

Review

Open Access

Impact of Nausea and Vomiting on Quality of Life in Cancer Patients During Chemotherapy

Enzo Ballatori*^{†1} and Fausto Roila^{†2}

Address: ¹Medical Statistics Unit, Dept. of Internal Medicine and Public Health, University, P. le Tommasi 2, L'Aquila, Italy and ²Medical Oncology Division, Policlinico Hospital, Via Brunamonti 51, 06122 Perugia, Italy

Email: Enzo Ballatori* - e.ballatori@libero.it; Fausto Roila - roila.fausto@libero.it

* Corresponding author †Equal contributors

Published: 17 September 2003

Received: 30 July 2003

Health and Quality of Life Outcomes 2003, 1:46

Accepted: 17 September 2003

This article is available from: <http://www.hqlo.com/content/1/1/46>

© 2003 Ballatori and Roila; licensee BioMed Central Ltd. This is an Open Access article: verbatim copying and redistribution of this article are permitted in all media for any purpose, provided this notice is preserved along with the article's original URL.

Abstract

It is commonly claimed that the nausea and vomiting accompanying cytotoxic chemotherapy have a negative impact on health-related quality of life. While this may seem self-evident, until a few years ago there was little empirical data demonstrating that the failure to control postchemotherapy emesis affects aspects of quality of life.

In spite of their limitations, several observational studies showed that nausea and vomiting associated with chemotherapy induced a decrease in health-related quality of life with respect to patients without nausea and vomiting. This has also been demonstrated after the adjustment for health-related quality of life before chemotherapy that is an important prognostic factor of chemotherapy-induced nausea and vomiting.

Furthermore, one study suggests that the optimal time of assessment of quality of life to evaluate the impact of chemotherapy-induced nausea and vomiting is day 4 if a 3-day recall period is used or day 8 when the recall period is 7 days.

In double-blind studies the efficacy, tolerability and impact on quality of life of the 5-HT₃ receptor antagonists was superior with respect to metoclopramide, alizapride and prochlorperazine. Similar results have been achieved with the combination of ondansetron with dexamethasone, the standard treatment for the prevention of acute emesis induced by moderately emetogenic chemotherapy, with respect to the metoclopramide plus dexamethasone combination. Instead, in another double-blind study, in patients submitted to moderately emetogenic chemotherapy, a 5-HT₃ antagonist did not seem to significantly increase complete protection from delayed emesis and the patients' quality of life with respect to dexamethasone alone. In conclusion, the evaluation of quality of life in randomized trials comparing different antiemetic drugs for the prevention of chemotherapy-induced nausea and vomiting can add important information useful for the choice of the optimal antiemetic treatment.

Introduction

About 20 years ago vomiting and nausea ranked as the most distressing side effects of cancer chemotherapy from the patients' point of view [1]. Unfortunately, despite

progress achieved with the 5HT₃ receptor antagonists chemotherapy-induced nausea and vomiting remains a distressing adverse event. In fact, in two studies carried out after their introduction in clinical practice, nausea still

ranks number 1 as the adverse event of chemotherapy of most concern to patients, with vomiting ranking as the 3rd and the 5th most distressing symptom [2,3].

This is probably due to the unsatisfactory efficacy of the available antiemetic drugs to prevent delayed emesis, a phenomenon which has been arbitrarily defined as vomiting and/or nausea beginning, or persisting for, more than 24 hours after chemotherapy administration [4]. Another reason is that often the results of clinical research are not transferred to clinical practice [5].

Clinical consequences of chemotherapy-induced emesis (CIE) include oesophageal tear, fractures, malnutrition, acid-base and electrolyte changes and patients' refusal to continue chemotherapeutic cycles, thus decreasing health-related quality of life (HRQL) and compromising treatment efficacy [6].

In this paper we analyse the impact of CIE on HRQL. A search of published articles in English language in the MEDLINE electronic bibliographic databases from 1976 to 2002 was carried out.

Abstracts were considered relevant if the article: 1) described the development and validation of an HRQL instrument used to assess HRQL in CIE; 2) described the impact of CIE on HRQL; 3) compared HRQL between different antiemetic drugs for the prevention of CIE. The electronic search was supplemented by a manual review of the bibliographies of the references retrieved.

Chemotherapy-induced emesis and health-related quality of life

It is commonly claimed that the nausea and vomiting accompanying cytotoxic chemotherapy have a negative impact on HRQL. While this may seem self-evident, there is little empirical data demonstrating that the failure to control postchemotherapy emesis affects aspects of quality of life other than directly related physical symptoms [6]. In fact, until 1992 studies that considered the impact of nausea and vomiting on a broader, multidimensional measure of quality of life were lacking. Furthermore, one study carried out in breast cancer patients showed that the important determinants of a good quality of life for them appear to be their ability to complete the activities of everyday living and their emotional well-being, while nausea and vomiting, when present, were not powerful independent predictors of variations in overall quality of life [7]. A possible criticism of this study is that most of these patients had not recently received chemotherapy and had no experience of nausea and vomiting. On the other hand, improvement in the control of nausea and vomiting lead to a smaller decrease in the quality of life of cancer patients in the few days following chemotherapy, but

other issues can be more important determinants of quality of life in the long term.

However, it was less clear precisely how important nausea and vomiting may be and to what extent their effects are independent of the other toxicities of chemotherapy and indeed of the effects of the diagnosis and disease itself [7]. Some studies have tried to answer to these questions (Table 1).

Studies without comparative purpose

Lindley et al. evaluated 122 patients with various cancers submitted to different emetogenic chemotherapies and different antiemetic prophylaxis [8]. Emesis (one or more episodes of vomiting and/or a nausea severity of 2.0 cm or more on a 10 cm visual analogue scale) was reported by 56% of patients. To evaluate emesis and its impact on quality of life three instruments were used before chemotherapy and 3 days after: a diary card where the number of vomiting and retching episodes occurring every day was recorded as well the severity of nausea, sedation and anxiety experienced by the patients; the Functional Living Index – Cancer (FLIC) a validated instrument to assess the patient's quality of life [9]; the Functional Living Index – Emesis (FLIE), an instrument created, pre-tested and revised prior the study, with questions modelled after those of the FLIC but specifically addressing the impact of chemotherapy induced nausea and vomiting on the physical activities, social and emotional function and ability to enjoy meals. The score of the FLIC (FLIE) was determined by summing the responses to the 22 (18) questions on a 7 point analogue scale and, therefore, the range of total scores possible is between 22 (18), all 1 responses on each scale, and 154 (126), all 7 responses on each scale. A higher score corresponds to a higher quality of life (less negative impact on the patient's functional living by nausea and vomiting).

The mean quality of life score for patients of the FLIC decreased significantly from 121 before to 110 three days after chemotherapy, but it was statistically significant only in those patients experiencing emesis (from 119 to 101) while in those not reporting emesis the score was not different following chemotherapy (from 124 to 122). Similar results were obtained with the FLIE: the mean score decreased from 118 before to 101 three days after chemotherapy, but the decrease was dramatic in patients who experienced emesis (from 115 to 85) as compared to a constant level for the non-emesis patient group. Chemotherapy and antiemetic therapy seem to contribute significantly to changes in quality of life observed. In fact, of patients who experienced chemotherapy-induced emesis, 23% were unable to go to work due to emesis, 22% reported they were unable to prepare meals due to emesis; 12% reported that emesis made them unable to care for

Table 1: Studies without comparative purpose

Author [ref.]	Pts (no.)	Cancer (type)	Chemotherapy (emetogenicity)	Antiemetics	HRQL assessment (times)	Selection of pts
Lindley [8]	122	various	various	various	FLIC and FLIE (before and after 3 days)	162 pts eligible, 140 agreed to participate, 122 evaluated HRQL
Berry [10]	109	various	various	OND use compassionate	FLIE (n.s.)	350 pts, 190 received similar CT, 109 evaluated HRQL
O'Brien [11]	92	various	Moderately and highly	DEX + MTC or PCP ± other	FLIE (before and after 2 and 5 days)	128 pts eligible, 112 agreed to participate, 107 evaluated HRQL (15 pts excluded for multiple days CT)
Osoba [12]	802	various	Moderately and highly	5-HT ₃ ± DEX	EORTC QLQ-C30 (before and after 7 days)	
Osoba [13]	802	various	Moderately and highly	5-HT ₃ ± DEX	EORTC QLQ-C30 (before and after 7 days)	Possible selection bias at HRQL evaluated before 2 nd cycle CT (70% of pts)
Rusthoven [16]	119	various	Moderately	Standard for Centers	EORTC QLQ-C30 (before and after 2 and 6 days)	124 pts eligible, 119 evaluated HRQL

CT: chemotherapy, DEX: dexamethasone, HRQL: Health-related quality of life, OND: ondansetron, PCP: prochlorperazine, 5-HT₃: 5-HT₃ antagonist, n.s.: not specified.

themselves; 12% reported that they were unable to take prescribed medications on at least two occasions due to emesis.

In another study, 109 patients that had previously experienced nausea and vomiting and/or side effects with the use of standard antiemetic agents were submitted in the following cycle of a similar chemotherapy regimen to a compassionate-use program of ondansetron (0.15 mg/kg i.v. every 4 hours for three daily doses) [10]. Two assessment tools were used to evaluate patient's conditions: a score ranging from 1 to 10 for physician's assessment and the FLIE questionnaire filled out by the patient. In this case the score for the 18 items of FLIE was added and transposed to a 100-point scale to give a final score, with a higher score indicating a better quality of life. The mean score was significantly better with ondansetron than with standard antiemetics (65.5 versus 39.5). The FLIE scores were higher for 76% of patients during ondansetron treatment as compared to previous chemotherapy with standard antiemetics. Possible criticisms are that (i) the difference in scores is probably overestimated because of the time of assessment (both after treatment with ondansetron), and (ii) the shortcomings in the study design (neither randomised, nor double-blind).

One study evaluated the effect of chemotherapy-induced nausea and vomiting on health-related quality of life before the 5-HT₃ antagonists became available [11]. In 92 patients submitted to moderately and highly emetogenic chemotherapy the incidence of nausea and vomiting for 5 consecutive days and their impact on quality of life was evaluated. Quality of life was assessed by the FLIE that was completed before chemotherapy, and on day 2 and 5 after. The summed scores were standardized to a 100 point-scale. Over the 5 days of the survey 72 patients

(78%) reported nausea or at least one emetic episode. The FLIE scores indicated significant worsening of functional status associated with chemotherapy, but an improvement after the first 24 hours following chemotherapy, an improvement that was greater for emesis than for nausea. On day 2 the main impact was from emesis, particularly with regard to leisure activities, household tasks and hardship on the family. On the other hand, nausea had a significantly greater impact than emesis on overall functioning, enjoyment of eating and hardship on the patient.

Two studies have been published by the Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group assessing whether prechemotherapy HRQL variables were associated with postchemotherapy nausea and vomiting and their relationship to patient and treatment variables [12] and the effect of postchemotherapy nausea and vomiting on HRQL [13] in 802 patients submitted to moderately and highly emetogenic chemotherapy. The HRQL used the questionnaire of the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) [14] completed by the patient from 0 to 7 days before chemotherapy (baseline) and at home 7 days after the chemotherapy (day 8) for both studies and on the first day of the second cycle of chemotherapy (day 15–29), for the second study.

The EORTC QLQ-C30 is a 30-item self-report questionnaire that contains questions exploring five functioning domains (physical, role, emotional, cognitive and social), an overall or "global" quality of life domain, three symptom domains (pain, fatigue, nausea/vomiting) and six single items (dyspnoea, insomnia, anorexia, diarrhoea, constipation, and financial difficulties). The raw scores for

each domain and single item are transformed to give a score lying between 0 and 100. For the functioning domains and global quality of life, a higher score indicates a better or higher level of functioning; for the symptom domains and single items, a higher score indicates a greater level of symptoms or problems. The patients filled out a diary card for the assessment of nausea and vomiting.

In the first study [12] patients were divided into two groups: those who did not report nausea or vomiting and those who had nausea and one or more emetic episodes in the week after chemotherapy administration. More than 98% of patients completed the baseline questionnaire. Nausea was reported by 75.6% and vomiting by 55.7% of patients during the study period.

At the univariate analysis, the mean pretreatment scores in patients who suffered from chemotherapy-induced nausea were significantly lower for physical, role, emotional, cognitive, and social functioning than in patients without nausea. Patients with nausea also had significantly higher fatigue, preexisting nausea, pain, insomnia, constipation, financial difficulties and daytime drowsiness scores.

Patients who vomited after chemotherapy had significantly worse physical, role and social functioning, and global quality of life scores before chemotherapy than patients who did not vomit. Furthermore, patients who vomited had significantly higher fatigue, preexisting nausea, pain, anorexia, constipation, financial difficulties, and daytime drowsiness scores before chemotherapy than those who did not suffer from vomiting.

On the other hand, pretreatment quality of life scores were not found significantly correlated with the intensity of postchemotherapy vomiting (1–2 episodes versus more than 2 episodes).

Five patient characteristics were positively associated with postchemotherapy nausea (females, history of motion sickness, drowsiness and prechemotherapy nausea) and two with postchemotherapy vomiting (ECOG performance status of 1 and 2 and consumption of 10 or less alcoholic drinks per week).

At the multivariate analysis, the variables remaining in the final model included low social functioning, prechemotherapy nausea, female gender, highly emetogenic chemotherapy and the lack of maintenance antiemetics after chemotherapy. A history of low alcohol intake was also associated with postchemotherapy vomiting while increased fatigue and lower performance status were associated with postchemotherapy nausea.

The risk of postchemotherapy vomiting increased from 20% in patients having no risk factors to 76% in those having any four of a total of six risk factors.

The predictive value of certain health-related quality of life domains for postchemotherapy vomiting showed in this study and not in the previous studies can be related to the different scoring systems of the EORTC and FLIC-FLIE questionnaires. In fact, the scoring of FLIC and FLIE questionnaires provides a single aggregate score as a measure of HRQL, whereas the scoring of the EORTC questionnaire provides separate scores for each domain and symptom. A single, aggregate score encompasses many domains and if only some of them have predictive value then those domains that do not have predictive value will mask the domains that do have predictive value. The result will be a dilution of the aggregate score that then, of itself, will not be predictive. This strongly supports the view that multidimensional instruments should be scored and analysed for the information provided by each of the separate domains. On the other hand, it is necessary to remember that the Canadian study is that with the largest number of patients enrolled and that the non-predictive value of HRQL scores of the previous studies could be due to the low number of patients evaluated.

In the second study [13] the patients were divided in four groups: those who experienced both nausea and vomiting, those with nausea without emetic episodes, those with no nausea but with vomiting, and those with neither nausea nor vomiting. To evaluate the impact of postchemotherapy nausea and vomiting on HRQL the change in scores between the baseline and day 8 after chemotherapy administration was calculated for each domain and symptom of the questionnaire and compared in the four subgroups of patients. On day 8, 94.8% of patients filled out the questionnaire while about 70% completed it on the day of their second cycle of chemotherapy.

On day 8 the group with both nausea and vomiting showed statistically significant worse physical, cognitive and social functioning, global quality of life, fatigue, anorexia, insomnia and dyspnea as compared to the group with neither nausea nor vomiting. Patients with only nausea but no vomiting tended to have less worsening in functioning and symptoms than those having both nausea and vomiting.

Increased severity of vomiting (> 2 episodes) was associated with worsening only of global quality of life and anorexia compared with 1–2 episodes of vomiting.

After 2–4 weeks from the chemotherapy all quality of life scores either returned to their baseline levels or were better than baseline.

In this study the effect of chemotherapy-induced emesis on HRQL was evaluated taking into account the prechemotherapy health-related quality of life status. In fact, the authors first subtracted the baseline scores from the day 8 scores and then used the difference to compare the subgroups of patients with and without postchemotherapy nausea and vomiting. In this way the non-emetogenic effects of chemotherapy on postchemotherapy quality of life could also be considered at least in part; in fact, comparing the differences in changed scores between patients who vomited, it was assumed that the effects of chemotherapy or other variables were likely to be similar in the two groups because of the large sample size.

Finally, another possible explanation for the apparently different results of these two studies with respect to the previous ones is that postchemotherapy quality of life was assessed 7 days after chemotherapy administration instead of 4 or 2 days.

The importance of the time of administration and of the time frame of quality of life assessment was evaluated in another Canadian study carried out in 650 patients submitted to moderately emetogenic chemotherapy [15]. The initial observation suggesting the necessity of this study was: despite the fact that patients who experienced greater nausea and vomiting reported a significantly worse quality of life, when quality of life was compared across treatment arms, which differed substantially in the control of emesis, no statistically significant difference in any quality of life outcome measures was found. The most likely explanation of this is that, as emesis is more intense in the first 2–3 days after chemotherapy, administering a questionnaire on day 8 (time frame: 7 days) could lead to attenuating the perceived effects of emesis on their HRQL.

In this study the participating centres were randomized to one of four quality of life assessment procedures. Patients in all centres completed a baseline questionnaire within 72 hours prior to study entry and a post-treatment assessment on either day 4 or 8 after chemotherapy. The selection of day 4 or 8 was randomized by centre. The time frames of the questionnaires were also randomly varied by centre to be either 7 days, as in the standard instrument, or 3 days, as a modified version.

When the quality of life questionnaire is administered on day 8, the changes in global quality of life are significantly greater when the recall period is 7 days than when it is 3 days (-10.3 versus -1.2, $P < 0.01$) and when a 3 day recall period is used the changes are significantly greater when

the questionnaire is administered on day 4 than on day 8 (-8.4 versus -1.2, $P < 0.001$). Furthermore, in this study the addition of dexamethasone to a 5-HT₃ antagonist significantly improved the control of emesis over the entire study period with respect to a 5-HT₃ antagonist alone. These results were parallel to those achieved on quality of life scores; in fact, patients receiving dexamethasone fared significantly better with respect to global quality of life, physical functioning and social functioning and symptom scales. Administering the questionnaire at the time of greatest symptoms, i.e. 3 days after chemotherapy, is the most sensitive means of detecting a treatment difference.

In another Canadian study, patients submitted to moderately emetogenic chemotherapy were monitored for nausea and vomiting and a modified version of the EORTC QLQC-30 questionnaire was administered before chemotherapy and on day 2 and day 6 to assess the impact nausea and vomiting had on quality of life of the patients [16].

Patients who experienced either nausea or vomiting had a decrease in quality of life from prechemotherapy levels on six functioning and five symptoms scale at day 2 and on four functioning and four symptom scales on day 6. Comparison of mean scores between the unmodified EORTC QLQC-30 and the nausea and vomiting versions demonstrated that the HRQL rating attributed to nausea and vomiting accounted for much, but not all, of the deterioration in HRQL scores in patients who experienced these symptoms. Therefore, other reasons for some of the decrease in health-related quality of life must be identified in future studies.

In conclusion, although observational studies present many risks of confounding bias, it seems that at least in part the CIE induced a decrease of HRQL. This has been also demonstrated after the adjustment for HRQL before chemotherapy that is an important prognostic factor of CIE. Finally, observational studies showed the importance of the time of administration and of the time frame of quality of life assessment. The possibility to identify the impact of CIE on HRQL is significantly greater when the questionnaire is administered on day 4 than on day 8, if a 3-day recall period is used, or when the questionnaire is administered on day 8, but the recall period is 7 days instead of 3 days.

Studies comparing the impact of different antiemetics on HRQL

Table 2 summarizes the comparative studies among different antiemetic regimens evaluating their impact on HRQL.

Table 2: Studies comparing the impact of different antiemetics on HRQL

Author (study) [ref.]	Pts (no.)	Cancer (type)	Chemotherapy (emetogenicity)	Antiemetics	HRQL assessment (times)	Selection of pts
Soukop (DB) [17]	184	Breast	Moderately	DEX + OND vs DEX + MTC	RSCL (before and after 6 days)	187 pts eligible, 184 evaluated HRQL, 2 questions excluded (> 5% of pts no response)
Clavel (DB) [19]	252	Breast	Moderately (FAC, FEC)	OND vs ALI	FLIC, FLIE (before and after 4 days)	259 pts eligible, 252 evaluated HRQL with FLIC and 246 with FLIE
Crucitt (DB) [20]	113	Breast LNH	Moderately	OND vs PCP	FLIC, FLIE (before and after 4 days)	133 pts eligible, 113 evaluable for efficacy, 57 evaluated HRQL
Lofters (DB) [21]	696	various	Moderately	OND ± DEX vs DOL ± DEX	EORTC QLQ-C30 (before and after 4 and 8 days)	703 pts eligible, 696 evaluated HRQL
Pater (DB) [22]	402	various	Moderately	DEX + OND or DOL vs DEX (delayed emesis)	EORTC QLQ-C30 (before and after 4 and 8 days)	407 pts eligible, 402 evaluated HRQL
Garbe (DB) [23]	90	Melan	Highly (dacarbazine)	TROP 5 mg vs TROP 10 mg	Mood, food intake, QL scales (before and after CT)	n.s.
Barrenetxea (DB) [24]	182	Breast	Moderately (FAC, FEC)	OND for 3 days vs OND+MTC vs OND 1 dose	FLIC (before and for 5 days)	n.s.
Lebeau (DB) [25]	338	various	Highly (cisplatin)	OND+MP vs OND+MP+MTP	FLIC, FLIE (before and after 4 days)	n.s.
Kobayashi (DB) [26]	141	various	Highly (cisplatin)	TROP vs PL (delayed emesis)	QOL-EVJ (before and daily for 30 days after)	146 pts enrolled, 141 eligible, 98 evaluated HRQL
Sorbe (R, O) [28]	259	various	Highly (cisplatin)	TROP vs MTC + DEX + LOR	23 items (before and after 7 days)	n.s.
Drechsler (R, O) [29]	191	various	Highly and Moderately	TROP vs TROP+DEX vs TROP+MTC	new scale (before and after CT)	n.s.
Torok (R, O) [30]	130	Ovary	Highly (cisplatin)	OND vs GRAN vs MTC	RSCL (before and daily for 5 days)	n.s.
Lachaine (O) [31]	52	Breast	Moderately	OND or MTC physician choice	EORTC QLQ-C30 (before and after 2 and 4 days)	58 pts eligible, 52 evaluated HRQL

ALL: alizapride, CT: chemotherapy, DB = Double-blind, DEX: dexamethasone, GRAN: granisetron, HRQL: Health-related quality of life, Melan: melanoma, MTC: metoclopramide, MTP: metopimazine O: open, OND: ondansetron, PCP: prochlorperazine, PL: placebo, R: randomized, TROP: tropisetron, 5-HT₃: 5-HT₃ antagonist, n.s.: not specified

Twelve out of 13 studies are randomized, and 9 of them were double-blind.

The first randomized double-blind study comparing different antiemetic prophylactic treatments that evaluated the impact on quality of life was carried out on breast cancer patients submitted to the first cycle of a cyclophosphamide-containing regimen [17]. Ondansetron (8 mg i.v. followed by 8 mg oral dosing three times daily for 5 days) was compared to metoclopramide (60 mg i.v. followed by 20 mg oral dosing three times daily for 5 days) during 6 cycles of chemotherapy. Both antiemetics were combined to a 16 mg single dose i.v. of dexamethasone before chemotherapy. Nausea and vomiting were recorded daily on a diary card while quality of life was assessed before each chemotherapy treatment and at the end of each 5-day treatment period using the Rotterdam Symptom Checklist questionnaire [18]. This includes 38 items summarized in three subscales (physical, psychological and functional activity). Each item of the physical and psychological subscales is rated on a four-point scale (0 = not at all, 1 = a little, 2 = somewhat, 3 = very much) as well as the items related to functional activity (0 = unable, 1 = only with help, 2 = without help, with difficulty, 3 = without help).

A separate analysis was performed for the psychological, physical and functional activity subscales. The "lack of sexual interest" and ability to "go to work" questions were excluded from the analyses since > 5% of patients failed to complete them.

Due to much missing data, the mean and not the total of each subscale was considered. The study showed that at the first cycle of chemotherapy ondansetron plus dexamethasone was significantly superior to metoclopramide plus dexamethasone (complete protection from vomiting over the 5-day treatment period in 81% and 48% of patients, respectively). Furthermore, ondansetron induced a statistically significant improvement in the psychological subscale scores with respect to metoclopramide. No differences were observed in the physical and functional activity subscales. Interestingly, patients' psychological distress was stronger before chemotherapy than after. This was probably due to the apprehension in receiving chemotherapy for the first time. Instead, physical parameters worsened to the same degree after chemotherapy reflecting associated side effects. During the 6 cycles of chemotherapy 67% of patients receiving ondansetron and 28% of patients receiving metoclopra-

mide had less than 3 emetic episodes. Over the 6 cycles quality of life results revealed a more pronounced difference in favour of ondansetron in the psychological subscale score as well as trends in favour of ondansetron in the physical and functional activity subscales. Unfortunately, quality of life data were not available for all patients for all 6 cycles; therefore, a possible selection bias favouring ondansetron cannot be excluded, especially considering that the analysis of the 6 cycles refers to 475 assessments of ondansetron-treated patients and 380 assessments of metoclopramide-treated patients.

Another randomized, double-blind study evaluating the impact of CIE on HRQL compared oral ondansetron (8 mg every 8–12 hours for 3–5 days starting 2 hours before chemotherapy) with alizapride (150 mg i.v. followed by 50 mg orally administered every 8–12 hours for 3–5 days starting 2 hours before moderately-highly emetogenic chemotherapy) [19]. Nausea and vomiting episodes were recorded on a diary card, while quality of life was assessed using the FLIC and the FLIE questionnaires filled out by the patients before chemotherapy and 4 days after. The total score for each questionnaire was obtained by calculating the average score for each item. Complete control of acute (57% versus 31%) and delayed (62% versus 48%) emesis was significantly superior in the ondansetron group than in alizapride group. Both groups experienced deterioration in FLIC and FLIE score from pretreatment to day 4. No difference in quality of life scores was shown between the ondansetron and alizapride groups when quality of life was measured by the FLIC, but when quality of life was measured by the FLIE, ondansetron was found superior to alizapride in preventing a decrease in quality of life following chemotherapy (mean difference in the scores for each question was 1.45 with ondansetron and 1.93 with alizapride, $P < 0.04$).

The third double-blind randomized study compared ondansetron (8 mg orally b.i.d. for 3 days) with prochlorperazine (10 mg orally b.i.d. for 3 days) in breast cancer and lymphoma patients submitted to moderately emetogenic chemotherapy [20]. Patients completed the FLIC and FLIE questionnaires before and at the end of the 3-day study period (day 4). Total scores were transformed to standardized scores so that the highest possible score on either scale equated to 100. Ondansetron was significantly superior to prochlorperazine in the complete control of emesis during the three days (60% versus 21%). Quality of life was evaluated in only 57 of 133 patients (34 receiving ondansetron and 23 prochlorperazine). Baseline scores of the FLIE did not differ between groups. Vomiting subscale scores were significantly different between groups (from 97.1 pre to 89.2 post treatment with ondansetron and from 96.7 pre to 70.4 post with prochlorperazine, $P < 0.01$). No significant difference was

seen for the nausea subscale scores. There were no significant differences between groups in FLIC scores at baseline or at the end of the 3-day study period.

In two randomized double-blind studies quality of life was evaluated with the EORTC QLQ-C30. In the first [21], carried out in patients submitted to moderately emetogenic chemotherapy, the efficacy of dolasetron and ondansetron on day 1 and on day 1–7 was compared as well as the efficacy of the addition of dexamethasone to both. In the first 24 hours dolasetron was significantly less effective than ondansetron but no difference was shown between the two drugs over 7 days. The addition of dexamethasone significantly improved the efficacy of both drugs during the entire period.

There were no statistically significant differences between ondansetron and dolasetron at baseline for any of the HRQL domains assessed. Post-treatment, there were no significant changes in global quality of life or other domains, except for diarrhoea (more common with dolasetron) and constipation (more common with ondansetron). Dexamethasone-treated patients fared significantly better with respect to global quality of life, physical functioning and social functioning and nausea, anorexia, diarrhoea, fatigue and pain.

In the second study [22] the efficacy of 5-HT₃ antagonists, ondansetron or dolasetron added to dexamethasone versus dexamethasone alone in the prevention of delayed emesis induced by moderately emetogenic chemotherapy was evaluated. Patients received in the first 24 hours a combination of a 5-HT₃ receptor antagonist plus dexamethasone. The continuation of the 5-HT₃ receptor antagonist improved slightly but not significantly, the complete control of delayed emesis (47% versus 41%). Minimal differences in quality of life were observed. Social functioning deteriorated significantly more in patients treated with dexamethasone alone than in those receiving the combination (-6.0 points versus -0.8 points in the combination). On the other hand, patients taking 5-HT₃ receptor antagonists reported a significantly greater increase in constipation (+26 points versus +13 points). Unfortunately, there is no method for weighting the sub-components of the QLQ-C30 with respect to their overall importance and, therefore, to balance symptomatic changes in one direction against functional changes in another.

A randomised double-blind study was carried out in advanced malignant melanoma patients submitted to dacarbazine administered in 1, 5 or 10 days, evaluating HRQL by unidimensional linear scales [23]. Two different doses of tropisetron were compared: 5 and 10 mg iv. Patients evaluated their mood, food intake and quality of

life by recording scores in a diary card every day from the day before chemotherapy until the end of the cycle. The scores ranged from 0 (very bad) to 8 (very good). The two dosages of tropisetron prevented vomiting in 93% and 98% of patients with 5 mg and 10 mg, respectively.

Their well being was maintained during the cycle of chemotherapy; in fact, mood and quality of life of the patients remained good as well as food intake.

In another study the efficacy of three antiemetic regimens (ondansetron 8 mg i.v. followed by 8 mg orally every 8 hours for 3 days vs ondansetron as above plus metoclopramide 10 mg every 8 hours for 3 days vs ondansetron 8 mg i.v. single dose) in breast cancer patients submitted to CMF or FEC chemotherapy was evaluated [24].

Quality of life impact was assessed by FLIC questionnaires completed by the patients during a 5-day period following chemotherapy. Chemotherapy cycles, and not patients, were considered as a statistical unit. Responses were evaluated in 182 cycles: in 116 cycles patients received CMF and in 66 FEC. The high-dose ondansetron regimen was similar (CMF-treated patients) or superior (FEC-treated patients) to the combination of ondansetron plus metoclopramide and always superior to the single dose of ondansetron. Quality of life was always worse with ondansetron single dose i.v. while no differences were shown between ondansetron for three days versus ondansetron plus metoclopramide.

A double-blind multicentre study evaluated two antiemetic regimens, in patients with vomiting or moderate to severe nausea in the previous cycle of cisplatin based chemotherapy despite antiemetic treatment with a combination of a 5-HT₃ antagonist plus a corticosteroid: ondansetron plus methylprednisolone versus ondansetron plus methylprednisolone plus metopimazine [25]. The impact on the patient's quality of life was assessed using the FLIC and the FLIE that were joined together in a single questionnaire. This questionnaire consisted of 28 items (all 22 of the FLIC and 6 of the FLIE) and was filled out by the patient prior to the start of chemotherapy and at the end of the third day of antiemetic treatment.

Complete protection from vomiting throughout the cycle of chemotherapy was achieved more frequently by patients receiving the triple combination (53% versus 38%, $P < 0.008$).

Modification in quality of life (FLIC questionnaire) was similar between the two treatment groups. The FLIE showed a decrease in quality of life that was inferior albeit not significantly with the triple combination.

In another double-blind study the role of tropisetron in the prevention of cisplatin-induced delayed emesis was evaluated. On the first day all patients received 5 mg oral tropisetron and then were randomly assigned to receive either tropisetron or placebo on days 2 through 5 [26]. A newly developed quality of life questionnaire was employed that consisted of seven scales: physical scale, mental and related symptom scale, respiratory condition related scale, social scale, an active scale, a scale for the influence of nausea and vomiting on patient's daily life, and a global scale [27]. This questionnaire was printed in diary form and filled out every morning.

The rate of complete protection from delayed emesis in the tropisetron group and placebo group was respectively 46.3% and 36.5%.

All scales, except social well being, changed immediately in both groups and reached a nadir on days 2–3, after that returning to the control levels during the two weeks after cisplatin administration. Tropisetron treated patients showed significantly better physical wellbeing, mental wellbeing, functional wellbeing and global quality of life scores with respect to placebo-treated patients.

Finally two open, randomized, multicenter studies have been published [28,29]. The first compared tropisetron (5 mg i.v. on day 1 followed by 5 mg oral every day on days 2–6) with a metoclopramide-cocktail (metoclopramide 3 mg/kg i.v. plus dexamethasone 20 mg i.v. plus lorazepam 1 mg oral on day 1 followed by metoclopramide 10 mg orally or 20 mg as suppositories three times a day on days 2–6) in patients submitted to consecutive cycles of cisplatin chemotherapy [28]. Nausea and vomiting were recorded on a diary card while quality of life was assessed by a non-validated questionnaire consisting of 18 questions about various symptoms and 5 questions about appetite and social life.

On day 1 of the first cycle complete control of vomiting was not significantly different (63% with tropisetron versus 64% with metoclopramide cocktail) while complete control of nausea was significantly superior with the cocktail (40% versus 61%). The rate of complete control of vomiting and nausea increased from day 1 to day 6 with both antiemetic regimens, and this also happened at the second cycle. Before both cisplatin cycles, the two groups did not differ in the responses to the 23 questions. In post-treatment evaluations in both treatment groups, the patients reported more nausea, vomiting, being ill, being tired or sleepy, and having more problems with eating than was reported in the pretreatment evaluation. Patients receiving tropisetron experienced significantly more constipation and headache than did those treated with the metoclopramide cocktail.

Another open, randomized, multicentre study compared tropisetron (5 mg i.v. day 1 and 2 followed by 10 mg orally until two days after the end of chemotherapy) with tropisetron (as above) plus dexamethasone (20 mg i.v. on day 1 and 2 followed by 4 mg i.v. or orally until two days after the end of chemotherapy) and with tropisetron (as above) plus metoclopramide (20 mg i.v. plus 10 mg orally b.i.d on day 1 followed by 10 mg t.i.d. orally until two days after the end of chemotherapy) in patients submitted to highly and moderately emetogenic chemotherapy [29]. Quality of life in this study was documented using a newly developed, validated but not yet published, colour scale. Tropisetron plus dexamethasone was significantly superior to tropisetron alone and tropisetron plus metoclopramide for both acute and delayed emesis. Quality of life was rated as "very good", or "good" by more than half the patients before starting therapy. The assessment after the first chemotherapy cycle did not reveal any general deterioration. No statistical difference was detectable between the groups; altogether 41% of the patients reported an improvement in their quality of life after the first cycle, while 33% stated their quality of life was unchanged and 33% deteriorated.

In these last two studies no data were reported in the paper either on the number of patients evaluated for quality of life or on the missing values. Considering that the evaluation is carried out in open studies the risk of selection bias and confounding is high.

Another open study compared in cisplatin-treated ovarian cancer patients the antiemetic efficacy of ondansetron, granisetron, and metoclopramide.

Quality of life was assessed before chemotherapy, on day 1 and during 5 days (every evening) using the Rotterdam Symptom Checklist. In the first cycle 85% of patients receiving ondansetron, 83% of those receiving granisetron and 60% of those receiving metoclopramide achieved complete protection from vomiting [30].

A statistically significant improvement in the psychological subscale scores after ondansetron and granisetron was observed with respect to metoclopramide. No differences were reported in the physical activity subscale.

In an open non-randomised study, breast cancer patients submitted to moderately emetogenic chemotherapy received an antiemetic prophylaxis based on ondansetron or metoclopramide. The selection of the regimen was left to the attending physician and represented current practice at the institution [31]. Complete control of acute emesis was 77% with ondansetron and 32% with metoclopramide in the first 24 hours and 83% and 55% on days 2–5, respectively.

With both antiemetic regimens the levels of quality of life 1 day after chemotherapy, assessed with the EORTC QLQ-C30, were lower than prior to chemotherapy on all five functional scales, except the emotional scale. On average, patients who received ondansetron had a better score on day 1 than prior to chemotherapy on this scale. The differences between groups were not statistically significant on any of the functional scales.

Global quality of life decreased more with metoclopramide than with ondansetron, but the difference was not statistically significant (-24 versus -17).

On day 3 all scores, except the emotional dimension, were lower than prior chemotherapy. Changes in scores on global quality of life were similar for both groups. For the role functioning scale, changes in scores were significantly better for ondansetron.

Conclusions

In spite of the fact that the impact of chemotherapy-induced nausea and vomiting on HRQL has a short-term effect, its evaluation can be useful for clinical decisions concerning the choice of antiemetic prophylaxis. Only the results of antiemetic randomized clinical trials can be used to reach this aim. Moreover, because of the subjectivity of the patient's answers, only a double-blind study can assure reliable results. Finally, only the correct choice of the antiemetic treatments to be compared can lead to useful results [32]. In fact, if the new antiemetic prophylaxis were compared to a treatment different from the best, no information about the differences between the mean scores of the two arms (new treatment and standard therapy) would be available. More precisely, the above mentioned difference could be due only to an inferior efficacy of the used comparator with respect to the standard antiemetic therapy. For similar reasons any comparison involving sub optimal antiemetic regimens could be regarded as useless for a specific clinical decision.

Only 9 out of 13 comparative studies identified in our research were randomized and double-blind; three of them were concerned with non-standard antiemetic therapies, and two were dose finding studies. Therefore, only the results of 4 studies can be regarded as useful for orienting the choice of an antiemetic prophylaxis.

Summarizing the results obtained by the comparative studies carried out until now, the efficacy, tolerability and impact on HRQL of antiemetic regimens containing 5-HT₃ receptor antagonists were found superior to those that referred to the earlier used antiemetic drugs (metoclopramide, alizapride and prochlorperazine). Furthermore, in one study the combination of ondansetron plus dexamethasone, still the standard treatment for the

prevention of acute emesis induced by moderately emetogenic chemotherapy, was evaluated against metoclopramide plus dexamethasone. Its results show that the first antiemetic prophylaxis, allowing a better control of nausea and vomiting during the first 24 hours, also lead to an improvement in the patients HRQL.

Among the 13 comparative studies, a great heterogeneity of instruments aimed at evaluating HRQL was detected: in 4 studies FLIC and/or FLIE, in 3 the EORTC QLQ-C30, in 2 the Rotterdam Symptom Checklist, in 2 a uniscale, in 2 an ad hoc designed instrument was used. The reasons of the choice of the instrument to use to assess the influence of emesis on HRQL are clearly described by Uyl-deGroot et al. [32].

In conclusion, even if the number of the published studies specifically aimed to evaluate the impact of the chemotherapy-induced emesis on HRQL can be considered sufficiently high, those showing results that are reliable and useful to orient the clinical decision are few. Also considering the improvement in antiemetic therapy obtained in the last few years, and the more frequent implementation of reliable antiemetic guidelines, as well as the recent increasing diffusion of lower emetogenic chemotherapies, more research should be performed to obtain results on the impact of CIE on HRQL useful to orient the choice of antiemetic therapy.

List of abbreviations used

CIE: Chemotherapy-induced emesis

HRQL: Health-related quality of life

Authors' contributions

The paper is the result of the interactive collaboration between the authors.

All authors read and approved the final manuscript.

References

- Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM and Tattersall MHN: **On the receiving end – patient perception of the side effects of cancer chemotherapy.** *Eur J Cancer Clin Oncol* 1983, **19**:203-208.
- De Boer-Dennert M, de Wit R, Schmitz PIM, Djontono J, van Beurden V and Verweij J: **Patient perceptions of the side-effect of chemotherapy: the influence of 5HT₃ antagonists.** *Br J Cancer* 1997, **76**:1055-1061.
- Griffin AM, Butow PN, Coates AS, Childs AM, Ellis PM, Dunn SM and Tattersall MHN: **On the receiving end: patient perceptions of the side effects of cancer chemotherapy in 1993.** *Ann Oncol* 1996, **7**:189-195.
- The Italian Group for Antiemetic Research: **Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy.** *N Engl J Med* 2000, **342**:1554-1559.
- The Italian Group for Antiemetic Research: **Transferability to clinical practice of the results of controlled clinical trials: the case of antiemetic prophylactic treatment for cancer chemotherapy-induced nausea and vomiting.** *Ann Oncol* 1998, **9**:759-765.
- Lindley CM and Hirsch JD: **Nausea and vomiting and cancer patients' quality of life: a discussion of professor Selby's paper.** *Br J Cancer* 1992, **66**(Suppl XIX):S26-S29.
- Bliss JM, Robertson B and Selby PJ: **The impact of nausea and vomiting upon quality of life measures.** *Br J Cancer* 1992, **66**(Suppl XIX):S14-S23.
- Lindley CM, Hirsch JD, O'Neill CV, Transau MC, Gilbert CS and Osterhaus JT: **Quality of life consequences of chemotherapy-induced emesis.** *Qual Life Res* 1992, **1**:331-340.
- Schipper H, Clinch J, McMurray A and Levitt M: **Measuring the quality of life of cancer patients: the Functional Living Index-Cancer: development and validation.** *J Clin Oncol* 1984, **2**:472-483.
- Berry WR, House W, Lee JT, Plagge PB, Meshad MW and Grapski R: **Results of a compassionate-use program using intravenous ondansetron to prevent nausea and vomiting in patients receiving emetogenic cancer chemotherapy.** *Semin Oncol* 1992, **19**(6 Suppl 15):33-37.
- O'Brien BJ, Rusthoven J, Rocchi A, Latreille J, Fine S, Vandenberg T and Laberge F: **Impact of chemotherapy-induced nausea and vomiting on patients' functional status and costs: survey of five Canadian centers.** *Can Med Assoc J* 1993, **149**:296-302.
- Osoba D, Zee B, Pater J, Warr D, Latreille J, Kaizer L and for the Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group: **Determinants of postchemotherapy nausea and vomiting in patients with cancer.** *J Clin Oncol* 1997, **15**:116-123.
- Osoba D, Zee B, Warr D, Latreille J, Kaizer L and Pater J: **Effect of postchemotherapy nausea and vomiting on health-related quality of life.** *Support Care Cancer* 1997, **5**:307-313.
- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JCJM, Kaasa S, Klee M, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw K, Sullivan M, Takeda F and for the European Organization for Research and Treatment of Cancer Study Group on Quality of Life: **The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international trials in oncology.** *J Natl Cancer Inst* 1993, **85**:365-376.
- Pater JL, Osoba D, Zee B, Lofters W, Gore M, Dempsey E, Palmer M and Chin C: **Effects of altering the time of administration and the time frame of quality of life assessment in clinical trials: an example using the EORTC QLQ-C30 in a large antiemetic trial.** *Qual Life Res* 1998, **7**:273-278.
- Rusthoven JJ, Osoba D, Butts CA, Yelle L, Findlay H and Grenville A: **The impact of postchemotherapy nausea and vomiting on quality of life after moderately emetogenic chemotherapy.** *Support Care Cancer* 1998, **6**:389-395.
- Soukop M, McQuade B, Hunter E, Stewart A, Kaye S, Cassidy J, Kerr D, Khanna S, Smyth J, Coleman R, Cunningham D, Powels T, Davidson N, Hutcheon A, Geen J, Slater A, Rustin G and Carney D: **Ondansetron compared with metoclopramide in the control of emesis and quality of life during repeated chemotherapy for breast cancer.** *Oncol* 1992, **49**:295-304.
- De Haes JCJM, Van Knippenberg FCE and Neijt JP: **Measuring psychological and physical distress in cancer patients: Structure and application of the Rotterdam Symptom Checklist.** *Br J Cancer* 1990, **62**:1034-1038.
- Clavel M, Bonneterre J, d'Allens H, Paillarse JM and and the French Ondansetron Study Group: **Oral ondansetron in the prevention of chemotherapy-induced emesis in breast cancer patients.** *Eur J Cancer* 1995, **31A**:15-19.
- Crucitt MA, Hyman W, Grote T, Tester W, Madajewicz S, Yee S, Wentz A, Griffin D, Parasuraman TV and Bryson J: **Efficacy and tolerability of oral ondansetron versus prochlorperazine in the prevention of emesis associated with cyclophosphamide-based chemotherapy and maintenance of health-related quality of life.** *Clin Ther* 1996, **18**:778-788.
- Lofters WS, Pater JL, Zee B, Dempsey E, Walde D, Moquin JP, Wilson K, Hoskins P, Guevin M, Verma S, Navari R, Krook JE, Hainsworth J, Palmer M and Chin C: **Phase III double-blind comparison of dolasetron mesylate and ondansetron and an evaluation of the additive role of dexamethasone in the prevention of acute and delayed nausea and vomiting due to moderately emetogenic chemotherapy.** *J Clin Oncol* 1997, **15**:2966-2973.

22. Pater JL, Lofters WS, Zee B, Dempsey E, Walde D, Moquin JP, Wilson K, Hoskins P, Guevin RM, Verma S, Navari R, Krook JE, Hainsworth J, Palmer M and Chin C: **The role of the 5-HT₃ antagonists ondansetron and dolasetron in the control of delayed onset nausea and vomiting in patients receiving moderately emetogenic chemotherapy.** *Ann Oncol* 1997, **8**:181-185.
23. Garbe C, Drechsler S, Fiedler H, Tilgen W, Landthaler M, Schroeder K, Kuehne KH and Faerber L: **Dose comparison of tropisetron (Navoban) 5 mg and 10 mg orally in the prophylaxis of dacarbazine-induced nausea and emesis.** *Semin Oncol* 1994, **21**(5 Suppl 9):12-16.
24. Barrenetxea G, Schneider J, Centeno MM, Romero H, de la Rica M and Rodriguez-Escudero FJ: **Chemotherapy-induced emesis: management of early and delayed emesis in milder emetogenic regimens.** *Cancer Chemother Pharmacol* 1996, **38**:471-475.
25. Lebeau B, Depierre A, Giovannini M, Rivière A, Kaluzinski L, Votan B, Hédoquin M, d'Allens H and the French Ondansetron Study Group: **The efficacy of a combination of ondansetron, methylprednisolone and metopimazine in patients previously uncontrolled with a dual antiemetic treatment in cisplatin-based chemotherapy.** *Ann Oncol* 1997, **8**:887-892.
26. Kobayashi K, Ishihara Y, Nukariya N, Niitani H, Furue H and Joint Research Group for Tropisetron Double-Blind Comparative Study: **Effects of anti-emetic drug (tropisetron) on quality of life during chemotherapy: use of a diary-type questionnaire and application of summary measures for assessment in a randomized, multicentre study.** *Respirology* 1999, **4**:229-238.
27. Ishihara Y, Nukariya N, Kobayashi K, Furue H and Niitani H: **The development of a new QOL questionnaire on chemotherapy-induced emesis and vomiting – investigation of reliability and validity.** *Gan To Kagaku Ryoho* 1996, **23**:745-755.
28. Sorbe BG, Hogberg T, Glimelius B, Schmidt M, Wernsted L, Hansen O, Sorensen BT, Raisanen I, van Oosterom AT and de Bruijn KM: **A randomized, multicenter study comparing the efficacy and tolerability of tropisetron, a new 5-HT₃ receptor antagonist, with a metoclopramide-containing antiemetic cocktail in the prevention of cisplatin-induced emesis.** *Cancer* 1994, **73**:445-454.
29. Drechsler S, Brunsch U, Eggert J, Grote-Kiehn J, Gosse H, Bangert M, Ukena D, Oehm C, Mezger J, Faerber L, Inhoff W, Untch M and Gallmeier WM: **Comparison of three tropisetron-containing antiemetic regimens in the prophylaxis of acute and delayed chemotherapy-induced emesis and nausea.** *Support Care Cancer* 1997, **5**:387-395.
30. Torok J, Thurzo L and Nyari T: **Serotonin antagonists and metoclopramide in the prophylaxis of cisplatin-induced vomiting in patients with ovarian cancer. Antiemetic and quality of life comparison.** *EHP* 1999, **5**:15-19.
31. Lachaine J, Laurier C, Langleben A and Vaillant L: **Cost-effectiveness and quality of life evaluation of ondansetron and metoclopramide for moderately emetogenic chemotherapy regimens in breast cancer.** *Crit Rev Oncol Hematol* 1999, **32**:5-12.
32. Uyl-de Groot CA, Wait S and Buijt I: **Economics and health-related quality of life in antiemetic therapy; recommendations for trial design.** *Eur J Cancer* 2000, **36**:1522-1535.

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."

Sir Paul Nurse, Cancer Research UK

Your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp

