drug was criticised by agencies on the basis of uncertainty of the ICER estimate rather than its high value. In many cases, other factors such as the drug's safety profile or population need influenced the direction of the recommendation, resulting in drugs with unacceptable ICERs being listed, e.g. PBAC's recommendation of sorafenib tosylate for hepatocellular carcinoma. Often, where submissions were made for coverage for the population with ICERs deemed excessive, recommendations were made for patient subgroups, hence the 'list with criteria' outcome. Publication of manufacturers' submissions to PBAC, provided indications of a calculated ICER range AUD (Australian Dollars) 15,000 – AUD 45,000; AUD 45,000 – AUD 75,000 or AUD 75,000 – AUD 105,000^{vi} rather than an explicit figure, although no information was given regarding why an ICER range was used. In contrast, all submissions to NICE and SMC provided a specific ICER value. There is some evidence of a threshold cost-effectiveness range for the agencies, particularly PBAC – up to AUD 75,000/unit^{vii}. SMC and NICE rejected drugs with ICERs upwards of GBP 22,000/QALY and GBP 50,000/QALY respectively, although there were a few exceptions, for example, dasatinib for chronic myeloid leukaemia (CML) in the case of SMC and in the case of NICE imatinib mesylate for gastrointestinal stromal tumours (GIST) with ICERs of GBP 44,456 – GBP 63,727 and GBP 59,000 per QALY respectively.

Motivations for HTA recommendations

Cost-effectiveness is not the sole motivation for the recommendations provided by HTA agencies examined; evidence of clinical benefit, non-inferiority versus comparators, population need, toxicity, efficacy/safety ratio and the availability of alternative treatments are also considered. However, for some agencies there appears to be a greater emphasis placed on cost-effectiveness – CDR/CED frequently cites value for money and SMC refers to the drug's 'economic case' as the primary criterion for a recommendation. For NICE, in particular, cost-effectiveness was the key driver, with cost implications frequently outweighing evident clinical benefit in instances where the ICER estimate lay beyond the 'threshold' of GBP 20,000 – GBP 30,000 discussed in the literature [6]. Yet, closer examination of individual ICER estimates submitted to NICE suggests that this threshold may not be as rigidly adhered to for orphan treatments. In some cases drugs with base case ICERs up to GBP 59,000 per QALY^{viii} were recommended even if they considered the drug not be cost-effective, though this just suggests that, for orphans, greater

weight is placed on other factors (patient need, ethics and lack of alternative treatments).

Given the scarcity of adequate clinical trial and cost data for some orphan drugs, agencies (particularly NICE and PBAC) frequently restricted criteria for listing or reimbursement to isolate patient subgroups in order to increase drug efficacy in these populations, reducing the cost-effectiveness outcomes to within acceptable levels.

Conclusions and policy implications

In many cases efficacy evidence and cost data used to inform cost-effectiveness calculations differs between different drugs within a single country and across countries, a result of the scarcity of clinical data and diverse HTA processes for orphan drugs. This undeniably results in highly uncertain and potentially erroneous economic estimates, impinging on patient access to potentially life-saving drugs. To achieve equity and ensure that treatments for rare diseases are available and can be accessed by patients in need, it is vital that HTA agencies incorporate more than just the economic case for orphan drugs into their decision-making processes.

The evident variability in the data incorporated into and methods used to conduct economic evaluations between HTA agencies, and its influence on final drug recommendations indicates the existence of a cross-border 'postcode' lottery in terms of access to medicines. Subjecting all drugs to the same cost-effectiveness rules for a country ensures that a minimum level of cost-effectiveness is achieved by all those recommended by an HTA agency and promotes efficiency in resource allocation

Figure 1: Comparison of ICER estimates (in US\$) across countries^v



decisions, but may not be optimal in ensuring equitable access to vital drugs for certain patient populations.

Consideration needs to be given to the inherent value of orphan drugs extending beyond what is reflected in basic cost/benefit comparisons. However, accurately quantifying the value of disease rarity and severity, societal preferences and a drug's level of innovation remains problematic and requires further research. Positive reimbursement decisions for expensive interventions for rare diseases do however need to be balanced against the opportunity cost of funding expensive orphan treatments for a few patients, rather than cheaper therapies for more prevalent diseases for multiple patients.

Designing HTAs to better incorporate or emphasise relevant qualitative aspects of rare diseases and associated treatments can help to provide a more reliable picture of the value of rare disease treatments, resulting in more balanced, less economically-driven decisions. Furthermore, by removing budget considerations from decisions through the provision of earmarked or central funding for specific rare diseases and creating a separate 'orphan drug' protocol policymakers can ensure objective, accurate and timely HTA of orphan drugs. Streamlining and standardising HTA processes, increasing international HTA collaboration and improving communication between HTA agencies and manufacturers will undoubtedly increase the efficiency and effectiveness of orphan drug appraisal procedures, while reducing the discrepancies in access to orphan drugs across countries.

ⁱ Common Drug Review (CDR)/Ontario Committee to Evaluate Drugs (CED), National Institute for Clinical Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC), *Tandvårds-och läkemedelsförmånsverket* (TLV), *Haute Autorité de Santé* (HAS) and Scottish Medicines Consortium (SMC).

ⁱⁱ Ambrisentan (Pulmonary arterial hypertension), Arsenic trioxide (Acute promyelocytic leukemia), Azacitidine (Acute myeloid leukemia), Azacitidine (Myelodysplastic syndrome), Dasatinib (Acute lymphoblastic leukemia), Dasatinib (Chronic myeloid leukemia), Eculizumab (Paroxysmal nocturnal haemoglobinuria), Idursulfase (Iduronate-2-sulfatase) (Hunter Syndrome), Imatinib mesylate (Acute lymphoblastic leukemia), Imatinib mesylate (Chronic eosinophilic leukaemia), Imatinib mesylate (Chronic myeloid leukaemia), Imatinib mesylate (Dermatofibrosarcoma protuberans), Imatinib mesylate (Gastrointestinal stromal tumour), Imatinib mesylate (Myelodysplastic syndrome), Lenalidomide (multiple myeloma), Levodopa / carbidopa monohydrate (Parkinson's disease), Nilotinib (Chronic myeloid leukemia), Paclitaxel (Ovarian cancer), Sildenafil citrate (Pulmonary arterial hypertension), Sitaxentan sodium (Pulmonary arterial hypertension), Sorafenib tosylate (Hepatocellular carcinoma), Sorafenib tosylate (Renal cell carcinoma), Temsirolimus (Renal cell carcinoma).

ⁱⁱⁱ In France, The *Amélioration du service médical rendu* (ASMR) classification delivered HAS, indicates the perceived benefit of a drug relative to their comparator(s) and impacts the reimbursement level and negotiated price of individual drugs in France [7].

^{iv} To enable cross-country comparison, ICER estimates were converted into US\$ based on spot rates on the day of HTA recommendation issue in the relevant countries, using Euro foreign exchange reference rates published by the European Central Bank [8].

^v Where an ICER measure was provided and considered in resulting recommendation decision.

^{vi} Approximately US\$14,100 – US\$42,200; US\$42,200 – US\$70,300 or US\$70,300 – US\$98,400/unit, converted from Australian Dollar (AUD) at European Central Bank spot rate of 1 AUD = US\$0.93695 on 15 September 2010 [8].

^{vii} Approximately US\$70,300/unit, converted from AUD at European Central Bank spot rate of 1 AUD = US\$ 0.93695 on 15 September 2010 [8].

^{viii} Imatinib mesylate for treatment of GIST. The assessment committee's model arrived at a lower base case estimate of GBP 32,000 per QALY, but this is still above the threshold. ICER submission for lenalidomide was approximately GBP 47,000 per QALY.

Authors

Stacey van den Aardweg

Panos Kanavos, PhD

Medical Technology Research Unit

LSE Health

London School of Economics and Political Science

Houghton Street

London WC2A 2AE, UK

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