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ORIGINAL ARTICLE

The influence of dexamethasone in the decrease of chemotherapy-induced nausea and vomiting

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Summary

Purpose: *The aim of this study was to determine the influence of dexamethasone in the decrease of cisplatin and etoposide-induced nausea and vomiting in patients treated for lung cancer during and after 2 chemotherapy cycles.*

Patients and methods: *The analysis included 60 patients with histologically proven lung cancer, who were divided in two groups. Group A consisted of 30 patients who received cisplatin and etoposide with standard antiemetic drugs: ondansetron [serotonin receptor antagonist (5-HT_3 antagonist)] and metoclopramide (dopamine receptor antagonist). Group B consisted of 30 patients who received the same chemotherapy regimen with the previous antiemetic therapy plus dexamethasone 8 mg intravenously (i.v.) per day during the 3 days of chemotherapy. During and after the 3-day therapy, patients filled in a questionnaire issuing adverse effects of chemotherapy concerning many symptoms including nausea and vomiting. The results were statistically processed.*

Results: *There was a significant decrease in the frequency and toxicity of nausea, acute and delayed vomiting in the group of patients who received antiemetic treatment with ondansetron, metoclopramide plus dexamethasone.*

Conclusion: *Dexamethasone administered with 5-HT_3 antagonists and dopamine receptor antagonists significantly decreases the chemotherapy-induced nausea and vomiting.*

Key words: antiemetic treatment, chemotherapy, dexamethasone, lung cancer, nausea, vomiting

Introduction

Chemotherapy, as one option for cancer treatment, causes quite a number of adverse effects in many cases. It is well known that every drug administered in its therapeutic dose cause some side effects to the patient. Usually the incidence of these side effects is less than 0.1%, but for antitumor drugs, it goes to over 90%. This is explained by the fact that antitumor drugs affect all rapidly dividing cells, including tumor cells, but also normal cells especially bone marrow cells, resulting in myelosupression, epithelial cells of the gastrointestinal tract, resulting in nausea and vomiting, germ cells of the reproductive organs with potential effect on fertility and hair follicle cells, resulting in alopecia.

There are some factors that are important in predicting the risk of chemotherapy-induced nausea and vomiting. They can be divided into factors related to chemotherapy itself, and the ones related with individual characteristics of the patient. The former include the emetic potential of specific antitumor agents e.g. cisplatin causes severe nausea and vomiting in almost every patient in contrast with e.g. bleomycin which rarely causes mild nausea and vomiting; the dose of antitumor drug(s) that is very common in the

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case of cisplatin; the route and rate of drug administration; and the combination of antitumor drugs. Factors related to patients are age (younger patients are more sensitive), gender (females are more sensitive), susceptibility of motion sickness which increases the risk for nausea and vomiting, history of chronic alcohol consumption (that decreases the risk of nausea and vomiting) and prior experience with chemotherapy [1-3].

The most common significant side effects of chemotherapy are nausea and vomiting. Many mediators take part in the pathogenesis of chemotherapy-induced nausea and vomiting such as serotonin, dopamine, substance P and neurokinin. Based on this fact, the mechanisms of antiemetic drugs include blocking receptors of these mediators that results in decreasing nausea and vomiting [4-6].

The combination of cisplatin and etoposide entered pulmonary oncology in the early 1980s and until now this is one of the most frequently used protocols, primarily in the treatment of small cell lung cancer (SCLC) and, relatively recently, as induction and adjuvant therapy in non-small cell lung cancer (NSCLC). Recently, many new antitumor agents have been introduced into clinical practice such as taxanes, gemcitabine and vinorelbine.

Because of the frequent adverse effects, anticancer drugs are given with supportive and symptomatic therapy and with special premedications of patients before starting chemotherapy. It is suggested that the ideal protective agent should prevent any toxicity, from side effects that are no life-threatening (alopecia) to irreversible morbidity (hearing loss, neurotoxicity) and potentially fatal events (severe cardiomyopathy and severe leukopenia / thrombocytopenia). It should not interfere with the efficiency of the antitumor drug, and should be easily administered and be relatively nontoxic [7].

There are many guidelines that recommend specific antiemetic drugs for decrease of chemotherapy-induced nausea and vomiting. These agents are 5-HT_3 antagonists (granisetron, ondansetron, tropisetron), dopamine receptor antagonists (metoclopramide) and corticosteroids (dexamethasone, methylprednisolone). Recently neurokinin-1 (NK 1) receptor antagonist (aprepitant) has been introduced in clinical oncology [8-10]. While for 5-HT_3 antagonists, dopamine receptor antagonists and NK 1 receptor antagonist the mechanism of antiemetic effect is well known, for corticosteroids it is still unclear. Some hypotheses exist concerning this issue. These are: central inhibition of interleukin synthesis in the hypothalamus, decrease of serotonin brain level, action on endorphine release, decrease of capillary permeability in the chemoreceptor trigger zone in the area postrema, stabilization of cell membrane and decrease of inflammation in the gastrointestinal tract after chemotherapy [11,12].

Chemotherapy causes 3 types of nausea and vomiting. The most common and best understood is acute nausea and vomiting, occurring within the first 24 hours of chemotherapy. Despite many efforts that have resulted in improved management, acute vomiting still occurs in one third of patients receiving high doses of cisplatin. This situation unfortunately can lead to patients refusing further therapy. Delayed nausea and vomiting occurs 24 hours or more after chemotherapy administration, and can last 6-7 days. This type of chemotherapy-induced adverse effect has been reported in 20-50% of all cisplatin-treated patients. The third type is anticipatory nausea and vomiting which begins prior to the administration of chemotherapy. It usually occurs in patients who had poor control of these symptoms during previous cycles of chemotherapy [13,14].

The purpose of this study was to determine the influence of dexamethasone in combination with 5-HT_3 antagonists and dopamine receptor antagonists on the decrease of chemotherapy-induced nausea and vomiting in lung cancer patients.

Patients and methods

This was a prospective study performed at the Institute for Pulmonary Diseases of Vojvodina in Sremska Kamenica, Serbia, approved by the ethical committee of the Institution. All patients gave written informed consent.

Eligible patients should have histologically proven lung cancer, no prior surgery or radiotherapy, normal blood cell count, normal renal and liver function and no prior episodes of nausea and vomiting.

The exclusion criteria were specific comorbidites: arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), peptic ulcer, glaucoma and psychiatric disorders.

Antiemetic therapy

Patients were divided into 2 groups (A and B) consisting of 30 individuals each. Thirty minutes before chemotherapy administration patients in both groups received ondansetron 8 mg i.v. in 250 ml 10% manitol on day 1 and metoclopramide 10 mg/day i.v. in 500 ml N/S, days 1-3. In addition, group B patients received dexamethasone 8 mg i.v. in 100 ml N/S, days 1-3.

Chemotherapy

Both groups received 2 cycles of cisplatin 60 mg/m^2 on day 1 with prehydration and forced diuresis plus etoposide 100 mg/m^2/day, days 1-3, with 3-weekly cycle repetition.

After the beginning of chemotherapy, the patients received a questionnaire to be filled in until the next chemotherapy cycle. For evaluation of toxicity grades of chemotherapy-induced nausea and vomiting the NCI (National Cancer Institute) criteria, version 2.0, were used.

The obtained results were statistically analyzed, classified, scaled and presented in Tables and Figures. To determine statistical significance we used SPSS for Windows.

Results

In group A included were 23 (76.67%) males and 7 (23.33%) females; in group B 24 (80%) males and 6 (20%) females. The average age in group A patients was 59.07 ± 8.62 years, and in group B 56.83 ± 8.47 years. There was no statistically significant difference concerning age (p=0.316) and gender (p=0.147) between the two groups.

Lung cancer types are shown in Table 1. In both groups NSCLC cancer cases prevailed.

Nausea

After the first chemotherapy cycle nausea was reported by 22 (73.33%) group A and 16 (53.33%) group B patients (p>0.05). After the second chemotherapy cycle the corresponding figures were 29 (96.67%) and 17 (56.67%) patients in groups A and B, respectively. The difference was significant (p= 0.0002), favoring group B (Figure 1).

Odds ratio revealed that there was 2.5-fold more chance for nausea in group A after the first chemotherapy cycle, but this ratio did not reach statistical significance (p=0.056). After the second chemotherapy cycle this chance was 22-fold higher for nausea to occur in group A (p=0.0021).

Table 2 shows the grades of nausea in specific time periods after the first chemotherapy cycle. There was a statistically significant difference between the two groups (p=0.04) in the first 3 days after chemotherapy administration with more toxicity in group A, while for the following period this difference disappeared.

Analysis of grades of nausea in specific time periods after the second chemotherapy cycle showed a statistically significant difference between the two groups (p=0.001) in the first 3 days after chemotherapy administration with more toxicity in group A, while for the following period this difference disappeared (Table 3).

Table 1. Frequency of lung cancer types in both groups of patients

Group	*Squamous cell n (%)*	*Adeno n (%)*	*Small cell n (%)*	*Large cell n (%)*	*Total n (%)*
A	11 (36.67)	9 (30)	9 (30)	1 (3.33)	30 (100)
B	13 (43.33)	6 (20)	11 (36.67)	0 (0)	30 (100)
Total	24 (40)	15 (25)	20 (33.33)	1 (1.67)	60 (100)

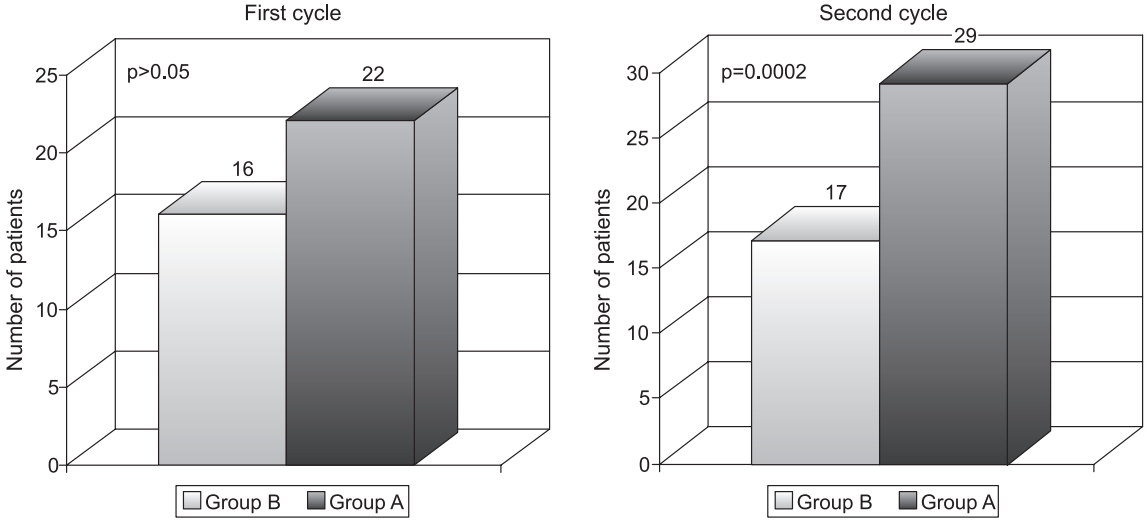

Figure 1. Frequency of nausea in both groups after the first and second chemotherapy cycle.

Table 2. Grades of nausea after the first chemotherapy cycle

Group	*Grade*	*Days after the first chemotherapy cycle*				
		*1-3**	*4-7*	*8-14*	*15-21*	*> 22*
		n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
A	0	17 (56.7)	19 (63.3)	27 (90.0)	30 (100.0)	30 (100.0)
	1	8 (26.7)	8 (26.7)	2 (6.67)	0 (0.0)	0 (0.0)
	2	4 (13.3)	3 (10.0)	1 (3.3)	0 (0.0)	0 (0.0)
	3	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
B	0	23 (76.7)	23 (76.7)	27 (90.0)	29 (96.7)	30 (100.0)
	1	6 (20.0)	5 (16.7)	3 (10.0)	0 (0.0)	0 (0.0)
	2	1 (3.3)	2 (6.6)	0 (0.0)	1 (3.3)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*More nausea in group A only on days 1-3 (p=0.04)

Table 3. Grades of nausea after the second chemotherapy cycle

Group	*Grade*	*Days after the second chemotherapy cycle*				
		*1-3**	*4-7*	*8-14*	*15-21*	*> 22*
		(n%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
A	0	11 (36.7)	14 (46.7)	26 (86.7)	29 (96.7)	30 (100.0)
	1	13 (43.3)	13 (43.3)	4 (13.3)	1 (3.3)	0 (0.0)
	2	5 (16.7)	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
B	0	27 (90.0)	18 (60.0)	27 (90.0)	30 (100.0)	30 (100.0)
	1	0 (0.0)	8 (26.7)	2 (6.7)	0 (0.0)	0 (0.0)
	2	3 (10.0)	4 (13.3)	1 (3.3)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*More nausea in group A only on days 1-3 (p=0.001)

Vomiting

After the first chemotherapy cycle acute vomiting was reported by 7 (23.33%) group A and in 4 (13.33%) group B patients (p=0.32). After the second chemotherapy cycle the corresponding figures were 8 (26.67%) and 2 (6.67%) (p=0.038) patients in groups A and B, respectively.

Acute vomiting after the first and second chemotherapy cycle was higher in group A, however significant difference between the two groups was found only after the second chemotherapy cycle (p= 0.037) favouring group A (Figure 2).

Odds ratio revealed 2-fold higher chance for acute vomiting to occur in group A after the first chemotherapy cycle, but this ratio was not statistically significant (p=0.16). After the second cycle this chance was approximately 5-fold higher for acute vomiting to occur in group A (p=0.026).

Tables 4 and 5 show acute vomiting after the first and second chemotherapy cycle. There was a difference between two groups after the second chemotherapy cycle but without statistical significance (p=0.09).

After the first chemotherapy cycle delayed vomiting was reported by 13 (43.33%) group A and 7 (23.33%) group B patients (p=0.10). After the second chemotherapy cycle the corresponding figures were 15 (50%) and 6 (20%) in groups A and B, respectively (p= 0.015).

Delayed vomiting after the first and second chemotherapy cycle was higher in group A, however statistically significant difference between the two groups was found only after the second chemotherapy cycle (p= 0.014) favoring group A (Figure 3).

Odds ratio revealed 2.5-fold higher chance for delayed vomiting to occur in group A after the first chemotherapy cycle (p=0.05). After the second cycle this chance was approximately 4-fold higher for delayed vomiting to occur in group A (p=0.009).

Analysis of delayed vomiting in specific time periods after the first chemotherapy cycle showed a statistically significant difference between the two groups (p=0.009) between the 4th and 7th day after chemotherapy administration, with more toxicity in group A (Figure 4).

After the second chemotherapy cycle a statistically significant difference was seen between the two groups (p=0.009) between the 4th and 7th day after

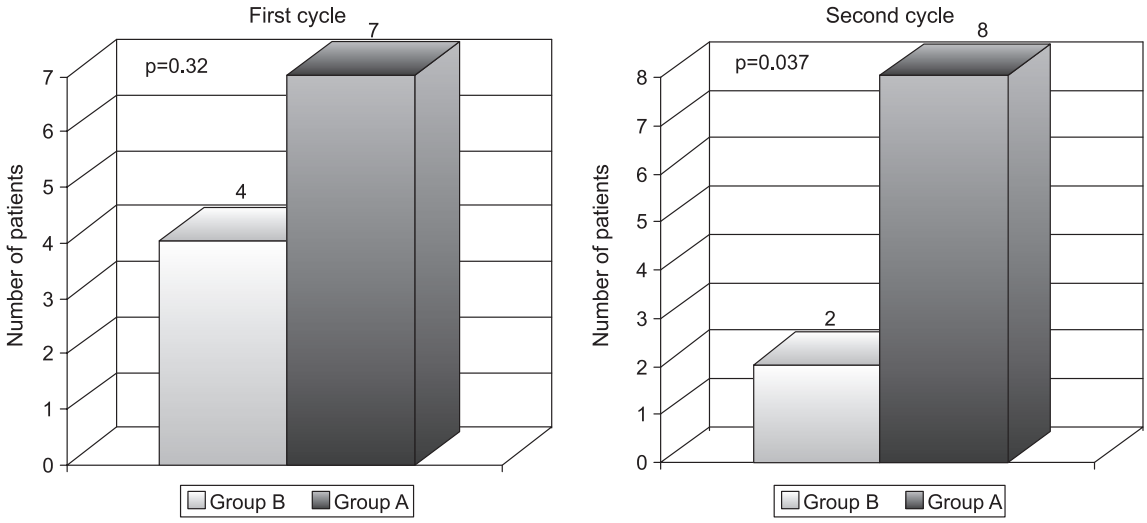

Figure 2. Acute vomiting in both groups after the first and second chemotherapy cycle.

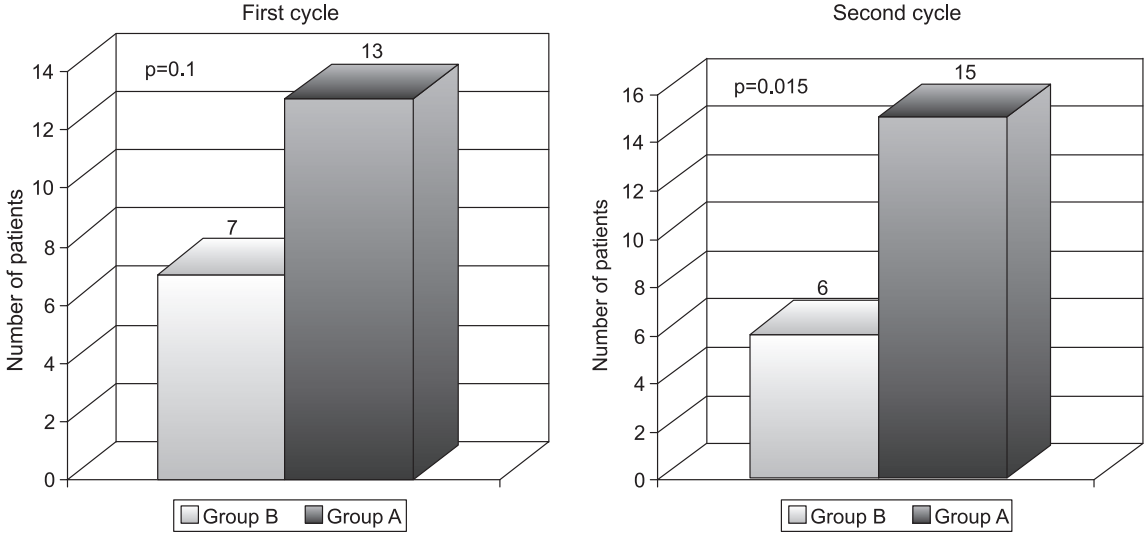

Figure 3. Delayed vomiting in both groups after the first and second chemotherapy cycle.

Table 4. Grades of acute vomiting after the first chemotherapy cycle

	Grade			
Group	*0*	*1*	*2*	*3*
	n (%)	*n (%)*	*n (%)*	*n (%)*
A	23 (76.67)	4 (13.33)	2 (6.67)	1 (3.33)
B	26 (86.67)	0 (0.00)	3 (10.00)	1 (3.33)

p = non significant

Table 5. Grades of acute vomiting after the second chemotherapy cycle

	Grade			
Group	*0*	*1*	*2*	*3*
	n (%)	*n (%)*	*n (%)*	*n (%)*
A	22 (73.34)	6 (20.00)	1 (3.33)	1 (3.33)
B	28 (93.33)	2 (6.67)	0 (0.00)	0 (0.00)

p = non significant

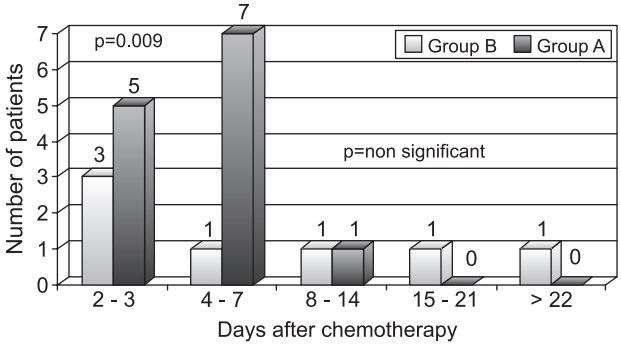

Figure 4. Delayed vomiting in both groups after the first chemotherapy cycle.

chemotherapy administration, with more toxicity in group A. Also a significant difference between groups (p=0.04) in the period between 8th and 15th day after chemotherapy administration was observed, with more toxicity in group B (Figure 5).

Discussion

A large number of studies has demonstrated that chemotherapy-induced vomiting was the symptom that most cancer patients fear most. From 1983 to 1995 this adverse effect fell from the first to the third place in comparison to chemotherapy-induced nausea which became the worst symptom in patients receiving chemotherapy [15,16].

Griffin et al. [17] estimated the influence of nausea on the quality of life in 155 cancer patients. That study showed that most of the patients experienced significant uneasiness caused by nausea compared to vomiting during acute, delayed and anticipatory periods. In that study acute nausea occurred in 51% of the patients and acute vomiting in 24%. Delayed nausea was present in 27% of the patients and delayed vomiting in 24%, while 17% of the patients had anticipatory nausea and 5% anticipatory vomiting.

In our study the frequency of nausea was higher after the first and second chemotherapy cycles (p=0.056 and p=0.0021, respectively) in the group of patients who received antiemetic therapy without dexamethasone (group A). Grade 3 nausea was seen in 1 patient in group A after both chemotherapy cycles. Comparing grades of nausea, a statistically significant difference between the two groups was found between the 1st to 3rd day during the first and second chemotherapy cycles, favoring the antiemetic regimen with dexamethasone. When the administration of dexamethasone stopped, this difference between the two groups disappeared. It seems that corticosteroids have a positive influence in decreasing chemotherapy-induced nausea,

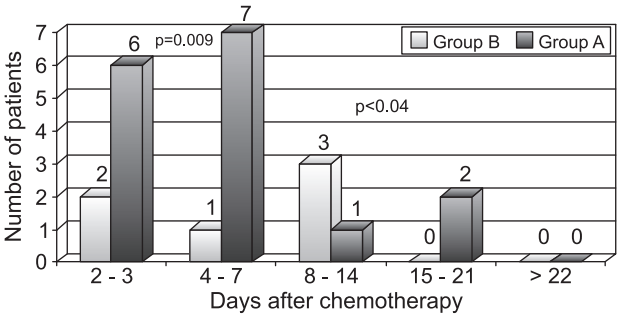

Figure 5. Delayed vomiting in both groups after the second chemotherapy cycle.

but this effect is linear with the time of chemotherapy administration, while there is no effect after the last day (3rd) of chemotherapy administration.

A metaanalysis of antiemetic studies established that antiemetic control after combination of corticosteroids and 5-HT_3 antagonists was superior to monotherapy [18]. The combination of these two agents is recommended as a standard for antiemetic control of moderate and mild emetogenic chemotherapy [19,20].

The recommended antiemetic treatment includes granisetron (10 μg/kg i.v), tropisetron (5 mg i.v.), ondansetron (16-32 mg i.v) or dolasetron (1.8 μg/kg i.v) with dexamethasone (8-10 mg i.v) [21].

Two double-blind randomized studies which included patients who received one high-dose cisplatin (>50 mg/m^2) compared the combination of ondansetron and dexamethasone with the combination of high-dose metoclopramide, dexamethasone and diphenhydramine or lorazepam [22,23]. The complete protection from nausea and vomiting was significantly superior with ondansetron and dexamethasone and the patients tolerated this regimen better. Complete protection from vomiting was maintened from the first to the third chemotherapy cycle in the group with ondansetron, but the protection from nausea was significantly decreased with this regimen [23]. This is one of the reasons that i.v. combination of 5-HT_3 antagonists and dexamethasone can be considered as a standard treatment.

There are some issues concerning the optimal dose of dexamethasone in the antiemetic regimens. In a study that included 531 patients who received cisplatin it was found that administration of a single dose of 20 mg dexamethasone for the prevention of acute vomiting was superior to 4, 8 and 12 mg, but this difference was not significant. Because the side effects of dexamethasone were mild and there was no significant difference between regimens, these authors recommend 20 mg dexamethasone i.v. as an optimal dose [24].

Many randomized clinical trials demonstrated that complete control of chemotherapy-induced vomiting is better compared to nausea [25-27]. It is considered that the highest therapeutic index is achieved by combining 5-HT_3 antagonists and corticosteroids, especially dexamethasone (8-20 mg i.v. or 4-20 mg per os). The most studied corticosteroids are methylprednisolone and dexamethasone. Advantages of dexamethasone include its various dose formulations and access in generic forms in many countries [8,20].

Ioannidis et al. [28] examined Medline data from 1996 to 1999 to identify randomized clinical trials which evaluated the use of dexamethasone for control

of chemotherapy-induced nausea and vomiting. The dose of dexamethasone used in the acute phase was 8-100 mg. Half of the studies used 20 mg dexamethasone. In every study dexamethasone was administered intravenously in the acute phase. It was estimated that dexamethasone decreased the chance for acute vomiting from 25 to 30%. Three studies with 189 patients, which compared dexamethasone with metoclopramide reported that dexamethasone is superior in the acute phase [29-31]. The only study which was included in this search and which compared dexamethasone with 5-HT_3 antagonists demonstrated that there was no difference in the efficiency of these two agents in the acute phase [32].

Good control of acute nausea and vomiting after the first chemotherapy cycle is crucial concerning the fact that vomiting in a previous chemotherapy cycle is a negative predictor for occurrence of this symptom in the following cycles [19,33].

It can be concluded that complete protection of acute nausea and vomiting after the first chemotherapy cycle is of paramount importance.

In our study we registered higher incidence of acute vomiting after the first and second chemotherapy cycle in patients who were treated without dexamethasone. After the second chemotherapy cycle this difference became statistically significant (p=0.026). A similar situation was noted in comparing grades of acute vomiting in both chemotherapy cycles, but without statistical significance.

Delayed vomiting occurs 24 hours after chemotherapy administration. There is evidence that the combination of oral metoclopramide and dexamethasone is effective in achieving complete protection of cisplatin-induced delayed vomiting in 50% of the patients and this combination is superior to monotherapy with dexamethasone or placebo [34]. There is also evidence that the combination of 5-HT_3 antagonists and dexamethasone is superior to serotonin receptor antagonist alone [35,36]. Taking into consideration its lower cost, the combination of metoclopramide and dexamethasone is considered a standard regimen for the prevention of delayed vomiting. In patients who do not tolerate metoclopramide, it can be substituted with ondansetron.

Three studies with 189 patients, which compared dexamethasone with metoclopramide, reported that dexamethasone is superior in the delayed phase [29-31]. Only one study compared dexamethasone with serotonin receptor antagonists and it was demonstrated that dexamethasone is superior in the delayed phase [32].

We have observed higher incidence of delayed vomiting after the first and second chemotherapy cycle in patients who had antiemetic therapy without dexamethasone. This incidence was statistically more significant after the second chemotherapy cycle (p=0.009 and p=0.005, respectively). We can assume that the control of vomiting during the initial chemotherapy cycle was not satisfactory.

Conclusion

Dexamethasone administered with 5-HT_3 antagonist (ondansetron) and dopamine receptor antagonist (metoclopramide) significantly decreases chemotherapy-induced nausea and vomiting. It is necessary to conduct large-scale randomized trials to confirm the beneficial effect of dexamethasone in combination with other antiemetic drugs in the control of chemotherapy-induced nausea and vomiting. Of importance is also the issue of cost-benefit, taking into consideration the high price of newer antiemetic drugs in comparison with dexamethasone combined with other standard antiemetics.

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