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Anticancer Original Research Paper

Chemotherapy-related toxicity in patients with non-metastatic Ewing sarcoma: influence of sex and age

Anna Paioli[1], Roberto Luksch[2], Franca Fagioli[3], Angela Tamburini[4], Marilena Cesari[1], Emanuela Palmerini[1], Massimo Eraldo Abate[1], Emanuela Marchesi[1], Alba Balladelli[5], Loredana Pratelli[6], Stefano Ferrari[1]

[1]Chemotherapy Unit of the Department of Musculoskeletal Oncology, Istituto Ortopedico Rizzoli, Bologna, Italy, [2]Pediatric Oncology Division, Istituto Nazionale Tumori, Milan, Italy, [3]Department of Pediatric Oncology, Ospedale Regina Margherita, Torino, Italy, [4]Pediatric Oncology Division, Meyer Hospital, Firenze, Italy, [5]Department of Experimental Oncology Laboratory, Istituto Ortopedico Rizzoli, Bologna, Italy, [6]Clinical Pathology, Istituto Ortopedico Rizzoli, Bologna, Italy

Influence of age and sex on chemotherapy-related toxicity was evaluated in children (3–9 years), adolescents (10–17 years), and adults (up to 40 years) with localized Ewing sarcoma (ES) enrolled in the ISG/SSG III protocol. Treatment was based on vincristine, doxorubicin, cyclophosphamide, ifosfamide, dactinomycin, and etoposide. High-dose chemotherapy with busulfan and melphalan was given in poor responder patients. The analysis was based on 2191 courses of standard chemotherapy and 230 patients. A lower risk of G4 leukopenia and thrombocytopenia, hospitalization, febrile neutropenia, and red blood cell (RBC) transfusions was observed in males. Use of granulocyte colony-stimulating factor (G-CSF) was more frequent in adults, while children more often received RBC transfusions. A significant correlation between sex and chemotherapy-related toxicity was observed in the study, whereas no significant differences in terms of bone marrow toxicity can be expected according to patient age. Further studies should analyse the role of pharmacokinetics, pharmacogenomics, and clinical characteristics.

Keywords: Age, Chemotherapy, Ewing sarcoma, Sex, Toxicity

Introduction

Ewing sarcomas (ES) arise in bone and soft tissues and represent the second most common primary malignant bone cancer in children and adolescents. However, they are also reported in adults, in particular, the extra-skeletal variety.[1] Treatment is complex, yet with the use of a multimodal approach within clinical trials, employing combination polychemotherapy and local treatment (surgery and/or radiotherapy), 5-year survival rates have improved for localized disease from $<$ 10% in the late 1960s to $>$ 60% today.[2–4]

The most active antineoplastic agents against ES are doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin, and etoposide.[5–9] Current clinical trials for non-metastatic ES use combinations of these six drugs for three to six cycles followed by local therapy and another six to ten cycles of chemotherapy.[10] In some clinical trials, poor responder patients receive intensified treatment with the addition of high-dose chemotherapy followed by stem cell rescue,[11–14] with an improved survival, nevertheless the use of high-dose chemotherapy in ES is still considered investigational.[10]

Treatment of adult patients, aged from 18 to 30–40 years, with localized ES, follows the same principles as those adopted for children and young adults.[10] However, tolerability of therapies in adults needs to be taken into account when transferring treatment protocols conceived for pediatric patients, and there are few data available on differences in tolerability to chemotherapy between adults, adolescents and children.[15]

Age is a well known prognostic factor for ES and younger patients have a better prognosis compared to older patients.[1,3,6,10,15,16] The prognostic significance of gender is controversial,[3,6] while it seems to influence chemotherapy-related toxicity.[17]

Aim of this study was to evaluate the influence of sex and age on chemotherapy-related haematological toxicity in patients with non-metastatic ES, treated according to the Italian–Scandinavian protocol for non-metastatic ES (ISG/SSG III). ISG/SSG III was a

Correspondence to: A. Paioli, Chemotherapy Unit, Istituto Ortopedico Rizzoli, Via Pupilli 1, 40136 Bologna, Italy. Email: annapaioli@yahoo.it

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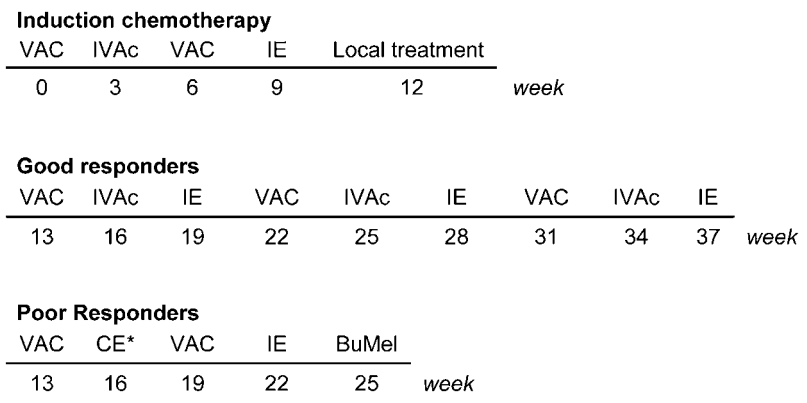

Figure 1 Italian Sarcoma Group/Scandinavian Sarcoma Group III chemotherapy schedule: V, vincristine 1.5 mg/m^2 (top dose 2 mg) i.v. push; A, doxorubicin 40 mg/m^2/die i.v. in 4 hours, days 1–2; C, cyclofosfamide 1200 mg/m^2 i.v. in 30 minutes with mesna equimolar dose; Ac, actinomycin D 1.5 mg/m^2 (top dose 2 mg) i.v. push; I, ifosfamide 3 g/m^2/die i.c. days 1–2–3, with 2000 ml/m^2/24 h of basal solution and mesna equimolar dose; E, etoposide 150 mg/m^2/die i.v. in 2 hours at days 1–2–3; CE* (mobilizing cycle), cyclophosphamide 4 g/m^2/die i.v. in 3 hours at day 1 with mesna and etoposide 200 mg/m^2/die i.v. in 2 hours at days 2–3–4; BuMel, busulfan 4 mg/kg/die in 4 days orally in four doses per day and melphalan 140 mg/m^2 i.v. in 1 hour.

cooperative non-randomized phase II multicentre study between the Italian Sarcoma Group (ISG) and the Scandinavian Sarcoma Group (SSG). The results of this study have been previously reported.[16]

Methods

Patients with a diagnosis of non-metastatic ES enrolled in the ISG/SSG III study who received chemotherapy treatment in Italian centres were selected.

Written informed consent from all patients or their guardians was obtained before registration.

Schedule and doses of the chemotherapy regimen are reported in Fig. 1.

Surgery was the preferred treatment option for local control. Radiotherapy was reserved for non resectable tumours or in case of inadequate surgical margins. Patients with good response continued on standard therapy using the same drugs and modality as in the induction phase.[11,16] Poor responders were given a different treatment including high-dose chemotherapy (busulfan and melphalan) with peripheral blood stem cells support, administered as last cycle.[16] A top dose was set at 2 m^2 for those exceeding this level; the top dose for vincristine and dactinomycin was 2 mg.

At baseline and before each chemotherapy course, haemoglobin, white blood counts, neutrophils, and platelets were assessed. No dose reductions were allowed, and when blood counts were low (neutrophil < 1000/ml, and/or platelet $< 100\,000$/ml), chemotherapy was delayed until recovery and values were rechecked every other day.

After each cycle, complete blood count was monitored every 2 days on day $+9$ to $+17$, starting from day 1 of chemotherapy infusion. Patients or guardians reported the complete blood count data by phone or fax. For each chemotherapy course, a toxicity data form was filled by patients or guardians and collected by the study nurse when the patient was hospitalized for the next chemotherapy cycle.

Data were prospectively collected in the chemotherapy department database and graded according to NCI Common Toxicity Criteria, version 2.0.[18] Toxicity assessment included evaluation of grade 4 haematological toxicity, use of granulocyte colony-stimulating factors (G-CSFs), episodes of neutropenia-related fever, need of hospitalization, red blood cell (RBC), and platelet (PLT) transfusions.

G-CSFs support was recommended to reduce neutropenia-related clinical sequelae and was given according to institutional guidelines. G-CSFs were not routinely administered after the first cycle. G-CSFs administration was mandatory when the previous course was followed by white blood count $< 1.0 \times 10^9$/l or neutropenic fever (temperature > 38.5°C and neutrophil count $< 0.5 \times 10^9$/l). G-CSFs must be stopped at least 24 hours before starting the next course of chemotherapy and when the total white blood count exceeds 10.0×10^9/l. G-CSFs were administered as a subcutaneous injection once-a-day, the dose for children was 5 μg/kg, for adults 300 μg if body weight was < 80 kg, and 480 μg if body weight was > 80 kg. After CE mobilizing cycle G-CSFs were given at higher doses because followed by peripheral blood stem cell harvest. Child dosage was 10 μg/kg, adults with body weight < 80kg were administered 600 and 900 μg when body weight was > 80 kg.

As a general guideline, RBC transfusions were recommended when hemoglobin value was < 8 g/l. PLT transfusions were indicated when signs of bleeding were seen and/or PLT values were $< 10.0 \times 10^9$/l.

Statistics

The analysis focused on haematological toxicity which was the most clinically relevant toxicity observed in ISG/SSG III.[16] The primary endpoint of the study was assessment of haematological toxicity and its correlation with age and sex. These two variables have a remarkable clinical interest. Chemotherapy regimens

for ES are primarily designed for a pediatric population, and it is interesting to investigate how adult patients can tolerate such intensive chemotherapy treatments. Regarding gender, this variable had been previously reported as related to chemotherapy toxicity in patients with ES[17] and our aim was to verify this observation in our population.

Variables such as location or size of primary tumour, lactate dehydrogenase, and histological response were not included in the present analysis because they were not patient-related and because previous analysis reported no correlation amongst these factors and chemotherapy-related toxicity.[17]

Study population consisted of patients enrolled in the ISG/SSG III protocol who received chemotherapy treatment in Italian centres. Patients were grouped into three age categories, children up to 9 years, patients aged from 10 to 17 years, and adults aged from 18 to 40 years, according to the ISG/SSG III protocol previously published.[16]

Toxicity data were prospectively collected and graded according to the NCI Common Toxicity Criteria version 2.0.[18] Toxicity assessment included evaluation of grade 4 haematological toxicity, use of G-CSFs, episodes of neutropenia-related fever, hospitalization related to haematological toxicity, delay in deliver therapy, incidence of stomatitis, and RBC and PLT transfusions.

All data related to chemotherapy toxicity following administration of standard courses delivered both in good and poor responder patients were included in the present analysis. Owing to the different pattern of toxicity, data of high-dose chemotherapy-related toxicity were excluded from the analysis. In order to have a complete haematological toxicity profile, the incidence of chemotherapy-related toxicity was assessed per patient and per cycle.[17,19] A subgroup analysis according to chemotherapy duration was performed.

Chi-square evaluated by the Monte Carlo exact method or Fisher's exact test when appropriate were used for comparison of categories. Logistic regression was performed to examine a possible interaction between sex and age groups.

Results

Three hundred patients were enrolled in the ISG/SSG III study, of which 244 were treated in Italian centres. Fourteen patients were excluded from the present analysis due to early progression or missing data. Median age of the 230 patients included was 15 years (range: 3–39 years), 39 patients were aged $\leq$ 9 years (17%), 110 from 10 to 17 years (48%), and 81 (35%) were $\geq$ 18 years old; 144 patients were male (63%) and 86 female (37%). The use of radiotherapy did not differ according to sex [68 (47%) males and 36 (42%) females ($P = 0.5$)], while it was lower in patients aged 3–9 years compared to the other age groups [10 (25%) 3–9 years, 51 (46%) 10–17 years, and 40 (49%) 18–39 years ($P = 0.04$)].

This analysis included 230 patients and 2191 courses of standard chemotherapy. No toxic deaths were reported. Overall, the incidence per cycle of G4 leukopenia was 66% and the incidence of G4 thrombocytopenia was 7%. Use of G-CSFs followed 69% courses, while RBC transfusions and PLT transfusions 20% and 5% respectively. Febrile neutropenia occurred in 17% of cycles and hospitalization for toxicity in 15%.

Toxicity and age

Table 1 summarizes toxicity data by age groups, analysis per cycle is reported in Table 1a and analysis per patient in Table 1b. In both analysis no statistically significant differences in terms of incidence of G4 leukopenia, G4 thrombocytopenia, febrile neutropenia, and PLT transfusions were seen across the age groups.

In the analysis per cycle, incidence of toxicity-related hospitalization decreased as age increased ($P = 0.006$) and a similar trend was seen in the analysis per patient, although differences were not statistically significant ($P = 0.2$). In both analyses, we observed that support with G-CSFs was given more frequently in adult patients than in the other age groups, whereas incidence of RBC transfusions was higher in patients aged 3–9 years.

In both the analysis per cycle and the analysis per patient, we observed no differences in terms of delay in treatment administration among age groups [35% of courses in patients aged 3–9 years, 32% in patients aged 10–17 years and 31% in adult patients ($P = 0.3$); 36 (92%) patients aged 3–9 years, 93 (85%) aged 10–17 years and 68 (84%) adult patients ($P = 0.4$)]. Most delays were related to haematological toxicity.

The same toxicity profile observed in the entire population was reported also when the analysis was separately performed in good responder patients and in poor responder patients (data not shown).

In 1469 courses, we also analysed the presence of stomatitis (G1 or higher), that occurred in 19% of cycles in paediatric patients, 24% in adolescents, and in 19% in adults ($P = 0.17$).

Toxicity and sex

In the analysis per cycle, we observed that, compared to male patients, females experienced a significantly higher incidence of G4 leukopenia, G4 leukopenia, use of G-CSFs, toxicity-related hospitalization, febrile neutropenia, and RBC transfusions as reported in Table 2a. Table 2b summarizes the analysis per patient where similar results were seen, although differences were not statistically significant in terms of incidence of G4 thrombocytopenia and use of G-CSFs.

Table 1 Incidence of toxicity by age

	Table 1a: toxicity per cycle				Table 1b: toxicity per patient			
	3–9 years	10–17 years	18–39 years	*P*-value	3–9 years (*n* = 39)	10–17 years (*n* = 110)	18–39 years (*n* = 81)	*P*-value
G4 leukopenia	71%	64%	65%	0.06	95% (37)	88% (97)	90% (73)	0.5
G4 thrombocytopenia	7%	7%	7%	1	28% (11)	26% (29)	23% (19)	0.8
G-CSFs‡	65%	62%	83%	0.0001	90% (35)	77% (85)	94% (76)	0.005
Hospitalization	19%	15%	12%	0.006	56% (22)	45% (49)	40% (32)	0.2
Febrile neutropenia	22%	17%	14%	0.04	69% (27)	65% (71)	52% (42)	0.1
RBC† transfusion	30%	20%	13%	0.0001	82% (32)	58% (64)	48% (39)	0.002
PLT* transfusion	4%	6%	4%	0.2	21% (8)	23% (25)	23% (19)	0.9

Note: *Platelets.
†Red blood cells.
‡Granulocyte-colony stimulating factors.

Analysis per cycle showed that a delay in chemotherapy administration occurred in 29% of cycles delivered in male patients and in 36% of courses delivered in female patients ($P = 0.001$). In the analysis per patient, one or more episodes of delay in chemotherapy administration were reported in 121 (84%) patients of male gender and in 76 (88%) patients of female gender ($P = 0.4$). Most of the delays were related to haematological toxicity. The same toxicity profile observed in the entire population was also reported when the analysis was separately performed in good and poor responder patients (data not shown). For 1469 courses we also analysed the presence of stomatitis (G1 or more), that occurred in 24% of cycles for females and in 17% of cycles for males ($P = 0.002$).

Multivariate analysis

Table 3 reports the logistic regression analysis performed to examine the possible interaction between sex and age groups. In the analysis per cycle, reported in Table 3a, sex was confirmed as an independent factor influencing bone marrow toxicity, hospitalization, need of RBC, and G-CSFs support. As reported in Table 3b, similar results were also observed in the analysis per patient, although a lower risk was seen in males compared to female patients for G4 leukopenia (RR: 0.34; 95% CI: 0.10–1.03), G4 thrombocytopenia (RR: 0.55; 95% CI 0.30–1.02) and use of G-CSFs (RR: 0.72; 95% CI: 0.32–1.62) did not reach statistical significance.

Age did not seem significantly related with bone marrow toxicity in terms of G4 thrombocytopenia and G4 leukopenia, however adulthood correlated with a higher use of G-CSFs and a lower use of RBC transfusions. In the analysis per cycle, children up to 9 years old were related to a higher risk of febrile neutropenia and hospitalization, while when analysed per patient, this did not achieved statistical significance.

Discussion

This study evaluated the influence of sex and age on chemotherapy-related toxicity in patients with non-metastatic ES, treated with the same chemotherapy protocol.

It is important to define the incidence of chemotherapy-related toxicity events per patient, however when treatment is cyclic, as in the present study, analysis of toxicity per cycle is considered more informative.[17,19] Indeed, analysis per patient showed that one toxicity event reported in a single course has the same impact as a series of toxicity events experienced by the same patient in subsequent cycles. In order to have a complete haematological toxicity profile, data analysis was performed both per cycle and per patient. In both analyses the role of sex and age on chemotherapy-related haematological toxicity was similar. In the analysis per cycle, statistical significance was achieved more often than in the analysis per patient; this could be related to a

Table 2 Incidence of toxicity by sex

	Table 2a: toxicity per cycle			Table 2b: toxicity per patient		
	Male	Female	*P*-value	Male (*n*)	Female (*n*)	*P*-value
G4 leukopenia	59%	78%	0.001	87% (125)	95% (82)	0.03
G4 thrombocytopenia	6%	10%	0.02	21% (30)	33% (28)	0.05
G-CSFs‡	60%	67%	0.02	83% (120)	88% (76)	0.3
Hospitalization	12%	19%	0.001	40% (57)	55% (47)	0.03
Febrile neutropenia	15%	21%	0.007	56% (80)	71% (61)	0.02
RBC† transfusion	14.5%	28%	0.0001	51% (73)	72% (62)	0.001
PLT* transfusion	4%	6%	0.1	18% (26)	31% (27)	0.02

Note: *Platelets.
†Red blood cells.
‡Granulocyte-colony stimulating factors.

Table 3 Logistic regression: toxicity and sex and age-groups

	Table 3a: toxicity per cycle			Table 3b: toxicity per patient		
	RR[§]	95% CI	*P*-value	RR[§]	95% CI	*P*-value
Grade 4 leukopenia						
Female	1			1		
Male	0.40	0.33–0.51	< 0.0001	0.34	0.10–1.03	0.06
18–40	1			1		
10–17	1.01	0.80–1.23	0.9	0.85	0.33–2.17	0.73
3–9	1.23	0.91–1.65	0.18	1.85	0.37–9.28	0.5
Grade 4 thrombocytopenia						
Female	1			1		
Male	0.57	0.40–0.82	0.003	0.55	0.30–1.02	0.06
18–40	1			1		
10–17	1.15	0.74–1.77	0.5	1.18	0.60–2.32	0.6
3–9	1.01	0.60–1.71	1	1.2	0.50–2.90	0.7
G-CSFs[‡]						
Female	1			1		
Male	0.80	0.64–0.98	0.03	0.72	0.32–1.62	0.4
18–40	1			1		
10–17	0.34	0.26–0.44	< 0.0001	0.23	0.08–0.63	0.004
3–9	0.37	0.27–0.50	< 0.0001	0.56	0.14–2.23	0.4
Hospitalization						
Female	1			1		
Male	0.56	0.44–0.73	< 0.0001	0.57	0.33–0.99	0.04
18–40	1			1		
10–17	1.32	0.98–1.79	0.07	1.24	0.69–2.24	0.5
3–9	1.69	1.18–2.40	0.004	1.84	0.84–4.03	0.1
Febrile neutropenia						
Female	1			1		
Male	0.68	0.53–0.86	0.002	0.52	0.29–0.92	0.03
18–40	1			1		
10–17	1.22	0.91–1.62	0.2	1.72	0.95–3.12	0.07
3–9	1.67	1.20–2.32	0.002	1.92	0.85–4.37	0.1
RBC[†] transfusion						
Female	1			1		
Male	0.44	0.35–0.56	< 0.0001	0.42	0.23–0.75	0.004
18–40	1			1		
10–17	1.73	1.30–2.30	0.002	1.64	0.90–2.96	0.1
3–9	2.69	1.94–3.72	< 0.0001	4.88	1.90–12.51	0.001
PLT* transfusion						
Female	1			1		
Male	0.69	0.45–1.04	0.08	0.49	0.26–0.92	0.03
18–40	1			1		
10–17	1.51	0.93–2.47	0.09	0.98	0.49–1.95	0.9
3–9	1.05	0.56–1.97	0.9	0.76	0.30–1.96	0.6

Note: *Platelets.
[†]Red blood cells.
[‡]Granulocyte-colony stimulating factors.
[§]RR: relative risk.

difference in sample size (230 patients versus 2191 cycles).

From our data, sex proved to be an important and independent factor that significantly affected bone marrow toxicity. Males correlated with a lower incidence of RBC transfusions, thrombocytopenia, leukopenia, febrile neutropenia, and toxicity-related hospitalization.

A similar correlation between sex and chemotherapy related toxicity is reported in literature. In the analysis of safety data from EUROE.W.I.N.G.-99, a multicentric study that included patients with ES treated in accordance to the VIDE (vincristine, ifosfamide, doxorubicin, and etoposide) schedule, female patients showed a higher haematological toxicity.[17] A higher susceptibility to chemotherapy-related toxicity in females with rhabdomyosarcoma and osteosarcoma was also reported.[20,21]

In our series, age does not seem to have the same impact. However, in adult patients we observed a lower hospitalization rate, while incidence of febrile neutropenia and RBC transfusions decreased as age increased. G4 leukopenia rate was similar among age groups, but patients over 18 years old more frequently received G-CSFs. This difference in supportive care may be expression of a different clinical approach between pediatric-oncologists and adult-oncologists. We cannot exclude that the different use of G-CSFs between pediatric and adult populations had some impact on the analysis performed. It is important to note that in adult patients the use of G-CSF was reported in 83% of cycles, while the incidence per cycle

of G4 leukopenia was 65%. On the other hand, when data were analysed per patient, a similar incidence of G4 leukopenia were seen, but 69% of young children had febrile neutropenia against 52% in adult patients. Based on these data, it is possible to affirm that a similar incidence of G4 leukopenia can be observed across the different age groups, but that wider use of G-CSF resulted in a lower incidence of neutropenic fever in adult patients.

Nevertheless, it is important to note that a previous monoinstitutional study analysing patients with osteosarcoma reported no differences in G-CSFs support among age groups, but children showed a higher incidence of G4 neutropenia and were more frequently hospitalized for neutropenic fever compared to adolescents and adults.[21] Moreover, EUROE. W.I.N.G.-99 reported that chemotherapy-related toxicity decreases as age increases, indicating a higher risk of haematological toxicity in pediatric patients.[17] A recent analysis performed in patients treated for rhabdomyosarcoma supports the hypothesis of a higher toxicity risk in younger children.[21]

The use of radiotherapy as local treatment could influence haematological toxicity and may be a bias for data analysis. For this reason, we evaluated the incidence of radiotherapy among patient groups. The use of radiotherapy did not differ according to sex, while it was lower in patients aged 3–9 years compared to the other age groups. In this subset of patients, however, we did not observe a lower susceptibility to haematological toxicity.

In the ISG/SSG III chemotherapy protocol, good responder patients overall received 13 courses of standard therapy, whereas poor responder patients, after four cycles of induction chemotherapy, received only four cycles of standard chemotherapy before administration of the last high-dose chemotherapy course, as reported in Figure 1. A subgroup analysis according to chemotherapy duration was performed and the role of age and sex on haematological toxicity was maintained.

Chemotherapy-related toxicity may be considered a surrogate marker of pharmacodynamic effect. In the present study, a higher incidence of bone marrow toxicity was observed in patients of female gender and, as already published, in the ISG/SSG III study good response after induction chemotherapy was more frequently observed in female patients, but this did not translate in a higher probability of 5-year event-free survival.[16]

The relation between female gender and higher probability of good response has been previously reported.[22] On the other hand, age is a well-recognized prognostic factor in ES, and also in our ISG/SSG III study,[16] younger patients had a higher probability of good response and a better probability of survival. In the present study, the higher incidence of bone marrow toxicity observed in younger patients was not statistically significant; however, they experienced febrile neutropenia, were hospitalized and received RBC transfusions more frequently than older patients, as reported in Table 3a.

A retrospective analysis of the National Australian Cancer Registry reported that for chemosensitive cancers like ES, osteosarcoma, and Hodgkin's lymphoma, almost all excess mortality seen in adults and young adults aged from 15 to 30–years (AYAs) compared to children occurs in males.[23] These gender-related differences in outcome correlated with toxicity. Male AYAs experienced less toxicity and lower response rates to chemotherapy than females. The issue of the possible use of chemotherapy-related toxicity as a pharmacodynamic surrogate marker is an open question and more specific studies are needed.

Biological reasons that determine these differences in terms of toxicity and response to chemotherapy are not well known. However, in the literature, there are some data about pharmacokinetic variability by sex and age of anticancer agents. Metabolism and clearance of most chemotherapy drugs is related to cytochrome P450 (CYP) isoenzymes, which play an important role in biotransformation of anticancer agents. Activity of CYP enzymes has a wide inter-patient variation, influenced by genetic polymorphisms, intake of drugs or foods.[24] Age and sex also influence CYP activity in different ways for different isoenzymes.[25] Cyclophosphamide and ifosfamide are anticancer pro-drugs metabolized and activated in the liver by cytochrome P450.[26] Pharmacokinetics of cyclophosphamide showed a considerable inter-patient variability, while pharmacokinetics of ifosfamide is markedly influenced by age, as well as by route of administration and liver and renal function.[27]

A possible role of age in doxorubicin pharmacokinetics is not well defined and high inter-patient variations have been reported.[28,29] A significant sex-related difference in doxorubicin pharmacokinetic profile has been demonstrated.[30] Furthermore, a body-composition related difference in doxorubicin metabolism and clearance has been shown, doxorubicin clearance decreases as the percentage of body fat increases.[31] A larger number of genetic polymorphisms have been reported in genes that mediate metabolism, transport and pharmacological activity of doxorubicin. Some single nucleotide polymorphism in the multidrug resistance gene ABCB1/MDR1 coding for p-glycoprotein have been shown to influence both pharmacokinetics and outcome in doxorubicin treatment.[32] Interesting, in our study, we observed a higher incidence of stomatitis in female patients, a well known doxorubicin-related adverse event.

Also metabolism of etoposide is significantly affected by ABCB1/MDR1 activity and different pharmacokinetics parameters were observed in females versus males.[33,34] Age can play a possible role in etoposide pharmacokinetics, children who underwent treatment with high-dose etoposide had a clearance at a range lower than that reported in the literature.[21,34]

Conclusions

In conclusion, in female patients with Ewing sarcoma, a higher incidence of chemotherapy-related haematological toxicity can be expected. Consequently, strategies of monitoring and management of haematological toxicity different from those used for the male sex should be planned in future studies.

Haematological toxicity did not differ among paediatric and adult patients. This supports the use of chemotherapy regimens conceived for children also in adult patients (up to 40 years of age) with ES.

Further studies investigating the role of pharmacokinetics and pharmacogenomics are needed to optimize the use of chemotherapy in patients with ES.

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