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Original article

Multinational study exploring patients' perceptions of side-effects induced by chemo-radiotherapy

Christina H. Ruhlmann [a,*], Trine Zeeberg Iversen [b], Meena Okera [c], Aida Muhic [d], Gunnar Kristensen [e,f,g], Petra Feyer [h], Olfred Hansen [a,i], Jørn Herrstedt [a,i]

[a] Department of Oncology, Odense University Hospital; [b] Department of Oncology, Copenhagen University Hospital, Herlev, Denmark; [c] Adelaide Cancer Centre, Royal Adelaide Hospital, Australia; [d] The Finsen Centre, Rigshospitalet, Copenhagen, Denmark; [e] Department for Gynecologic Cancer; [f] Institute for Cancer Genetics and Informatics, Oslo University Hospital; [g] Institute for Clinical Medicine, Oslo University, Norway; [h] Department of Radiation Oncology, Vivantes Clinics Neukoelln, Berlin, Germany; and [i] Institute of Clinical Research, University of Southern Denmark, Denmark

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ABSTRACT

Purpose: We aimed to prospectively assess the incidence, severity and patients' perceptions of side-effects induced by radiotherapy and concomitant weekly cisplatin.

Patients and methods: This multinational survey included patients with a diagnosis of gynaecological or head and neck cancer scheduled to receive radiotherapy and concomitant weekly cisplatin. Patients completed a questionnaire prior to anti-cancer treatment and after 3 weeks of treatment. Baseline frequency and severity of symptoms were compared to frequency and severity after 3 weeks of treatment, and patients were asked to rank the five most severe symptoms experienced.

Results: An increase in the severity as well as in the mean number of symptoms (18 compared to 24) was observed during treatment. Patients ranked 7 of the 10 most feared baseline symptoms as non-physical, whereas 8 of the 10 most feared symptoms after 3 weeks of treatment were physical. Nausea was ranked as the 5th most severe symptom during treatment, despite 98% of patients receiving antiemetic prophylaxis.

Conclusion: Patients with head and neck cancer or gynaecological cancer suffer from a number of primarily non-physical symptoms before starting combined chemo-radiotherapy. After 3 weeks of treatment patients score 8 of the 10 most feared symptoms as physical. Future trials focusing on the prevention of side-effects in patients receiving radiotherapy and concomitant chemotherapy are highly warranted.
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The role and significance of supportive care has become increasingly important due to the increased use of multi-modality and multi-targeting antineoplastic treatments. New drug discovery and potential synergism of approved antineoplastic treatment combinations constantly challenge oncologists to provide effective treatment regimens with low side-effect profiles.

Patients' perceptions of physical and non-physical symptoms experienced during the course of chemotherapy were investigated retrospectively by Coates and colleagues in 1983 [1]. These patients, all diagnosed with advanced cancer, ranked the 5 most feared symptoms as: 'vomiting' (1), 'nausea' (2), 'hair loss' (3), 'thought of coming to treatment' (4), and 'length of treatment' (5). The research group repeated the study in 1993, when new supportive care drugs (e.g. antiemetics) had become available [2]. This study, besides from including patients with advanced cancer, also included patients receiving adjuvant chemotherapy (primarily cyclophosphamide, methotrexate, and fluorouracil (CMF)). The five most severe symptoms were 'nausea' (1), 'tiredness' (2), 'hair loss' (3), 'effect on family' (4), and 'vomiting' (5). Thus, 'nausea' replaced 'vomiting' as the adverse event considered as the most troublesome adverse event by the patients; a finding that was confirmed in 1997 [3]. Furthermore a subsequent study found that nausea has a significantly higher impact on patients' quality of life than vomiting [4].

The patients' own perceptions of side-effects induced by radiotherapy and concomitant chemotherapy have not been properly investigated, but it is well known that patients undergoing combined modality treatment are subjected to more unpleasant and severe acute and long-term side-effects than those receiving radiotherapy or chemotherapy alone [5–7]. Consequently, this study was designed to address three issues; (I) to prospectively compare the incidence and severity of symptoms before and after 3 weeks of radiotherapy and concomitant cisplatin, (II) to assess the patients' perceptions of the symptoms (ranking of symptoms according to

* Corresponding author at: Department of Oncology, Odense University Hospital, Sdr. Boulevard 29, Entrance 109, DK-5000 Odense C, Denmark.
E-mail address: c.ruhlmann@dadlnet.dk (C.H. Ruhlmann).

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severity) before and after 3 weeks of treatment, and (III) to explore risk factors for nausea and vomiting.

Patients and methods

Study design and patient selection

This prospective, multicentre, observational study to prospectively identify patients' perceptions of side-effects to radiotherapy and concomitant weekly cisplatin was conducted in 6 centres in four countries (Denmark (3), Australia (1), Norway (1), and Germany (1)). Eligible patients were $\geqslant$18 years of age with histologically confirmed cervical-, vulvar-, or head and neck cancer. Patients were chemo- and radiotherapy naïve. Patients were scheduled to receive External Beam Radiation Therapy (EBRT) and concomitant weekly cisplatin 40 mg/m^2, (in Australia, patients with head and neck cancer received concomitant cisplatin 100 mg/m^2 every third week). EBRT was given as five fractions per week (Mondays through Fridays) in a dose of 1.8–2.0 Gy per fraction and delivered as either Intensity-Modulated Radiation Therapy (IMRT)-technique with 5–7 fields or as box-technique. The patients treated in Danish centres for head and neck cancer in addition received nimorazole (a hypoxic radiosensitizer) 1200 mg/m^2 concomitant to radiotherapy. Women with gynaecological cancer were not allowed to receive brachytherapy during the 3 week study period. Patients were required to be able to read, understand, and complete the study questionnaires themselves. The study was approved by The Danish Data Protection Agency (approval number 2008-41-2929), and reported to the Regional Ethics Committees.

Assessment methods

The methodology used in this study was an approximation and an extension of the methods applied by Coates and colleagues [1]. Patients were asked to complete a 54 item questionnaire before start of chemo-radiotherapy and after 3 weeks of treatment (hereafter referred to as pre-treatment and post-treatment). Hence, post-treatment questionnaires assessed the side-effects after 15 fractions of EBRT and 3 weekly cycles of cisplatin. The questions represented 37 physical symptoms and 17 non-physical symptoms graded on a 4-point Likert scale ('not at all', 'a little', 'quite a bit', and 'very much'). Patients ranked the five most severe symptoms from most to least severe. The following patient and treatment data were collected: age, gender, diagnosis, radiotherapy and chemotherapy regimens, and antiemetic treatment.

Statistical analysis

Data were collected on a web-based database. The incidence of symptoms post-treatment compared to pre-treatment was analysed using McNemar's test. The severity of symptoms was analysed using the Wilcoxon matched pairs signed rank test. For this purpose the Likert scale was assigned numeric values as follows: 'not at all' valued 1, increasing to value 4 for the worst grade. The relative severity (patients' ranking) of symptoms was analysed as follows: five points were allocated to the symptom ranked as most severe, decreasing to 1 point for the symptom ranked as 5th. The points allocated to each symptom were then added and divided by the number of patients in the sample, to give an overall score for each symptom. The analysis was performed for both pre- and post-treatment data, and patients' responses were compared according to diagnosis [1]. Prior to data collection it was decided to explore nausea and vomiting data further, referring to the impact of nausea and vomiting on quality of life [4]. Logistic regression (univariable and multiplicative model) was used to analyse the relationship for both nausea and vomiting post-treatment, with respect to diagnosis, age, use of aprepitant, and nimorazole. Test for interaction and model checking (goodness-of-fit test) were performed for P-values $\leqslant$0.05.

Results

Patient and treatment characteristics are presented in Table 1. A total of 167 patients entered the study and completed the pre-treatment questionnaire. After 3 weeks of treatment, 88% (147 patients) completed the post-treatment questionnaire. Reasons for not completing the second questionnaire were: treatment cancelled (1), questionnaire not handed out (8), questionnaire not returned (8), and undisclosed reasons (3). Antiemetic prophylaxis was prescribed to 98% of patients. A total of 98% received a serotonin receptor antagonist (RA) and 96% a corticosteroid. Fewer patients treated for head and neck cancer received a neurokinin $(NK)_1$ RA compared with the gynaecological cancer group (29% versus 43%).

The pre-treatment mean number of physical symptoms was 10 (range 0–26) compared to 16 (range 0–33) post-treatment, and the mean number of non-physical symptoms was 8 (range 0–17) both pre- and post-treatment. The frequencies (proportions of patients reporting) of all symptoms pre- and post-treatment are listed in Supplementary Tables 1 and 2 for physical and non-physical symptoms, respectively. In summary, a significant increase in the number of patients reporting a symptom was observed for 32 of the 37 physical symptoms, and for 5 of 17 non-physical symptoms. A significant decrease in the incidence was seen for 4 of 17 non-physical symptoms ('worrying', 'crying', 'concerns about the thought of coming for treatment', and 'concerns about the length of treatment (chemotherapy)'), whereas no decrease was seen for any of the physical symptoms.

A statistical significant increase in the severity of symptoms was observed for 32 of the 37 physical symptoms, and for 5 of 17 non-physical symptoms (Supplementary Tables 1 and 2). This was in accordance with the increase in incidences. A statistically significant decrease in severity was seen for 5 of 17 non-physical

Table 1
Patient and treatment characteristics.

Patients (N)	167
Diagnosis (N)	
Gynaecological cancer	90
Head & neck cancer	77
Age (median)	
All [range 21–78 years]	56
Gynaecological cancer [range 21–78 years]	54
Head & neck cancer [range 41–77 years]	57
Gender, head & neck cancer only (%)	
Female	26
Male	74
Treatment (median)	
Cisplatin dose [range 40–100 mg/m^2]	40
Radiation dose [range 50–70 Gy]	64
Radiation dose per fraction [range 1.8–2 Gy]	2
Hypoxic radiosensitizer, head & neck cancer only (%)	
Nimorazole	71
Antiemetic prophylaxis (%)	
Any prophylaxis	98
5-HT_3 RA	98
Corticosteroid	96
NK_1 RA	38
Antiemetic rescue medication (%)	
Dopamine RA	66
Benzodiazepine	14

Abbreviations: 5-HT_3: serotonin; NK_1: neurokinin1; RA: receptor antagonist.

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