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TROPISETRON IN THE PREVENTION OF CHEMOTHERAPY – INDUCED ACUTE EMESIS IN PEDIATRIC PATIENTS*

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SUMMARY: Mutafoğlu Uysal K, Olgun N, Sarıalioğlu F. (Department of Pediatric Oncology, Dokuz Eylül University, Institute of Oncology, İzmir, Turkey). Tropisetron in the prevention of chemotherapy-induced acute emesis in pediatric patients. Turk J Pediatr 1999; 41: 207-218.

We evaluated the antiemetic efficacy of tropisetron for control of acute emesis during grade 3 or 4 emetogenic chemotherapy in children. Tropisetron was administered as a single intravenous dose of 0.2 mg/kg an the first day and intravenously or orally with the same dose on subsequent days. A total of 125 courses of highly emetogenic chemotherapy was administered to 22 children with a median age of 14 years (range: 3-18 years). All 22 patients received tropisetron for at least two courses. Overall complete response on day I was observed in 80 out of 125 courses (64%). The response rates were consistent over multiple courses; a complete and major response rate on the first day of Course I (n: 22 courses) and Course II (n: 22 courses) was observed in 73 and 77 percent of cases, respectively. When the results were analyzed according to the daily schedules, overall complete response for grade 4, grade 3 and grade 1-2 emetogenic treatment days was 59, 85 and 75 percent, respectively. In this study, cost effectiveness for tropisetron was also determined; the cost per successfully controlled course was 162 USD. No side effects of tropisetron other than mild diarrhea and dry-mouth were documented in this study. In conclusion, the results of this study confirmed that tropisetron is a safe, well tolerated and effective antiemetic drug for the prevention of acute emesis in children and adolescents during highly emetogenic chemotherapy. *Key words: acute emesis, tropisetron, children, adolescent, antiemetic.*

Nausea and vomiting are among the most distressing and debilitating side effects of chemotherapy. Highly emetogenic drugs may result in dehydration and electrolyte imbalance which may potentiate the risk of toxicity related to anticancer drugs. Emesis and nausea are potentially more hazardous in children than in adults because of appetite loss and acute disturbances in nutritional status and electrolyte balance. Intensification of chemotherapy regimens administered to children with cancer usually results in highly emetogenic protocols which are frequently administered over several days- a trend which has considerably increased the risk of emesis.

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None of the traditional antiemetics is entirely effective either alone or in combination, and their side effects, such as extrapyramidal reactions and marked sedation, are frequently observed in children[1-3]. Over the past few years, 5-HT3 receptor antagonists have proved remarkably effective in the prevention of nausea and vomiting in children[4-9]. Tropisetron is a selective antagonist of the 5-HT3 receptor. In some previous studies, a high safety and efficacy profile for tropisetron in children was reported[6-9]. The aim of this study was to confirm the reported efficacy and safety of tropisetron in the prevention of nausea and vomiting in children receiving emetogenic chemotherapeutic regimens.

Material and Methods

Twenty-two children receiving chemotherapy for the treatment of malignant diseases were studied. The patients were recruited from the children routinely treated at our center. All the patients had histopathologically proven malignant diseases and were scheduled to receive at least two courses of highly emetogenic chemotherapy. No patient was excluded based on prior chemotherapy or radiotherapy.

In this study, a single daily dose of tropisetron of 0.2 mg/kg, with a maximum of 5 mg, was used. Tropisetron (Navoban® ampule 5 mg/5 ml; Sandoz, Basel, Switzerland) was given intravenously (i.v.) 15 minutes before the chemotherapy on the first day. On the subsequent days, patients received tropisetron with the same i.v. dose if i.v. route was maintained. Otherwise, it was given orally in capsule form (Navoban® capsule 5 mg; Sandoz, Basel, Switzerland) or as a drink solution immediately after diluting the appropriate amount of tropisetron from the ampule in orange juice one hour before food intake. Following the last dose of chemotherapy, tropisetron was continued for five days if the regimen contained cisplatin (CDDP), otherwise it was continued for three days. Corticosteroids were allowed only if they were part of the chemotherapy protocol or were given as a premedication to prevent hypersensitivity reactions. All the patients had adequate renal and hepatic functions prior to the therapy.

Chemotherapy regimens were classified by emetic grade[1-4] as adapted from Bleiberg et al.[10] (Table I). The grade of a course was determined by the highest emetic grade of each agent at the dose used. Chemotherapy of emetic grade 3 was upgraded when combined with grade 2 or 3 emetogenic agents. Regimens containing at least two drugs of grade 2 were considered as grade 3.

Chemotherapy protocos used during the study were heterogeneous, so we also classified the data according to the daily-administered emetogenic drugs using the same criteria as for emetogenic potential. Examples of this classification are given in Table II.

Table I: Criteria for Emetic Grade of Chemotherapeutic Agents* (dose in mg/m^2)[10]

Grade 1	Grade 2	Grade 3	Grade 4
Bleomycin	Dactinomycin < 0.3	Cisplatin ≥ 20	Cisplatin ≥ 60
Etoposide	Cyclophosphamide < 300	Carboplatin ≥ 150	Dactinomycin ≥ 0.45
Procarbazine	Doxorubicin < 45	Dactinomycin ≥ 0.3	Cyclophosphamide ≥ 1000
Mercaptopurine	Ifosfamide < 1000	Chlormethine ≥ 6	Cytarabine ≥ 1000
Thioguanine	Methotrexate < 3000	Cyclophosphamide ≥ 300	Ifosfamide ≥ 3000
Vinblastine		Cytarabine ≥ 150	
Vincristine		Dacarbazine ≥ 100	
		Daunorubicin ≥ 45	
		Doxorubicin ≥ 45	
		Ifosfamide ≥ 1000	
		Methotrexate ≥ 3000	

* Only the drugs used in this study are included.

Table II: Examples of Daily Schedule-Based Classification of Chemotherapy Regimens

Regimen	Drugs (mg/m^2)	Daily Schedule	Emetogenic Grade
ICE	Ifos (1500)	Day 1: Ifos/E	3
	Carbo (500)	Day 2: Ifos/E	3
	E (100)	Day 3: Ifos/E/Carbo	4
ABVD	Doxo (25)	Day 1: Doxo/Bleo/VBL/DTIC	4
	Bleo (10)		
	VBL (6)		
	DTIC (375)		
NHL-BFM 90	Dexa (10)	Day 1: Dexa/Ifos/VCR/MTX/*it	3
B-cell AA Block	Ifos (800)	Day 2: Dexa/Ifos	2
	E (100)	Day 3: Dexa/Ifos	2
	ARA-C (150x2)	Day 4: Dexa/Ifos/E/ARA-C	4
	VCR (1.5)	Day 5: Dexa/Ifos/E/ARA-C/*it	4
	MTX (1000)		

Ifos: Ifosfamide, Carbo: Carboplatin, E: Etoposide, Doxo: Doxorubicin, Bleo: Bleomycin, VBL: Vinblastine, DTIC: Dacarbazine, Dexa: Dexamethasone, ARA-C: Cytosine arabinoside, VCR: Vincristine, MTX: Methotrexate, Pred: Prednisolone, *it: Triple intrathecal therapy including MTX(6)+ARA-C(15)+Pred(5).

The antiemetic efficacy of tropisetron was assessed using a grading scale based on the combined measure of both emesis and nausea. The response to tropisetron per 24-hour period for each course was graded as:

Complete response : No vomiting, nor nausea.

Major response : 1-2 vomits or mild nausea.

Minor response : 3-5 vomits and/or less than 5 hours of moderate nausea interfering with daily activities.

Failure (no response) : More than 5 vomits and/or at least 5 hours of severe, bedridden nausea.

The cost effectiveness of tropisetron was also evaluated by determining its cost for the total 125 courses. Total cost was divided by the number of courses with complete control of acute emesis to calculate the cost per successfully controlled course. Results are given in US dollar (USD).

Results

A total of 22 children (11 boys and 11 girls) who received emetogenic chemotherapy were studied. Their median age was 14 years (range 3 to 18 years). Some characteristics of the patients are given in Table III. Four patients had received chemotherapy prior to the study and five had radiotherapy previously. There were two patients with a central nervous system tumor removed surgically without any trace, with no signs of increased intracranial pressure that might induce emesis.

Table III: Patient Characteristics

Total number of patients	: 22
Male/female	: 11/11
Median age (range) in years	: 14 (3-18)
Age groups	
< 10 years	: 3
≥ 10 years	: 19
Diagnosis	
Osteosarcoma	: 4
Hodgkin's disease	: 4
Ewing's sarcoma	: 4
Non-Hodgkin's lymphoma	: 3
Rhabdomyosarcoma	: 2
Malign mesenchymal tumor	: 2
Central nervous system tumor	: 2
Germ cell tumor	: 1

A total of 125 courses of grade 3 or 4 emetogenic chemotherapy were administered to 22 children (median:6, range: 2 to 15 courses) using 15 different regimens for the treatment of eight different types of tumors (Table IV). The duration of the regimens differed largely, from one to six days. These regimens contained different combinations of anticancer drugs. In some of the multiple-day courses, the emetogenic potential for each subsequent day was different. Some of the protocols like PNET III (UKCCSG 9102), NHL-BFM 90 B cell protocol, and CCG 94-7921 osteosarcoma protocol consisted of sequential blocks (courses), each of which included different emetogenic combinations (Table IV). Because of these variations, it was not possible to evaluate response rate in terms of control of daleyad emesis since some protocols were single-day

regimens and others had a duration of up to six days. Therefore, the efficacy results for tropisetron are given as "first day response during a course" which is consistent with control of acute emesis to provide uniformity between these heterogeneous chemotherapy courses. In this study, subgroup analyses could not be performed because of the small number of each unique course. Combination chemotherapy was administered on a single day for 28 courses (22%) and on multiple days for 97 courses (78%). All 22 patients received tropisetron at least during two courses of chemotherapy. Corticosteroids were part of the chemotherapy regimen in 13 courses (10%), and were administered as part of a premedication protocol with diphenhydramine to prevent allergic reactions in 10 courses (8%). Seventeen out of 125 courses contained CDDP; of these patients were under routine premedication with corticosteroid and diphenhydramine.

Antiemetic efficacy was also velauated using the daily schedule based responses in a total of 342 days of chemotherapy.

Table IV: Chemotherapeutic Regimens Used During the Study

Regimen	Tumor types	Emetic grade of the combination	Duration of a course	No. of courses	Corticosterold (cs) diphenhydramine (dph)
1. Single day regimens					
VAC	Soft tissue sarcoma	4	1	8	-
ABVD	Hodgkin's disease	4	1	15	-
MOPP	Hodgkin's disease	3	1	3	cs
COPP	Hodgkin's disease	3	1	2	cs
2. Multiple-day regimens (same drugs in each course)					
ICE	Resistant tumors	4	3	29	-
CEV/CE	Resistant tumors	4	3	15	-
VAI	Soft tissue sarcoma	4	5	3	-
CDDP+Paclitaxel	Resistant tumors	4	6	4	cs+dph
PVB	Germ cell tumors	4	3	6	cs+dph
3. Multiple-day regimens (different drugs in sequential courses)					
NHL-BFM 90-B cell	B cell NHL	3-4	5	6	cs
ALL-Rezidive BFM 90	Relapsed NHL	4	6	2	cs
PNET III	Medulloblastoma	4	3	3	-
EICESS 92	Soft tissue sarcoma	4	3	11	-
CCG 94-7921	Osteosarcoma	3-4	1-5	9	-
Osteosarcoma protocol	Osteosarcoma	4	2	9	-

Efficacy Results for the Courses: Overall complete response on day 1 was observed in 80 out of 125 courses (64%). A complete and major response rate on day 1 of Course I, Course II and overall 125 courses was observed in 73, 77 and 80 percent, respectively (Fig. 1). There were seven CDDP-containing courses given without corticosteroid. In this group, none of the patients was a complete responder on day 1: there were one major and five minor responses and one failure. On the other hand, CDDP courses given with corticosteroid and diphenhydramine (n: 10) resulted in five complete and four minor responses and one failure noted on the first day. When we excluded the courses with CDDP

and courses including diphenhydramine and/or corticosteroid, complete response was 68 percent on day 1 (n: 95 courses). There were 13 non-CDDP courses given with dexamethasone. In this latter group, 11 of the 13 courses resulted in a complete response on the first day. There were a limited number of patients in subgroups on different schedules. This study was not designed to test the hypothesis based on these smaller subgroups. Therefore, subgroup analyses could not be performed and statistics are purely descriptive.

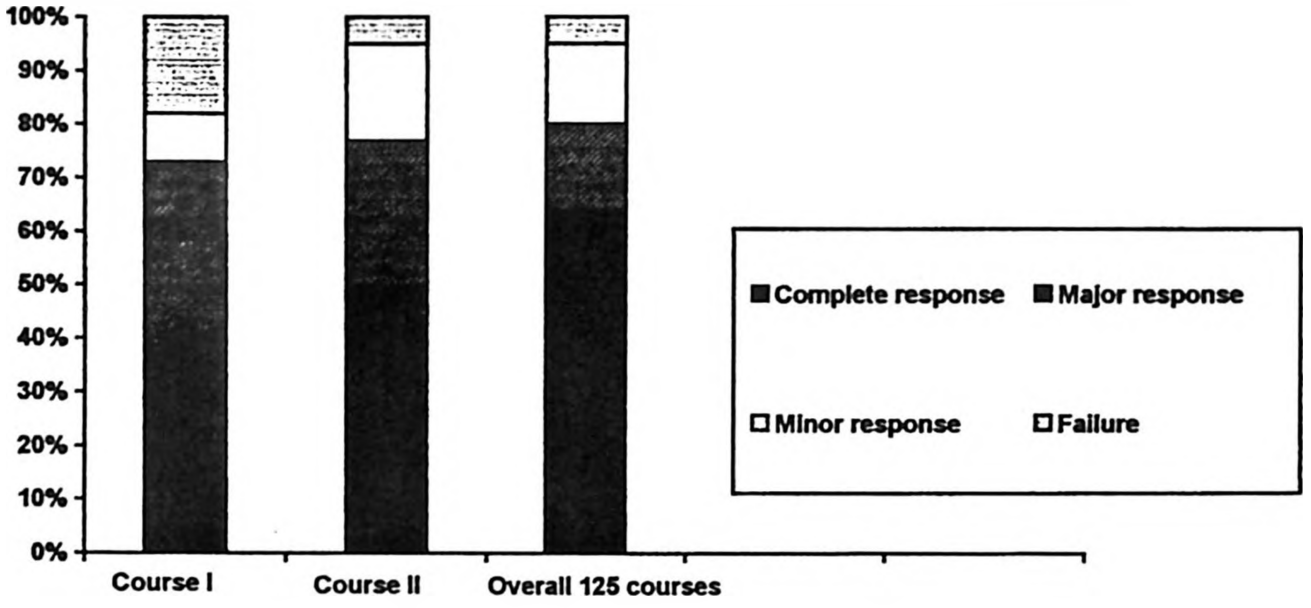


Fig. 1: Efficacy results for the first (Course I) and second (Course II) 22 courses and for the total 125 courses.

Efficacy Results for the Daily Schedules: A total of 342 days of emetogenic chemotherapy were administered during the study. Complete control of emesis was achieved in 246 (72%) days, while major and minor responses were observed in 42 (12%) and 39 (11%) days, respectively. Complete response rate was 59 percent for grade 4, 85 percent for grade 3 and 75 percent for grade 1-2 emetogenic daily schedules (Tables V-VI-VII). When CDDP-containing courses and courses administered with corticosteroids were excluded from the analyses, complete response rates for grade 4, 3 and 1-2 emetogenic daily schedules were 62, 84 and 82 percent, respectively. Response rates according to the daily emetic schedules are given in Figure 2.

Safety Results: A mild and self-limited diarrhea in two courses (1.6%) and dry-mouth in three courses (2.4%) were observed during the study. Routine microbiological examinations did not reveal any specific etiology for diarrhea. No other systemic or local side effect was observed.

Cost Effectiveness Analyses: A total of 302 ampules and 316 capsules were used during the study. Total cost of the antiemetic drug was 1,2950 USD. The cost per successfully controlled course was 162 USD.

Table V: Efficacy Results for Grade 4 Emetogenic Daily Schedules

Daily Emetogenic Regimen (mg/m²)	No of Days	Response (Days)				cs/dph
		Complete	Major	Minor	Failure	
Ifos (1500)/E(100)/Carbo (500)	35	30	3	2	0	-/-
Ifos (2000)/E (100)/Doxo (20)/±VCR (1.5)	18	6	7	2	3	-/-
Ifos (2000)/E (100)/Act-D (0.5)/VCR (1.5)	16	6	6	4	0	-/-
Doxo (25)/Bleo (10)/VBL(6)/DTIC (375)	15	9	2	3	1	-/-
Ifos (1800)/Act-D (0.15)/±VCR (1.5)	15	11	1	3	0	-/-
Ifos (1800)/Doxo (25)	10	7	3	0	0	-/-
CDDP (120)/Doxo (25)	8	0	1	5	2	-/-
CYC (600)/Doxo (60)/VCR (1.5)	8	7	1	0	0	-/-
CDDP (120)	6	1	0	5	0	+/+
Bleo (15)/CYC (600)/Act-D (0.6)	6	1	1	2	2	-/-
Dexa (20)/VCR (1.5)/ARA-C (2x2000)/*it	2	2	0	0	0	+/-
Dexa (20)/ARA-C (2x200)	2	2	0	0	0	+/-
Dexa (20)/6 TG (100)/DNR (50)/Ifos (400)	1	1	0	0	0	+/-
Dexa (20)/6 MP (100)/ARA-C (2x2000)	1	1	0	0	0	+/-
Total (%)	143 (100)	84 (59)	25 (17)	26 (18)	8 (6)	

cs: crticosteroid, dph: Diphenhydramine, Ifos: Ifosfamide, Carbo: Carboplatin, E: Etoposide, Doxo: Doxorubicin, VCR: Vincristine, Act-D: Actinomycine D, Bleo: Bleomycin, VBL: Vinblastine, DTIC: Dacarbazine, CDDP: Cisplatin, CYC: Cyclophosphamide, Dexa: Dexamethasone, ARA-C: Cytosine arabinoside, 6TG: 6 Thioguanine, DNR: Daunorubicin, 6MP: 6 Mercaptopurine *it: Triple intrathecaltherapy including MTX(6)+ARA-C(15)+Pred(5).

Table VI: Efficacy Results for Grade 3 Emetogenic Daily Schedules

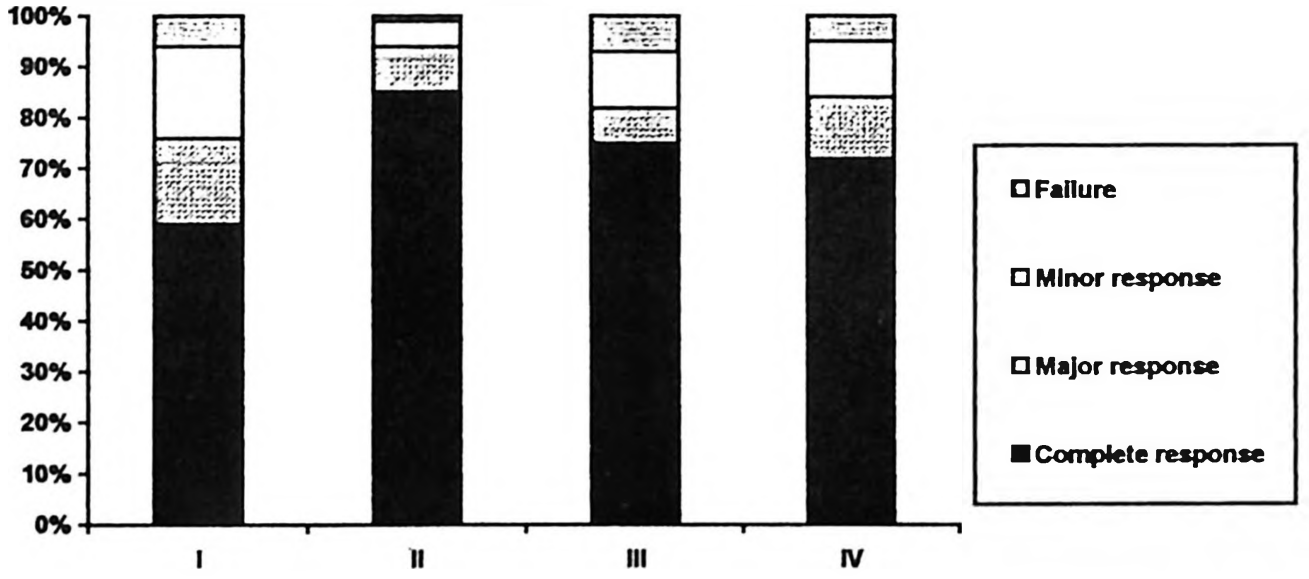
Daily Emetogenic Regimen (mg/m²)	No of Days	Response (Days)				cs/dph
		Complete	Major	Minor	Failure	
Ifos (1500)/E(100)	70	60	8	2	0	-/-
CDDP (20)	20	17	3	0	0	-/-
Carbo (500)/E (100)	7	5	0	1	1	-/-
Carbo (500)/E (100)/VCR (1.5)	6	4	0	1	1	-/-
MTX (18000)	6	5	1	0	0	-/-
Ifos (1800)	4	4	0	0	0	-/-
Meclor (6)/VCR (1.5)/Proc (100)/Pred (40)	3	1	0	2	0	+/-
Dexa (10)/CYC (200)/Doxo (25)	2	2	0	0	0	+/-
Dexa (10)/CYC (200)/Doxo (25)/*it	2	2	0	0	0	+/-
Dexa (10)/VCR (1.5)/MTX (1000)/Ifos(800)/*it	2	2	0	0	0	+/-
CYC (600)/VCR(1.5)/Proc(100)/Pred (40)	2	2	0	0	0	+/-
Dexa(10)/VCR(1.5)/MTX(1000)/CYC(200)/*it	2	2	0	0	0	+/-
Dexa(10)/Ifos(800)E(100)/ARA-C(150x2)	2	2	0	0	0	+/-
Dexa(10)/Ifos(800)E(100)/ARA-C(150x2)/*it	2	2	0	0	0	+/-
Dexa(20)/6TG(100)/VCR(1.5)/MTX(1000) /Ifos(400)/*it	1	1	0	0	0	+/-
Total (%)	131 (100)	111 (85)	12 (9)	6 (5)	2 (1)	

cs: crticosteroid, dph: Diphenhydramine, Ifos: Ifosfamide, E: Etoposide, CDDP: Cisplatin, Carbo: Carboplatin, VCR: Vincristine, MTX: Methotrexate, Mechor: Meclorethamine, Proc: Procarbazine, Pred: Prednisolone, Dexa: Dexamethasone, CYC: Cyclophosphamide, Doxo: Doxorubicine, ARA-C: Cytosine arabinoside, 6TG: 6 Thioguanine, *it: Triple intrathecal therapy including MTX(6)+ARA-C(15)+Pred(5).

Table VII: Efficacy Results for Grade 1-2 Emetogenic Daily Schedules

Daily Emetogenic Regimen (mg/m²)	No of Days	Response (Days)				cs/dph
		Complete	Major	Minor	Failure	
E (100)	22	17	1	2	2	-/-
VBL(6)	6	5	1	0	0	+/+
VBL(6)/Bleo(10)	6	0	3	2	1	+/+
Doxo(30)	6	1	0	3	2	-/-
Paclitaxel(135)	4	4	0	0	0	+/+
Dexa(20)/Ifos(800)	4	4	0	0	0	+/-
Dexa(10)/CYC(200)	4	4	0	0	0	+/-
Dexa(10)/E(100)	4	4	0	0	0	+/-
Dexa(20)/6TG(100)/Ifos(400)	3	3	0	0	0	+/-
Dexa(20)/6MP(100)	3	3	0	0	0	+/-
Dexa(20)/VCR(1.5)/L-Asp 25000 U/m²	2	2	0	0	0	+/-
Dexa(20)/VCR(1.5)/L-Asp 25000 U/m²	2	2	0	0	0	+/-
Dexa(10)/E(100)*it	2	2	0	0	0	+/-
Dexa(20)/VCR(1.5)MTX(1000)/6MP(100)/*it	2	2	0	0	0	+/-
Total (%)	68 (100)	51 (75)	5 (7)	7 (11)	5 (7)	

cs: crticosteroid, dph: Diphenhydramine, E: Etoposide, VBL: Vinbastine, Bleo: Bleomycin, Doxo: Doxorubicin, Dexa: Dexamethasone, Ifos: Ifosfamide, CYC: Cyclophosphamide, 6TG: 6 Thioguanine, 6MP: 6 Mercaptopurine, VCR: Vincristine, L-ASP: L-Asparaginase, MTX: Methotrexate, *it: Triple intrathecal therapy including MTX(6)-ARA-C(15)+Pred(5).



I. Efficacy for days with grade 4 emetogenic potential.
II. Efficacy for days with grade 3 emetogenic potential.
III. Efficacy for days with gradel-2 emetogenic potential.
IV. Efficacy for the total 342 days.

Fig. 2: Efficacy results according to the daily emetic schedules.

Discussion

Efficacy of an antiemetic drug used in multiple-day chemotherapy regimens depends on several factors. The duration of these regimens may differ largely from one protocol to another. Emetic grade of the drugs administered on each

day of the multiple-day regimen may be significantly different. For example, BFM 90 NHL B cell protocol consists of three different "five-day block" administered sequentially fortnightly. Each of these blocks includes a different combination of chemotherapeutics with the emetic grade of a given day changing from grade 2 to grade 4. It is not appropriate to classify a "five-day block" as a grade 4 emetic regimen since the patients receive only low emetogenic drugs on some of the days while high emetogenic combinations are given on the other days. Therefore, only first day responses were evaluated in our study, on each of which grade 3 or grade 4 emetogenic drugs were administered.

The results obtained in this study were mostly in agreement with the previous studies regarding tolerability and efficacy of tropisetron in the control of acute emesis in children and adolescents[5-9]. Side effects of tropisetron were almost totally absent as was the case in the previous studies performed in children. In terms of efficacy, complete response rate on day 1 was 64 percent for the total of 125 courses and failure rates were low (5% on day 1). Gershanovich et al.[13] reported a complete response of 69 percent on the first day of chemotherapy courses in children. In another study[6], 67 percent overall complete response was observed on day 1 in a total of 455 courses administered to pediatric patients Cefalo et al.[7] reported a good control (less than 2 emetic episodes per day) in 64 percent of the 184 treatment days in a pediatric population. The results of another study[8] showed a complete response rate of 77 percent in previously treated pediatric patients receiving non-CDDP regimens.

In the present study, the number of courses with CDDP was small, so a comparison between CDDP and non-CDDP courses was not possible. In seven courses with CDDP but without corticosteroid, there was no complete response on the first day. In a previous study[9], a complete response rate of 53 percent was reported on day 1 in children receiving CDDP-containing regimens. The control of emesis improved in 10 CDDP courses administered with dexamethasone and diphenhydramine (5 complete responses on day 1). We also observed better response rates for the control of acute emesis when corticosteroids were part of the protocol in non-CDDP courses; 85 percent complete response was achieved on the first day. These results confirmed the previously reported results about the increased efficacy of tropisetron with the addition of dexamethasone, as is true for all 5HT3 receptor antagonists[11, 13]. In this study, corticosteroid-containing CDDP courses also included diphenhydramine. Diphenhydramine is an effective antiemetic for motion sickness and may be used in combination with other antiemetics to potentiate effectiveness. This additional antiemetic effect probably played a role in the improved response rates observed in corticosteroid-containing courses. Control of acute emesis for the first and second courses was similar. This finding indicates a consistent response for tropisetron over courses based while on multiple chemotherapy.

In our study, emetogenic chemotherapy was given according to 15 different protocols resulting in heterogeneous data for the evaluation of the antiemetic response. Therefore, another evaluation based on the daily schedules was performed. Overall complete response rate for grade 3 and 4 emetogenic daily schedules was 85 and 59 percent, respectively, while low emetogenic (grade 1, 2) daily schedules resulted in a 75 percent compelete response. Because of the limited number of subgroups, statistical analyses could not be performed. In any case, several factors might have interfered with these results. There were some schedules given with diphenhydramine and/or corticosteroid (mainly dexamethasone). Administration of corticosteroids in 18 out of 131 treatment days probably improved the response rate for the grade 3 emetogenic daily schedules. Another important factor we had to overlook was the effect of the previous day's emetic schedule over a given day. For example, six days with vinblastine and bleomycin combination, which is known to be low emetogenic (grade 1), resulted in three major and two minor responses, and no complete response was noted. This combination is part of a protocol (PVB) containing CDDP on day 1, so this poor response can easily be explained by the delayed effect of CDDP. Additionally, our study population consisted mostly of adolescents (86% of the whole group), whose memory of previous episodes of emesis is a major problem interfering with the incidence and severity of nausea and vomiting[14].

In this study, the cost of tropisetron per successfully controlled course was 162 USD. In 45 courses (36%), nausea and vomiting could not be completely controlled. Our study was not designed to test the hypothesis based on subgroups; subgroup analyses could not be performed because of the limited number of each unique course. Therefore, the results are merely descriptive and can be used only to generate further hypotheses. We are planning a prospective trial using daily administered emetic drug based data for multiple-day regimens in order to design anantiemetic porotocol for children which is equally effective but lower in cost than the commonly used antiemetic regimens. Even though the advantages of the 5-HT3 receptor antagonists over traditional antiemetics are generally acknowledged, it is of interest to compare these drugs. A careful review of the literature by Roila et al.[15] revealed 22 comparative studies among the 5-HT3 receptor antagonists. The authors stated that several of these trials have some important shortcomings, especially in the study design, the size of the population studied and the type of antiemetic treatment selected, making their conclusions difficult to interpret. However, some randomized, double-blind studies have shown that the antiemetic activity and tolerability of ondansetron, granisetron and tropisetron are almost identical, at least in the prevention of cisplatin-induced emesis[16-20]. Therefore, from the efficacy and safety point of view, there is no reason to prefer one compound over the other. From the economic perspective, however, differences may exist and choice should be based on acquisition cost in each country, taking into account optimal dose and schedule.

In spite of the large number of studies investigating the efficacy of antiemetic agents in adults, only a few double-blind, randomized and multicentric studies have been reported for children and adolescents. Since the data from adult cancer patients cannot be extrapolated to pediatric oncology practice, multicentric trials in children will provide important clues to develop a consensus about the best practices and to encourage adherence to them.

In conclusion, the results of this study confirmed that tropisetron is a safe, well tolerated and effective antiemetic in prevention of acute emesis induced by high emetogenic regimens in children and adolescents. A single daily dose seems to be advantageous for both the patient and the physician.

REFERENCES

1. Allen JC, Gralla R, Reilly L, et al. Metoclopramide: dose related toxicity and preliminary antiemetic studies in children receiving cancer chemotherapy. J Clin Oncol 1985; 3: 1136-1141.
2. Terrin BN, McWilliams NB, Maurer HM. Side effects of metoclopramide as an antiemetic in childhood cancer chemotherapy. J Pediatr 1984; 104: 138-140.
3. Sarıalioğlu F, Akyol H, Büyükpamukçu M, Akyüz C, Çevik N. High dose metoclopramide and dexamethasone for prevention of cisplatin-induced emesis in pediatric patients. Proceedings of the 15th International Congress of Chemotherapy. İstanbul, Turkey July 19-24, 1987: 266-268.
4. Pinkerton CR, Williams D, Woote C, et al. 5 HT3 antagonist ondansetron: an effective outpatient antiemetic in cancer treatment. Arch Dis Child 1990; 65: 822-825.
5. Lemerle J, Amaral D, Southal DP, et al. Efficacy and safety of granisetron in the prevention of chemotherapy-induced emesis in paediatric patients. Eur J Cancer 1991; 27. 1081-1083.
6. Benoit Y, Hulstaert F, Vermylen C, et al. Tropisetron in the prevention of nausea and vomiting in 131 children receiving cytotoxic chemotherapy. Med Pediatr Oncol 1995; 25: 457-462.
7. Cefalo G, Rottoli L, Armiraglio A, et al. Tropisetron (ICS 205-930) in pediatric oncology: first results in patients refractory to antiemetic metoclopramide-based treatments. Am J Pediatr Hematol Oncol 1994; 16: 242-245.
8. Hachimi-Idrisis S, De Schepper J, Maurus R. Prevention of emesis by ICS 205-930 in children receiving cytotoxic chemotherapy. Eur J Cancer 1993; 29: 854-856.
9. Berberoğlu S. Prevention of emesis by tropisetron in children receiving combined chemotherapy with cisplatin. Pediatr Hematol Oncol 1995; 12: 479-483.
10. Bleiberg H, Van Belle S, Paridaens R. Compassionate use of tropisetron in patients at high risk of severe emesis. Ann Oncol 1993; 4 (Suppl): 43-45.
11. Sorbe B, Hogberg T, Himmelmann A, et al. Efficacy and tolerability of tropisetron in comparison with a combination of tropisetron and dexamethasone in the control of nausea and vomiting induced by cisplatin-containing chemotherapy. Eur J Cancer 1994; 30A: 629.
12. Van Belle SJP, Cocquyt VF, Bleiber H, et al. Optimal combination therapy with Navoban (tropisetron) in patients with incomplete control of chemotherapy-induced nausea and vomiting. Anti-Cancer Durgs 1995; 6 (Suppl): 22-30.
13. Gershanovich M, Kolygin B, Pirgoch N. Tropisetron in the control of nausea and vomiting induced by combined cancer chemotherapy in children. Ann Oncol 1993; 4: (Suppl): 35-37.
14. Dolginn MJ, Katz ER, Doctors SG, et al. Caregivers' perception of medical compliance in adolescents with cancer. J Adolesc Health Care 1986; 7·22-27.

15. Rolia F, Ballatori E, Tonato M, et al. 5-HT3 receptor antagonists: differences and similarities. Eur J Cancer 1997; 33: 1364-1370.
16. Italian Group for Antiemetic Research. Ondansetron versus granisetron, both combined with dexamethasone, in the prevention of cisplatin-induced emesis. Ann Oncol 1995; 6: 805-810.
17. Jantunen IT, Muhonen TT, Kataja VV, et al. 5-HT3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy- a randomised study. Eur J Cancer 1993; 29A: 1669-1672.
18. Marty M, Kleisbauer JP, Fournel P, et al. Is Navoban (tropisetron) as effective as Zofran (ondansetron) in cisplatin-induced emesis? Anti-Cancer Drugs 1995; 6: 15-21.
19. Navari R, Hesketh P, Hall S, et al. On behalf of the Granisetron Study Group. Comparative clinical trial of granisetron and ondansetron in the prophylaxis of cisplatin-induced emesis. J Clin Oncol 1995; 13: 1242-1248.
20. Noble A, Bremer K, Goedhals L, et al. A double-blind, randomised, crossover comparison of granisetron and ondansetron in 5-day fractionated chemotherapy: assesment of efficacy, safety and patient preference. Eur J Cancer 1994; 30A: 1083-1088.