

Effectiveness of oral ondansetron in the management of nausea and vomiting induced by moderately emetogenic chemotherapy

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Introduction. Nausea and vomiting are, in the opinion of patients, the most feared side-effects of chemotherapy. Their occurrence during the initial cycle of chemotherapy increases the risk of anticipatory and refractory emesis during the subsequent courses. This implies the importance of emesis prevention at the very onset of chemotherapy.

The antiemetic effectiveness of 5-HT₃ receptor antagonists has been confirmed in many clinical trials which included patients treated with chemotherapy and radiotherapy. Consequently a certain "overuse" of these drugs has created an economical problem. Although the principles of prophylaxis and management of emesis after both highly and slightly emetogenic regimens are rather precise, there are no clear recommendations for the prophylaxis of emesis induced by moderately emetogenic chemotherapy.

The aim of our study was to compare the antiemetic effectiveness of oral ondansetron and metoclopramide in the management of emesis during moderately emetogenic chemotherapy. We also assessed the influence of supportive therapy with ondansetron on the quality of life of patients treated with chemotherapy.

Material and methods. 76 chemotherapy naive patients (50 M; 26 F), were entered into this prospective randomized study. 62 patients who received at least three courses of moderately emetogenic chemotherapy were available for analysis. Both chemotherapy and supportive therapy were given on an out-patient basis. Beginning with the initial course of chemotherapy all patients received the following antiemetic treatment: group I – 8 mg of ondansetron orally and 8 mg of dexamethasone i.v. one hour before chemotherapy and then ondansetron after 4 and 8 hours from the first administration; group II – 40 mg of metoclopramide i.v. and 8 mg of dexamethasone i.v. one hour before chemotherapy and 20 mg of metoclopramide orally after 4 and 8 hours from the first administration. Non-parametric Mann-Whitney's and chi-square tests were applied to compare the differences in the intensity of nausea and vomiting between both studied groups. The subsequent parameters (body weight, level of physical and psychological functioning) were analysed by *t*-Student and *F* Snedecor's tests.

Results. Our study confirmed that the antiemetic treatment with ondansetron was significantly more efficient than treatment with metoclopramide only in the group of women and concerning frequency of acute vomiting. The positive influence of this type of treatment was observed on the improved psychological well-being, considered to be one of the determinants of quality of life.

Ocena skuteczności doustnego leczenia ondansetronem u chorych poddanych chemioterapii o średnim potencjale emetogennym

Wstęp. Wymioty i nudności są, w opinii pacjentów, najbardziej uciążliwymi efektami ubocznymi chemioterapii. Wystąpienie tych objawów przy pierwszym kursie leczenia zwiększa ryzyko wytworzenia się zespołu wymiotów nawykowych przy kolejnych podaniach, dlatego niezwykle ważne jest zapobieganie nudnościom i wymiotom od momentu rozpoczęcia leczenia chemicznego. Skuteczność działania przeciwwymiotnego setronów potwierdzono w licznych badaniach z udziałem chorych poddanych leczeniu chemicznemu i radioterapii. W wyniku tych badań pojawił się jednak problem ekonomiczny, wynikający ze zbyt częstego stosowania tych leków. O ile strategie postępowania w zakresie zapobiegania nudnościom i wymiotom u chorych leczonych lekami o silnym lub słabym potencjale emetogennym są w miarę precyzyjnie ustalone, to zalecenia odnośnie postępowania u chorych leczonych lekami o średnim potencjale emetogennym nie są jednoznacznie określone.

Celem badania było porównanie skuteczności działania przeciwwymiotnego ondansetronu, podawanego doustnie, w porównaniu do metoklopramidu, podczas stosowania chemioterapii o średnim potencjale emetogennym. Dodatkowo oceniany był wpływ leczenia wspomagającego z ondansetronem na jakość życia chorych, poddanych leczeniu chemicznemu.

Materiał i metodyka. Doświadczenie miało charakter prospektywnie zaplanowanej, randomizowanej próby klinicznej. Do badania zakwalifikowano łącznie 76 chorych (50 kobiet i 26 mężczyzn), którzy nigdy wcześniej nie otrzymywali leczenia chemicznego. Ocenie poddano grupę 62 chorych, spośród których każdy otrzymał minimum trzy pełne serie zaplanowanej chemioterapii o średnim potencjale emetogennym. Leczenie chemiczne, jak też wspomagające, podawane było z założenia w warunkach ambulatoryjnych. Wszyscy chorzy, począwszy od pierwszej serii leczenia, otrzymywali leczenie przeciwwymiotne: jedna grupa – 8 mg ondansetronu doustnie wraz z deksametazonem (8 mg) godzinę przed wlewem cytostatyków oraz ondansetron po 4 i 8 godzinach od pierwszego podania; druga grupa – 40 mg metoklopramid dożylnie wraz z deksametazonem (8 mg) godzinę przed wlewem cytostatyków i następnie po 4 i 8 godzinach metoklopramid doustnie w dawce 20 mg.

W celu porównania różnic pomiędzy badanymi grupami w zakresie natężenia nudności i wymiotów, użyto testów nieparametrycznych Manna-Whitneya i chi-kwadrat. Do analizy statystycznej pozostałych cech (masa ciała, poziom funkcjonowania psychologicznego i fizycznego) wykorzystano test t-Studenta oraz test F Snedecora.

Wyniki. Badanie odowodniło, że leczenie przeciwwymiotne, przy pomocy ondansetronu, jest znamienne skuteczniejsze, w porównaniu do metoklopramid, jedynie w grupie kobiet w zakresie częstości występowania wymiotów ostrych. Wykazano też pozytywny wpływ tego rodzaju leczenia na poziom funkcjonowania psychologicznego, rozumianego jako jeden z wymiarów jakości życia chorych.

Key words: ondansetron, nausea and vomiting, moderately emetogenic chemotherapy, quality of life

Słowa kluczowe: ondansetron, nudności i wymioty, chemioterapia o średnim potencjale emetogennym, jakość życia

Introduction

Nausea and vomiting are the most frequent side-effects of chemotherapy. Although in the majority of cases they do not present as life threatening events, yet they can often lead to electrolyte disturbances, body weight loss and deterioration. They may also lead to psychologically determined anticipatory and refractory emesis. It was confirmed in many studies, that nausea and vomiting are the most distressing side-effects of chemotherapy reported by the patients [1, 2].

There are two distinct phases of emesis identified in patients receiving chemotherapy: acute – occurring within 24 hours after chemotherapy – and delayed – beginning about 18-24 hours after chemotherapy and lasting even for several days. The intensity of nausea and vomiting after administration of the same drug may vary among individuals and is influenced by many therapy-related factors (the chemotherapeutic drug and its dose or concomitant medication); patient-related factors (age, sex, general status, previous alcohol intake, nourishment) and psychological factors.

The occurrence of nausea and vomiting during the initial cycle of chemotherapy increases the risk of anticipatory and refractory emesis during the subsequent courses and thus implies the importance of prevention of emesis from the beginning of chemotherapy [3].

Owing to the discovery of trigger mechanisms of chemotherapy related vomiting new and relatively efficient antiemetic drugs have become available. The most effective appear to be 5-HT₃ receptor antagonists. Ondansetron, with the longest history of clinical use, an elective antagonist of central and peripheral serotonin receptors, inhibits the vomiting reflex caused by chemotherapy-induced release of serotonin in the small intestine. Dexamethason applied concomitantly strengthens its efficacy. It has been assumed that metoclopramide may be an adequate alternative to oral 5-HT₃ receptor antagonists in case of moderately emetogenic chemotherapy.

The introduction of 5-HT₃ receptor antagonists significantly improved patients' tolerance of highly emetogenic chemotherapy. Their efficacy has been confirmed in many clinical trials concerned with chemotherapy and radiotherapy. Consequently the very wide use of these drugs evolved into an economical problem.

Although the principles of prophylaxis and management of emesis after highly and weakly emetogenic regimens are rather precise, yet the recommendations for prophylaxis of emesis induced by moderately emetogenic chemotherapy remain unclear [4-7]. The aim of this study was to set and evaluate a simple antiemetic regimen applicable in chemotherapy centers (including out-patient clinics).

The aim of study:

The primary aim of the study was to compare the antiemetic efficacy of oral ondansetron (Atossa™, Anpharm) and metoclopramide (Polpharma) during moderately emetogenic chemotherapy.

The secondary aim of the study was to assess the influence of supportive therapy with ondansetron on the quality of life of patients treated with chemotherapy.

Material and methods

We conducted a prospective, randomized study. All patients enrolled submitted informed consent. The study was conducted in two centers simultaneously: the Chemotherapy Department of Rydygier's Memorial Hospital in Cracow and the Chemotherapy Department of the Centre of Oncology in Lublin. The study protocol had been approved by applicable Ethic Committees.

Seventy six patients (50 women and 26 men) entered the study – 66 patients in Cracow and 10 in Lublin. Sixty two patients, who had received at least three courses of planned moderately emetogenic chemotherapy, were evaluated. 14 patients did not receive three complete courses of chemotherapy. The observation was interrupted due to:

- progression of disease with treatment modifications – 9 patients,
- death due to progression of disease – 5 patients.

The evaluated 76 patients were divided in two groups: A (female – 27, male – 14) and B (female – 23, Male – 12). The randomization was based on the date of birth: even numbers were assigned to group A, odd – to group B.

All patients were chemotherapy-naïve and had histologically confirmed neoplastic disease indicating chemotherapy with moderately emetogenic agents (usually doxorubicin and/or cyclophosphamide) administered over one day.

Additional criteria were as follows: patient status (WHO) – 0-2, survival without treatment expected to exceed 6 weeks, age 18-70 years, haematology, liver and renal function adequate for conducting chemotherapy. Pregnancy, psychiatric disorders, lack of compliance and presence of a second malignancy were exclusion criteria.

Median age in group A was 53.3 years (24-74 years); in group B – 55 years (30-79 years). Table I presents the information on diagnosis and treatment of all patients entered in the study.

Schedule of antiemetic treatment

Chemotherapy and concomitant medication was administered in the out-patient setting. The efficacy of antiemetic therapy was evaluated during three courses of chemotherapy.

All patients received antiemetic treatment according to the following schedules:

- Group A: 8 mg of ondansetron (oral); 8 mg of dexamethasone (i.v.) one hour before chemotherapy and ondansetron 4 and 8 hours after the first administration;
- Group B: 40 mg of metoclopramide (i.v.); 8 mg of dexamethasone (i.v.) one hour before chemotherapy and 20 mg of metoclopramide (oral) 4 and 8 hours after the first administration.

The frequency and intensity of nausea and vomiting were analyzed with the observation card of chemotherapy side effects. Observations were collected on seven subsequent days following chemotherapy.

Rules of assessment of the antiemetic effect:

- complete response – no nausea and vomiting;
- partial response – 1-2 episodes of vomiting and/or nausea not interfering with normal activity,
- minimal response – 3-5 episodes of vomiting and/or nausea interfering with normal activity,
- no response – more than 5 episodes of vomiting and/or nausea rendering a patient bed-ridden.

The quality of life of patients was evaluated according to the Rotterdam Symptom Checklist [8], applied to evaluate the level of psychological and physical functioning disturbances.

Control measurements of body weight were also performed during the study.

Statistical analysis

Statistical analysis was performed for the following variables: vomiting, nausea, level of physical and psychological functioning and body weight.

Intensity of nausea and vomiting were ordinal variables of integer values. Non-parametric Mann-Whitney's and chi-square tests were applied to compare the differences between the studied groups.

Body weight was a continuous interval characteristic.

The level of physical and psychological functioning as a sum of multiple factors (according to Central Limit Theorem) were assumed to be variables with near-normal distribution.

Non-related variables were examined with the use of t-Student test in order to establish the significance of variations of mean values of parameters in a given measurement between groups A and B. Significance was assumed for $P < 0.05$.

In order to establish the significance of differences of means in one group (A or B), but in different time-points, one-way ANOVA for related variables was applied (F Snedecor's test). The use of both tests was justified by the results of Kolmogorow-Smirnow' test of normal distribution of analyzed data.

Results

Statistical analysis of the data from patients' diaries comparing the number of observed side effects (i.e. nausea and vomiting in the period from the day of administration of chemotherapy till the 7th day after chemotherapy) revealed significant differences between the two groups concerning acute vomiting (occurring within the first 24 hours). The calculated value of Z statistics (Mann-Whitney's test) equals – 3.450 ($p = 0.001$). There were no significant differences with reference to age and sex between the groups, so the percentage of patients with no side-effects (complete response to antiemetic treatment) was calculated. The results are presented in Table II.

Table I. Clinical characteristics of patients according to the diagnosis and treatment (number of patients in group A + B is given in brackets)

Diagnosis/Treatment	FAC	FAM	CHOP	VAC	Total
Breast cancer	31 (18 + 13)				31 (18 + 13)
Stomach cancer		18 (10 + 8)			18 (10 + 8)
Lymphoma			16 (7 + 9)		16 (7 + 9)
Lung cancer				11 (6 + 5)	11 (6 + 5)
Total	31 (18 + 13)	18 (10 + 8)	16 (7 + 9)	11 (6 + 5)	76 (41 + 35)

Table II. The percentage of patients with complete response to antiemetic treatment in group A and B (the results for women and men are presented separately)

Side effects Sex	AC–N		DEL–N		AC–V		DEL–V	
	F	M	F	M	F	M	F	M
Group A	42.3	50.0	21.8	46.7	92.3	80.0	75.6	86.7
Group B	30.2	62.5	25.4	56.3	63.5	84.4	61.9	87.5

Abbreviations: AC–N – acute nausea, DEL–N – delayed nausea, AC–V – acute vomiting, DEL–V – delayed vomiting

After statistical analysis of the data presented in Table II it can be concluded that:

- nearly all women in group A (92.3%) were completely protected from acute vomiting, significantly more than in group B (63.5%) - ($p=0.001$);
- in women from group B acute nausea was observed twice as often than in women ($p=0.01$);
- in both groups the frequency of delayed nausea was significantly higher in women than in men (group A - $p<0.05$; group B - $p<0.01$).

Summarizing the results of the efficacy of antiemetic treatment it can be stated that concomitant treatment with ondansetron and dexamethasone was significantly more efficient than with metoclopramide and dexamethasone only in the subgroup of women and the difference was significant only for acute emesis.

The results of quality of life measurements obtained with the Rotterdam Symptom Checklist indicate better psychological functioning of patients in group A only during the 2nd cycle. Psychological well-being of patients receiving ondansetron (group A) continuously improved during treatment. Both the physical and psychological well-being remained more stable in patients in group A than in group B (lower values of respective subscales and low values of standard deviation).

Patients from group A rated their physical functioning as better during subsequent courses of chemotherapy. No difference was observed however, according to the physical functioning of patients in both groups.

It is worth stressing that patients from both groups reported worsening of physical well-being during consecutive cycles of chemotherapy. Tables III and IV show the results of comparison of median values indicating the level of activity disturbances in psychological and physical aspects.

Summarizing the quality of life assessment it can be assumed that there was no statistically significant differ-

ence in both psychological and physical functioning between patients receiving ondansetron with dexamethasone and metoclopramide with dexamethasone. However, one may observe a clear trend towards better psychological tolerance of chemotherapy by patients receiving antiemetic treatment with ondansetron.

Alterations of mean body weight of patients during

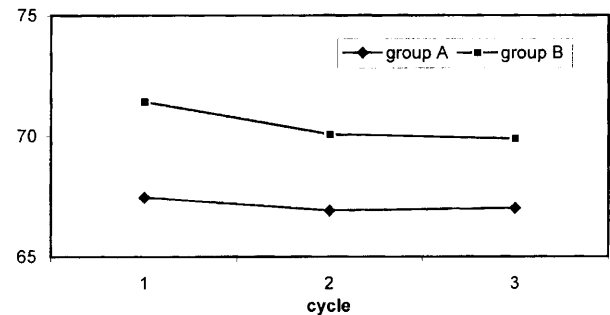


Figure 1. Mean body weight during subsequent chemotherapy courses

the study is presented on Figure 1.

The mean body weight of patients from group B was higher than that of patients from group A at every check-point. However these differences are not statistically significant due to a relatively high value of standard deviation of this variable in both groups.

As a result of analysis of variance for related data it was shown that in group A the change in body weight between subsequent measurements was not significant. In group B there was a drop in body weight between point I and points II and III ($p = 0.05$).

Discussion

The results obtained in this study should be analyzed in the view of the data concerning the side effects of mode-

Table III. The comparison of mean values of psychological distress in group A and B and at subsequent points of measurement

Point of measurement	Group A		Group B		Results for t-Student test for groups A and B		
	Mean	Standard deviation	Mean	Standard deviation	t	df	p
I	15.12	4.23	17.00	6.73	-1.302	61	>0.19
II	13.26	4.33	16.21	5.52	-2.325	61	<0.05
III	13.88	4.27	16.14	5.94	-1.703	61	>0.09
value of F statistics in ANOVA between measurements I, II, III	F = 3.52 df=2 p<0.05		F = 0.64 df = 2 p>0.53				

Table IV. The comparison of mean values of physical distress in group A and B and at subsequent points of measurement

Point of measurement	Group A		Group B		Results for t-Student test for groups A and B		
	Mean	Standard deviation	Mean	Standard deviation	t	df	p
I	26.35	6.34	28.07	7.09	-1.005	61	>0.31
II	30.00	6.02	31.21	7.99	-0.668	61	>0.50
III	32.18	7.84	32.10	7.38	-0.038	61	>0.97
value of F statistics in ANOVA between measurements I, II, III	F = 13.639 df=2 p<0.001		F = 8.367 df = 2 p>0.001				

rately emetogenic chemotherapy and the results from similar studies [9, 10]. Both cyclophosphamide and doxorubicin are moderately emetogenic agents and the intensity and timing of side effects depend on their dosage. After treatment with cyclophosphamide emesis begins after some 10-12 hours and can persist for another 6 to 8 hours. Following combined treatment with cyclophosphamide and doxorubicin emesis occurs already after 6 hours and can last for up to 6 to 10 hours. Standard anthracycline-based multi-drug regimens like FAC, CAV, FAM induce vomiting in 60-90% patients. Emesis is increased in female patients, ambulatory patients, subjects suffering from motion sickness, while it is decreased in males, inpatients, and patients with a history of high alcohol intake.

Antiemetic treatment with metoclopramide (alone or in combination with corticosteroids) given three times daily in the dose 20 mg i.v. or i.m. results in good antiemetic prophylaxis (less than two episodes of vomiting) in 40-60% of patients. Introduction of 5-HT₃ receptor antagonists, preferably in combination with corticosteroids, can increase this rate up to 70-95%. Usually antiemetics are given intravenously. It must be stressed that in our study ondansetron was given orally. In a similar study reported by Frascini [10], oral ondansetron of 8 mg three times daily produced complete antiemetic control in 85% of 60 patients during chemotherapy with cyclophosphamide and doxorubicin. This result is well comparable with the results of our study. It can be supposed that oral therapy with antiemetics may be a preferable option during moderately emetogenic chemotherapy. It is cost-effective, less time-consuming for medical staff and generally preferred by the patient. However, one must keep in mind that when vomiting starts this option is not effective and then antiemetics should be administered intravenously. On the other hand, both our results and those from similar studies clearly show that for most of the patients oral treatment is effective and this effect is preserved during subsequent courses of chemotherapy.

Considering the pharmaco-economic aspect, the results of our study suggest that women are more likely to benefit from 5-HT₃ receptor antagonists administration during moderately emetogenic chemotherapy than men. In case of male patients antiemetic strategy can depend upon other factors including the financial status of the center. This strategy can be recommended as treatment of choice for preventing nausea and vomiting caused by moderately emetogenic chemotherapy.

Conclusions

1. Antiemetic treatment with oral ondansetron administered during moderately emetogenic chemotherapy was significantly more efficient than metoclopramide only in the subgroup of female patients. This primarily applies to the frequency of acute vomiting.
2. Quality of life in the aspect of psychological functioning during chemotherapy was better in the group re-

ceiving ondansetron as compared to the group receiving metoclopramide.

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