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Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists

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Summary In 1983, Coates conducted a survey that ranked the side-effects perceived by patients receiving chemotherapy in the order of their severity. Vomiting and nausea were found to be the two most distressing side-effects. They have an impact on quality of life and compliance with treatment. The development of 5HT3 antagonists has been a major step forward in the prevention and treatment of chemotherapy-induced nausea and vomiting. Presently, these antiemetics are routinely used as concomitant therapy in emetogenic chemotherapy regimens. The purpose of this study was to evaluate the impact of 5HT3 antagonists on patient perceptions of the side-effects of chemotherapy. Coates' survey was replicated in patients who received 5HT3 antagonists for acute nausea and vomiting resulting from emetogenic chemotherapy. Patients received the survey to identify those physical and non-physical side-effects that they attributed to chemotherapy and were asked to rank the five most distressing side-effects. Of the 197 patients who consented to take part in the study, 181 were evaluable. Nausea, hair loss and vomiting were described as the three most distressing side-effects of chemotherapy. Eighty per cent of all the patients actually experienced nausea and 57% experienced vomiting. Hair loss appeared to be more distressing to women ($P < 0.001$) but, in other aspects, gender, age and marital status did not influence the ranking of the three most distressing side-effects. Constipation was ranked as 6th and was not identified as a distressing side-effect in 1983. Nausea and vomiting remain to be the first and third most distressing side-effects of chemotherapy, even though the incidence and severity of acute nausea and vomiting are now significantly reduced.

Keywords: chemotherapy; nausea; vomiting; side-effects; serotonin antagonists

Nausea and vomiting have been reported by patients, nurses and physicians as the most distressing side-effects of chemotherapy (Coates et al, 1983; Love et al, 1989; Pritchard, 1989; Cooper, 1992; Martin, 1992; Youngblood et al, 1994). The introduction of the 5HT3 antagonists Tropisetron, Ondansetron and Granisetron have significantly reduced the incidence of these distressing side-effects. Physicians and nurses have observed that 5HT3 antagonists have contributed to an improvement of quality of life and compliance with treatment (Seynaeve et al, 1991*a*). However, the impact of these new drugs on patients' perceptions of chemotherapy-induced side-effects has not yet been investigated (Manson et al, 1993). Unfortunately, some health care workers extrapolate data on the improvement of antiemetic efficacy in the phase of acute emesis to represent the total experience of emesis in treated patients. They tend to believe that a decrease in the incidence and severity of acute emesis reduces the patients' distress accordingly. This might not be the case (Love et al, 1989; Bliss et al, 1992; Schmoll, 1992; Jansen et al, 1993; de Wit et al, 1996) as delayed emesis remains a serious problem. Therefore, we believed a reassessment and re-ranking of the most distressing side-effects of chemotherapy perceived by patients was warranted. In addition, the most distressing side-effects of chemotherapy during each course of treatment may be crucial for the planning of appropriate interventions and for identifying possible research questions (Martin, 1992; Youngblood et al, 1994; de Wit et al, 1996).

We studied the patients' perceptions of physical and non-physical side-effects of current chemotherapy, using the questionnaire previously used by Coates et al (1983) in an era before the introduction of the 5HT3 antagonists. Patients ranked their side-effects in order of distress. Influencing factors, such as the number of treatment courses and patient characteristics, were also analysed for their effect on the order of distress. The ranking of nausea and vomiting was than compared with the results published by Coates in 1983 and by Griffin in 1996.

PATIENTS AND METHODS

Eligibility criteria for the study included the following: age ≥ 18 years; treatment with emetogenic chemotherapy and concomitant 5HT3 antagonists for the prevention and/or management of acute nausea and vomiting from the first treatment cycle on. Patients were treated with chemotherapy in the outpatient department or were admitted to the hospital. Patients entered the study during any cycle of chemotherapy.

For the prevention of acute nausea and vomiting, patients were treated with either Ondansetron 8 mg or Tropisetron 5 mg as single agent or in combination with dexamethason 10 mg. Both were administered intravenously 15 min before the start of chemotherapy. For delayed nausea and vomiting, various antiemetics were prescribed.

Patients were informed by the participating physicians or the study nurses about the objectives of the study. After consenting, the nurse explained how the questionnaire was to be completed. All patients gave verbal informed consent according to the rules of

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Table 1 Group A – physical symptoms

1	Feeling sick (nausea)
2	Being sick (vomiting)
3	Itching at injection site
4	Shaking all over
5	Change in the way things taste
6	Changes in how things smell
7	Not having regular bowel action (constipation)
8	Loss of liquid or frequent bowel action (diarrhoea)
9	Pins and needles in fingers and toes
10	Numbness in fingers or toes
11	Loss of weight
12	Weight gain
13	Increased hair growth on legs
14	Constantly tired
15	Giddiness on standing up
16	Loss of appetite
17	Sore mouth
18	Sore throat
19	Shortness of breath
20	Skin rash
21	Bruise easily
22	Difficulty sleeping
23	Pain passing water (painful urination)
24	Coloured urine
25	Ringing in ears
26	Deafness
27	General aches and pains
28	Tummy ache (abdominal pain)
29	Swollen tummy (abdominal fullness)
30	Periods stop
31	Periods become irregular
32	Changes in skin colour
33	Hot flushes
34	Heart beating fast (palpitations)
35	Headache/migraine
36	Loss of hair
37	Increased thirst
38	Passing more water than usual (increased urination)
39	Dry skin
40	Acne (pimples)
41	Increased appetite
42	Trouble with swallowing
43	Nose bleeds
44	Cannot taste things
45	Fingernails go brown

Table 2 Group B – non-physical symptoms

1	Loss of sexual feeling
2	Loss of sexual ability (not getting aroused)
3	Feeling low, miserable (depression)
4	Thought of coming for treatment
5	Length of time treatment takes at the clinic
6	Feeling bad tempered (irritability)
7	Having to have an injection
8	Having to come to clinic rather than private doctor
9	Affects my family or partner
10	Feeling of not coping generally with treatment
11	Feeling of having to have treatment that I do not think will do any good
12	Feeling of having to have treatment that I do not want
13	Crying more often
14	Feeling angry
15	Cannot concentrate
16	Affects my work/home duties
17	Affects my social activities
18	Infertility (cannot have children)
19	Trouble finding somewhere to park near the clinic
20	Trouble getting to the clinic
21	Not having the chance to ask the doctor questions
22	Forget things
23	Not seeing the same doctor each time
24	Cannot get clothes to fit
25	Not understanding what is happening
26	Feeling anxious or tense
27	Having to wait for treatment with other patients
28	Feeling that the treatment is damaging my body

our institute. The survey was conducted using the questionnaire used previously by Coates et al (1983). Side-effects were divided in two groups: group A (Table 1) comprised 45 physical side-effects and group B (Table 2) compised 28 non-physical side-effects. It was possible to add side-effects experienced by the patient that were not included in the listings. Patients were asked to circle all side-effects that they attributed to their chemotherapy. Subsequently, they ranked the five most distressing side-effects that they experienced from each group in order of severity. The two groups of five physical and non-physical side-effects were combined and patients then ranked the five most distressing side-effects regardless of group. We agreed to use a self-reporting questionnaire as it allows for privacy and facilitates the disclosure of symptoms or side-effects of a sensitive nature (Youngblood et al, 1994). For analysis of the data, we allocated 5 points to the most distressing side-effect decreasing to 1 point for the side-effect ranked as the least distressing. Limited demographic data were collected; age, gender, marital status, diagnosis, prior chemotherapy regimens, the current chemotherapy regimen and number of treatments given, the antiemetic treatment regimen and response to chemotherapy. Age was grouped into less than 45 years, 45–60 years and over 60 years.

Chemotherapy regimens were grouped into cisplatin based, doxorubicin based and those comprising neither of the two drugs. If the statistical analysis listed two items ranked as equally distressing, both items were allocated the next lower number in sequence. Corrections were not made for disease-related symptoms in the side-effects that patients reported as relating to their chemotherapy.

The relative severity of side-effects was analysed using descriptive statistical methods (ranking the data) and tabulated against the patient characteristics, diagnosis, treatment and response. When a correlation was found with the chi-square test, the exact test for $r \times c$ was formally performed. Patient characteristics, diagnosis, treatment and response were combined with the severity of each side-effect separately and formally tested with Fisher's exact test for a 2ck table; for these analyses, severity was expressed as a dichotomy: belonging to the five most severe side-effects (yes/no). The usual level of 5% was used as the level of statistical significance.

RESULTS

Two hundred patients were asked to participate in the study and 197 patients completed the questionnaire. Eight patients filled out the questionnaire incorrectly and upon analysis eight additional questionnaires demonstrated inconsistencies and were also excluded from the final analysis. The characteristics of the 181 evaluable patients are shown in Table 3. Fifty-six patients were treated in the outpatient department, 125 received their treatment as inpatients. Chemotherapy regimens and the antiemetics used to prevent chemotherapy-induced acute and delayed emesis are listed in Table 4. Patients had received 1–20 courses (mean, four) of chemotherapy at the time of completing the questionnaire;

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Table 3 Patient characteristics

No. of evaluable patients	181
Male/female	101/80
Mean age (range) (years)	50 (18–78)
Marital status	
Spouse	141
No spouse	40
Alone	24
Not alone	157
Tumour types	
Breast cancer	50
Soft-tissue sarcoma	26
Testicular cancer	20
Small-cell lung cancer (SCLC)	14
Head and neck cancer	13
Non-small-cell lung cancer	10
Ovarian cancer	9
Mesothelioma	7
Miscellaneous	32

Table 4 Chemotherapy given and antiemetics used

Chemotherapy	
Including cisplatin	89
Cisplatin	40
Cisplatin/ifosfamide	17
BEP	15
VIP	6
Other	11
Including doxorubicin	25
Doxorubicin/ifosfamide	15
Other	10
Neither cisplatin nor doxorubicin	65
FEC	26
CMF	21
ICE	7
Other	11
Both	2
Antiemetics	
Day 1	
Ondansetron	11
Ondansetron/dexamethasone	81
Tropisetron	32
Tropisetron/dexamethasone	57
Days 2–5	
Domperidon	63
Metoclopramide	44
Zofran ± methylprednisolone	10
Tropisetron	8
Ondansetron + dexamethason	6
Ondansetron	6
Dexamethasone	4
Various	40

BEP: bleomycin, etoposide, cisplatin; VIP: etoposide, ifosfamide, cisplatin; CDDP: cisplatin; VP16: etoposide; DOXO: doxorubicin; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; CMF: cyclophosphamide, methotrexate, fluorouracil; ICE: ifosfamide, carboplatin, etoposide; Other: less than four equal regimens.

17 patients had received prior chemotherapy. The mean number of selected physical side-effects was eight (range 0–26) and of non-physical side-effects was five (range 0–17). Patients ranked nausea, hair loss and vomiting as the most distressing side-effects; the ten most distressing side-effects are listed in Table 5. Table 6 lists the analysis of the ten most distressing side-effects by gender, age and marital status compared with the overall ranking, which is given in the top row of the table. Items ranked in the top ten subanalysis that were not listed in the top ten of the overall analysis are listed on the right side of the table. The ranking of the four most distressing side-effects was quite consistent for gender, age and marital status.

Compared with men, women ranked hair loss significantly higher than vomiting ($P < 0.001$), and they also ranked feeling miserable (depression), anxious or tense higher than men. Men were more concerned by the thought of coming for treatment, the length of time treatment takes at the clinic ($P = 0.006$) and by infertility.

Infertility caused more distress in the younger patients ($P < 0.001$). The ranking of effects on family and partner and of feeling anxious or tense decreased with age, while the ranking of constipation and of having to have an injection increased. The thought of coming for treatment affected older patients less ($P = 0.045$). Crying more often was important to the patients aged 45–60 years ($P = 0.048$).

Patients living alone were obviously less concerned about the effects on family or partner. Constipation was ranked lower in patients living alone, the influence on loss of appetite and taste was ranked higher.

Table 7 shows the analysis by tumour type and chemotherapy regimen. The subgroups are smaller and a wider variability was found. The testicular cancer patients were predominantly in the

Table 5 Ten most distressing side-effects of chemotherapy

Rank	1983	1995
1	Being sick (vomiting)	Feeling sick (nausea)
2	Feeling sick (nausea)	Loss of hair
3	Loss of hair	Being sick (vomiting)
4	Thought of coming for treatment	Constantly tired
5	Length of time treatment takes at the clinic (24)	Having to have an injection
6	Having to have an injection	Constipation (–)
7	Shortness of breath (15)	Thought of coming for treatment
8	Constantly tired	Affects family or partner
9	Difficulty sleeping (21)	Feeling low, miserable (depression) (14)
10	Affects family or partner	Feeling anxious or tense (13)

Numbers in parentheses indicate the ranking number in the opposite column.

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Table 6 Most distressing side-effects by sex, age and marital status

	Feeling sick (nausea)	Loss of hair	Being sick (vomiting)	Constantly tired	Having to have an injection	Constipation	Thought of coming for treatment	Affects family or partner	Feeling low, miserable (depression)	Feeling anxious or tense	
Entire group	1	2	3	4	5	6	7	8	9	10	
Sex											
Male (80)	1	3	2	4	6	7	5	8	11	13	Infertility (10)
Female (101)	1	2	3	4	5	7	10	8	6	9	
Age (years)											
< 45 (63)	1	3	2	4	8	11	7	5	12	9	Affects my work (11) Infertility (6)
45–60 (76)	1	2	3	4	7	8	5	9	7	10	
> 60 (42)	1	3	2	4	6	5	13	15	8	17	Shortness of breath (8) Loss of taste (9) Loss of appetite (10)
Marital status											
Spouse (141)	1	2	3	4	6	5	8	7	9	10	
No spouse (40)	1	2	3	4	5	14	6	11	9	7	Loss of appetite (8) Infertility (10)
Alone (24)	1	3	2	4	6	20	7	13	6	9	Loss of appetite (8) Change in the way things taste (10)
Not alone (157)	1	2	3	4	6	5	8	7	9	10	

Items ranked in the top ten subanalysis that were not listed in the top ten of the overall analysis are listed on the right side of the table.
If two items were ranked as equally distressing, e.g. < 3 >, this number was not listed and both items were allocated the next lower rank number instead (2 × < 4 >).

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Table 7 Most distressing side-effects by tumour type, chemotherapy, tumour response and course number

	Feeling sick (nausea)	Loss of hair	Being sick (vomiting)	Constantly tired	Having to have an injection	Constipation	Thought of comingfor treatment	Affects family or partner	Feeling low, miserable (depression)	Feeling anxious or tense	
Entire group	1	2	3	4	5	6	7	8	9	10	
Tumour types											
Sarcoma (26)	2	1	4	3	5	10	8	8	11	9	Shortness of breath (6)
Testis (20)	1	5	3	10	18	23	18	4	32	15	Infertility (2) Change in the way things taste (10) Length of time treatment takes at the clinic (6) Affects my work/home duties (7) Feeling that the treatment is damaging my body (8)
Head and neck (13)	1	–	2	4	14	19	24	7	10	4	Feeling of not coping with treatment (5) Sleeping disorders (7) Loss of taste (8)
SCLC (14)	2	1	3	5	9	–	4	7	10	–	Cannot concentrate (7) Change in the way things taste (9)
Breast (50)	1	2	3	4	8	7	9	12	5	6	Hot flushes
Chemotherapy											
CDDP (89)	1	2	3	4	5	6	7	8	9	16	Length of time treatment takes at the clinic (10)
Doxorubicin (25)	2	1	4	3	7	–	8	5	12	7	
Neither (65)	1	2	3	4	7	6	10	9	5	8	
Entire group (181)	1	2	3	4	5	6	7	8	9	10	
Tumour response											
CR + PR (31)	1	2	3	6	13	9	12	4	7	23	Feeling that the treatment is damaging my body (5) Length of time treatment takes at the clinic (9)
SD (47)	1	2	3	4	5	7	6	16	10	12	Shortness of breath (8) Change in the way things taste (9)
Course of treatment											
1 + 2 (38)	1	2	3	4	6	7	19	9	16	6	Shortness of breath (11) Difficulty sleeping (8)
3 (26)	1	4	3	2	26	8	7	7	5	10	Affects my work/home duties (9)
4 (35)	1	2	3	6	4	11	9	6	7	14	Loss of appetite (11) Affects my social activities (8) Feeling that the treatment is damaging my body (5)
5 (42)	1	2	3	4	6	7	6	8	9	10	
≥ 6 (40)	1	2	3	4	10	10	6	11	5	23	Affects my work/home duties (8) Feeling that the treatment is damaging my body (5)

Items ranked in the top ten subanalysis that were not listed in the top ten of the overall analysis are listed on the right side of the table.
If two items were ranked as equally distressing, e.g. < 3 >, this number was not listed and both items were allocated the next lower rank number instead (2 × < 4 >).
CR, complete response; PR, partial response; SD, stable disease.

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Table 8 The incidence of nausea and vomiting vs the overall top five rating

Course of treatment	Incidence (%)	Top five rated (%)	Mean[a]
Nausea			
1 + 2	76	59	4.1
3	81	76	4.3
4	77	78	3.8
5	79	66	4.1
≥ 6	88	60	4.1
Vomiting			
1 + 2	60	48	4.0
3	61	68	3.2
4	46	75	3.8
5	52	55	3.5
≥6	65	58	3.3

[a]The mean relative severity of the points allocated from 1 (least severe) to 5 (most severe).

younger age ranges. They ranked infertility as a high distressor ($P < 0.001$) and feeling miserable (depression) was ranked low. None of the head and neck cancer patients mentioned loss of hair and none of the small-cell lung cancer (SCLC) patient listed constipation or feeling anxious or tense as distressing side-effects. Patients receiving doxorubicin regimens reported hair loss as most distressing and appeared much more concerned with the effects on their families or partner. Patients receiving cisplatin rated the length of time that the treatment takes in the clinic as highly distressing compared with other patients. This could be related to the time required for pre- and post-hydration. Statistical analysis revealed that vomiting ($P = 0.04$), weight gain ($P = 0.01$) and hot flushes ($P = 0.03$) were important to patients receiving neither cisplatin nor doxorubicin; a group predominantly consisting of breast cancer patients as seen in Table 4. Table 7 shows the results according to tumour type, tumour response and the number of courses. Responding patients had considerably less anxiety and tension, and less difficulty with the thought of coming for treatments and having a needle. They were very concerned, however, about the effects on their families or partner. The thought that the treatment had damaged the body was experienced as highly distressing by patients who had achieved a complete response ($P < 0.001$).

Analysis of the number of treatment courses given demonstrated that the thought of coming for treatment and depression became more distressing after multiple treatment courses, whereas feeling anxious or tense decreased. During multiple treatment courses, the patients' distress related to the affects on partner and family firstly increased and then subsequently decreased. Sleeping problems are mentioned more frequently during course 1 and 2. Fatigue is predominant by course 3.

Table 8 shows the percentage of patients who identified nausea and vomiting as a side-effect of their chemotherapy per course number and, subsequently, the percentage of these patients who included these side-effects in their overall top five ranking; in addition, the mean severity ascribed to these side-effects is presented.

DISCUSSION

The introduction of 5HT3 antagonists for the prevention of chemotherapy-induced nausea and vomiting is frequently considered to be one of the most important achievements in supportive care in the last decade. Nevertheless, physicians and other health care workers may overestimate this achievement. The ten most distressing side-effects of the overall groups analysis in the present study and the results reported by Coates et al (1983) are listed in Table 5. The objective of this study was to investigate the current status of patient perceptions of side-effects rather than to compare our results with those reported by Coates et al (1983), and clearly several factors hamper such a comparison. Firstly, our patients received more intensive chemotherapy, partly related to the availability of 5HT3 antagonists; secondly, Coates' patient population consisted predominantly of women. Still, our results do show that, despite the use of 5HT3 antagonists as denominator for participation to this study, patients ranked nausea and vomiting as the first and third most distressing side-effects of chemotherapy, which is almost similar to the results of over a decade ago (Coates et al, 1983). This is also consistent with the findings of Griffin et al (1996) who identified nausea as the major problem in a similar survey. Obviously, the question is why the increased ability to prevent nausea and vomiting is not reflected in the patients' perception of this side-effect. First of all, as has already been suggested by others (Cooper, 1992), the frequency and/or severity of symptoms may not be correlated with the levels of distress expressed by the patient. For a patient, for instance, 10 days of minor nausea may be more distressing than 1 day of severe vomiting. Secondly, the 5HT3 antagonists have improved the prevention and treatment of acute nausea and vomiting rather than the delayed nausea and vomiting. Thirdly, the studies that have been performed on the efficacy of 5HT3 antagonists over multiple courses appear to show that their effect is not maintained (de Wit et al, 1996). With increasing numbers of treatment cycles, there is a progressive loss of efficacy. This may influence the patients' perception for the whole treatment period. Table 8 demonstrates that a high percentage of patients already experience some nausea and vomiting during the first two courses. Nevertheless, in the first two courses of treatment, patients ranked nausea and vomiting as highly distressing in our study, again suggesting the relative importance of the level of distress vs the severity and frequency of the side-effects. Our study was not designed in a way to enable such an analysis, but the option should be considered in further research projects. In addition Table 8 outlines that the majority of the patients who experience nausea and vomiting describe the side-effects as one of the five most distressing side-effects and rank it very highly.

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Hair loss remains an important distressing side-effect for patients, which is not surprising given the fact that there are no effective methods to circumvent this side-effect. This was also found in the study of Griffin et al (1996). Compared with men, women ranked hair loss as being more distressing than vomiting, even though it is well known that they are more susceptible to the latter. This stresses the sociopsychological relevance of hair loss to women. Some of the gender differences with reference to hair loss may also be explained by the fact that men are often faced with some age-related hair loss. Patients treated with cisplatin-based regimens also ranked hair loss as highly distressing. Cisplatin monotherapy does not cause hair loss but, in patients participating in this study, it was combined with drugs that are well known to induce hair loss. Head and neck cancer patients did not report hair loss as a distressing side-effect, as none of these patients received any drug that causes hair loss. In comparison to the study performed by Coates et al (1983), the length of time treatment takes in the clinic is no longer perceived as one of the ten most distressing factors. This may reflect the fact that in the last decade there has been a shift from hospital admissions to outpatient treatment. However, as in the Coates' study (Coates et al., 1983), the length of time that treatment takes, as well as having to wait for treatment, did cause more distress in men.

Constipation is a new problem compared with 1983, now being perceived as one of the ten most distressing factors. This is a well known side-effect of 5HT3 antagonists (Seynaeve et al, 1991*b*), and the fact that all patients entered in this study received these drugs presumably explains the high ranking of this symptom. This may be a very important observation. Although we are able to control nausea and vomiting better, this is not reflected in the patients' perception of this side-effect and, moreover, this control is achieved at the cost of other side-effects such as constipation, which is apparently adding to the level of distress for the patient – another reason for a careful reappraisal of the implementation and dosing of the 5HT3 antagonists. Surprisingly, this was not identified as a distressing symptom by Griffin et al (1996).

A few distressing side-effects are no longer ranked high in the present study compared with the previous study of Coates et al (1983). One such side-effect is shortness of breath; the reason for this being no longer ranked high is unclear. It may be that the selection of patients has changed and, presently, mainly patients with a better performance score and/or an earlier stage of disease are treated with chemotherapy. Difficulty in sleeping is also ranked lower. In view of the fact that feeling depressed, anxious or tense are still ranked high, any improvement in this respect can be excluded in trying to explain this finding. Whether night medication is either more effective or used more appropriately remains to be elucidated.

A few other issues also warrant attention. Infertility as a result of chemotherapy appeared to be of major concern to patients with testicular cancer, even though it is well known that many of these patients appear to be infertile before the start of chemotherapy (Drasga et al, 1983). Clearly, the information given to these patients is not sufficient in this respect. Young patients are more anxious and are more concerned with the effects on their families than older patients. This perhaps reflects an increased difficulty in coping with the fact of death due to disease, for the first symptom, and the higher probability for these patients to have important parental tasks, for the latter.

The results of our study indicate that we should remain alert to the patients' perception of the side-effects of chemotherapy, which may differ from the perception of health care workers. We do not want to underestimate the importance of the introduction of new effective means of supportive care, such as the 5HT3 antagonists, but would like to caution for overoptimistic interpretation of their relevance. Only full control over nausea and vomiting will result in a change of patients' perception. For this reason, 'complete response' should be the main end point for studies on antiemetics as well as for the development of new antiemetics. This is clearly not in agreement with the optimistic results reported in the literature, in which the end point is usually major instead of complete control.

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