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Sequential high-dose chemotherapy for children with metastatic rhabdomyosarcoma

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ABSTRACT

Aim: The RMS4.99 study was designed to explore the role of multiple sequential high-dose chemotherapy cycles administered early in the treatment of children with metastatic rhabdomyosarcoma.

Patients and methods: Seventy patients were enrolled and received three cycles of initial standard chemotherapy, followed by a course of cyclophosphamide and etoposide to obtain peripheral blood stem cells (PBSC), then three consecutive high-dose combinations followed by PBSC rescue. This was followed by surgery and/or radiotherapy, after which a final maintenance treatment with six courses of vincristine, actinomycin D and cyclophosphamide was administered.

Results: Sixty-two patients underwent the high-dose chemotherapy phase. The 3-year overall survival (OS) and progression free survival (PFS) rates for the 70 patients were 42.3% (95% confidence interval [CI] 39.5–53.6) and 35.3% (95% CI, 24.3–46.5), respectively. By multivariate analysis survival correlated strongly with age > 10 years. In a subset of patients with only one or no unfavourable prognostic factors (age > 10 years, unfavourable site of primary tumour, bone or bone marrow involvement and number of metastatic sites >2) the PFS was significantly higher, i.e. 60.5% at 3 years.

Conclusion: Our study confirms that patients with favourable prognostic characteristics have a better survival. The use of sequential cycles of high-dose chemotherapy did not appear of benefit for patients with metastatic rhabdomyosarcoma.

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1. Introduction

The prognosis for children with cancer has improved dramatically in the last 30 years, but there are still certain types of patients for whom little or no progress has been made. Children with metastatic rhabdomyosarcoma (RMS) are among them, with 3-year event-free survival rates ranging from 20 to 30%.[1–3] These figures have not changed over time, despite the use of new drugs and the intensification of treatment. There is consequently an evident need for novel strategies.

In an attempt to overcome drug resistance, high-dose chemotherapy with stem cell rescue has been tested in patients with malignancies that carry a poor prognosis. A benefit has emerged in children with metastatic neuroblastoma,[4] while it remains uncertain for other solid tumours.

In RMS, megatherapy has been used as a consolidation treatment in children achieving complete tumour remission after intensive chemotherapy, but unfortunately no significant improvement in survival has been obtained.[5,6]

In 1999, the Soft Tissue Sarcoma Committee (STSC), affiliated to the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP), started its RMS4.99 study, based on the hypothesis that administering high-dose chemotherapy earlier than in previous experiences might help to prevent the occurrence of drug resistance and improve survival.

2. Patients and methods

As of September 2006, 70 eligible patients with metastatic RMS, ranging in age from 0.9 months to 20.9 years (median 9.4 years), had been enrolled on the RMS4.99 protocol. Histology was reviewed centrally by the STSC pathology panel. The extent of the primary tumour was assessed according to the TNM pretreatment staging system, where T1 refers to tumours confined to the organ or tissue of origin, while T2 lesions invade contiguous structures; T1 and T2 tumours are further classified as A or B according to their diameter being $\leqslant$ or > 5 cm, respectively; N0 and N1 mean without or with regional lymph node involvement.

The treatment plan is shown in Fig. 1. After the usual diagnostic work-up (including MRI, CT scan and ultrasound, bone scintigraphy, bone marrow aspiration and biopsy), a 9-week induction phase was administered according to the CEVAIE regimen, i.e. CEV (carboplatin 500 mg/m^2, epirubicin 150 mg/m^2, vincristine 1.5 mg/m^2); IVA (ifosfamide 9 g/m^2, vincristine 1.5 mg/m^2, actinomycin D 1.5 mg/m^2); IVE (ifosfamide 9 g/m^2, vincristine 1.5 mg/m^2, etoposide 600 mg/m^2).[5,7] After Induction, the tumour response was evaluated. Patients with stable or progressive disease abandoned the study, as did patients with persistent major bone marrow infiltration. Those with minimal infiltration received one more chemotherapy cycle and underwent bone marrow reassessment before proceeding to the sequential high-dose (SHD) phase. Cyclophosphamide 2 g/m^2 on days 1 and 2, and etoposide 200 mg/m^2 on days 1, 2 and 3, were administered to obtain a minimum of 8×10^6/kg CD34 peripheral blood stem cells (PBSC). At least 2×10^6/kg CD34 PBSC had to be used for each infusion. This was followed by three consecutive high-dose combinations, with G-CSF support and PBSC rescue. The drugs administered included: thiotepa (150 mg/m$^2 \times 2$ on day 1) and melphalan (60 mg/m^2 on day 2) in the 1st cycle; cyclophosphamide (2 g/m^2 on days 1 and 2) and thiotepa (150 mg/m$^2 \times 2$ on day 3) in the 2nd cycle; and melphalan (80 mg/m^2 on day 1) in the 3rd cycle. During the SHD phase, the planned interval between cycles was 3 weeks and chemotherapy cycles were not to begin unless all the following conditions were met: 0.5×10^9/l neutrophils + 50×10^9/l platelets + absence of any major organ dysfunction. After delaying for 1 week, however, a lower, but stable neutrophil and/or platelet count was considered sufficient for the following cycle to start, providing the patient was in good condition.

Surgery was planned, if feasible, after the SHD phase. This was followed by radiotherapy, including the primary and metastatic sites, wherever feasible. Irradiation of parameningeal tumours was recommended earlier, after the induction phase. Young children (<3 years) with a completely-resected embryonal RMS avoided irradiation. A hyperfractionated accelerated radiotherapy strategy was used, with two daily

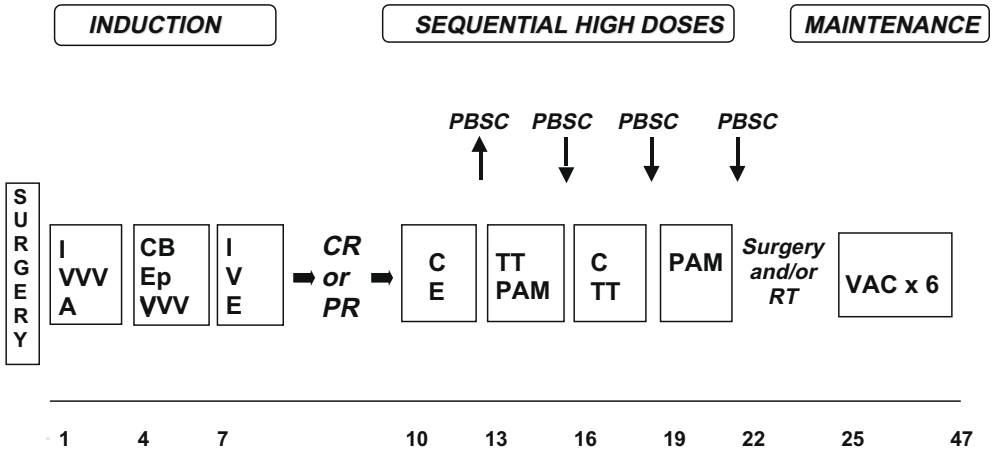

Fig. 1 – Treatment schema. Abbreviations: PBSC = peripheral blood stem cells; I = ifosfamide, V = vincristine, A= actinomycin D, CB = carboplatin, Ep = epirubicin, C = cyclophosphamide, E = etoposide, TT = thiotepa, PAM = melphalan, CR = complete remission, PR = partial remission, RT = radiotherapy.

fractions of 1.6 Gy, reaching a total dose of 44.8 Gy. Any macroscopically evident residual disease was 'boosted' up to a total dose of 54.4 Gy. Pulmonary irradiation with 12 Gy was recommended in cases with lung metastases.

Finally, a 'maintenance' chemotherapy was planned, involving six courses of VAC (vincristine 1.5 mg/m^2, actinomycin 1.5 mg/m^2, cyclophosphamide 1 g/m^2; all given on day 1). Treatment had to start 4–6 weeks after the last high-dose cycle, with at least 0.75 × 10^9/l neutrophils and 50 × 10^9/l platelets.

In June 2002, the protocol was modified and the IVADo regimen replaced the CEVAIE combination in the induction phase. The IVADo included ifosfamide 6 g/m^2, vincristine 1.5 mg/m^2, actinomycin D 1.5 mg/m^2 and doxorubicin 60 mg/m^2. Details of this pilot study have already been published.[8]

2.1. *Definition of response and statistics*

A formal assessment of the primary tumour and all metastatic sites had to be done after the induction (week 9) and SHD phases, and at the end of the whole treatment. Standard response criteria were used: complete response (CR) = no remaining evidence of disease; partial response (PR) = a reduction in tumour size of more than 50% of the sum of the products of the two maximum perpendicular diameters of each measurable lesion; heterogeneous response (HR) = a PR at one or more, but not all sites, with no progressive disease; objective response (OR) = a reduction of less than 50%, but more than 25%, in the sum of the products of the two maximum perpendicular diameters of each measurable lesion. Stable disease or a less than 25% reduction in the size of lesions was recorded as no response (NR). An increase in tumour size or the detection of new lesions was defined as progressive disease (PD). Responses had to persist for at least 4 weeks after their assessment.

The assessment of tumour response underwent no systematic central review, but for difficult cases the centres participating in the study could send radiological documentation to the coordinating centre in Padova.

Toxicity was graded according to the Common Toxicity Criteria, v.2.0. Survival curves were calculated using the Kaplan–Meier method, considering: overall survival (OS), from diagnosis to latest follow-up or death from any cause, progression-free survival (PFS), from diagnosis to first progression, relapse, death from any cause or latest contact for children who never experienced an event. The log-rank test was used to compare survival rates between different subgroups of patients in univariate analysis, considering patients' characteristics (age < 10 versus ⩾ 10 years and gender) and tumour features (histological subtype, site, size, invasiveness, lymph node involvement, type and number of metastases). A p-value of less than 0.05 was considered statistically significant. A multivariate analysis was conducted using Cox's proportional hazards regression method to determine the independent prognostic influence of pretreatment factors on survival, using the variables correlated with OS and PFS at univariate analysis. The study was approved by the Ethics Committees of all centres taking part and informed consent was obtained for all patients enrolled on the protocol.

Table 1 – Clinical characteristics of the patient population.

Total no. of patients	70
Sex	
Male/female	33/37
Age	
< 1 year	1
< 10 years	38
⩾10 years	32
Histology	
RMS embryonal	25
RMS alveolar	44
RMS n.o.s.	1
Primary tumour site	
Orbit	1
Head and neck PM	12
Head and neck not PM	2
GU bladder prostate	5
GU not bladder prostate	7
Limbs	18
Abdomen/pelvis	16
Other Sites	8
Unknown	1
Invasiveness	
T1	21
T2	48
Not known	1
Primary tumour size	
⩽5 cm	10
>5 cm	57
Not known	3
Regional nodal involvement	
Yes	35
No	34
Not known	1
Metastatic sites	
Lungs	32
Bone marrow	22
Bone	27
Distant lymph nodes	18
Pleural/peritoneal nodules	8/4
Subcutaneous	8
Liver	5
Other sites	9
No. of organs with metastases	
1	38
2	14
>2	18

Abbreviations: RMS: rhabdomyosarcoma, n.o.s.: not otherwise specified,PM: parameningeal, GU: genito-urinary.

3. Results

The clinical characteristics of the study population are given in Table 1. As expected, alveolar RMS was more common, most tumours being large (85% > 5 cm) and invasive (69% T2). The primary tumour was most often located in the extremities (26%), and abdomen/pelvis (22%), both generally considered unfavourable sites.

The distribution of metastases was as usual, the lung (45% of patients), bone (38%) and bone marrow (31%) being the most frequently involved organs, and were the only metastatic sites in 25%, 8% and 7% of cases, respectively. Metastases had spread to more than one organ in

47% of patients. Distant nodes were infiltrated in 18 patients.

3.1. Treatment

Initial chemotherapy consisted of the CEVAIE regimen in 30 patients and the IVADo in 40. Tumour response was evaluable at 9 weeks in 68 patients, and 14 CR were documented, while 40 patients had a PR, one an OR, and four had a HR. The response rate (CR+PR) was 79%. No differences were noted on comparing the rate of response to CEVAIE (80%) versus IVADO (75%).

The SHD chemotherapy was administered to 62 patients, but was interrupted in five children due to toxicity (3) or evidence of tumour progression (2). The SHD phase was not implemented in eight patients due to PD during the initial chemotherapy (4), or due to very poor general conditions (3) or, in one case, due to the persistence of bone marrow disease despite additional chemotherapy cycles. The planned interval from the mobilising cycles to the administration of the third HD cycle was 63 days, but the actual median interval was 84 days (range 50–182) for the patients completing the SHD phase. Tumour evaluation after the SHD phase in the 62 patients treated revealed an increase in the number of CR (to 26), but tumour progression or recurrence was evident in 12 cases. The primary tumour was resected after SHD in 13 patients, but surgery was considered complete in only seven cases. Radiotherapy was administered to 45 patients (64%). Most patients received 44.8 Gy, but nine children received a boost up to 50–57 Gy. No radiotherapy was given to 25 patients for various reasons, i.e. an event occurred before the scheduled irradiation (15 patients), young children with complete tumour remission (8), or at the centre's discretion (2). Overall, 41 patients received the maintenance treatment after the SHD phase.

3.2. Toxicity

Three patients died of treatment-related complications: two were in poor general condition at diagnosis and presented a septic shock early in the treatment, while one developed an intractable capillary leak syndrome after abdominal radiotherapy. Overall, more patients experienced grade IV toxicity while on the IVADo regimen (Table 2). More severe infections were reported during the SHD phase, however, with two children developing fungal infections and one with interstitial pneumonia; the SHD phase had to be stopped in two of these three cases. Grade IV myelotoxicity was common throughout the treatment but three children had a prolonged myelodepression that made it impossible to complete the high-dose cycles (one patient) or maintenance chemotherapy (two patients). Finally, VAC chemotherapy was well tolerated but one child had an episode of interstitial pneumonia after the first cycle: she recovered fully and completed the treatment.

3.3. Outcome

With a median follow-up of 5 years (2.5–9.6), 19 patients are currently alive in first CR and two in second CR (21 and 49 months after relapsing). Three more patients are reportedly alive with disease. One other child is being treated for a rhabdoid tumour that developed 6 years after the diagnosis of RMS and one died while in CR after developing meningitis 9 months after completing the treatment. The most frequent reason for treatment failure was local recurrence (with/without metastases), which occurred in 18 patients, followed by PD and metastases (with/without local failure) in 15 and 14 cases, respectively.

The 3-year OS and PFS for the 70 patients were 42.3% and 35.3%, respectively (Fig. 2). On univariate analysis, children < 10 years old had a better PFS than older patients (47.4% versus 21.1%; p=0.008). Nodal involvement negatively influenced PFS, which was 32.4% for N1 patients as opposed to 48.3% for N0 cases (p=0.02). PFS correlated significantly with the number of metastatic sites. For patients with one to two metastatic sites at diagnosis the PFS was 39.7%, whereas it was 22.2% for patients with three or more ($p < 0.04$). A significant better OS was evident in younger children (54.3%), N0 cases (63.7%), and those with up to two metastatic sites (47.2%).

Table 2 – Chemotherapy phase and number of patients with grade 3/4 non-haematologic toxicity.

	CEVAIE regimen	IVADo regimen	SHD chemotherapy
No. of evaluable patients	29	33	55
No. of cycles analysed	102[a]	110	180
Type of toxicity#			
- Infection	2/-	1/1	4/3
- Gastro-intestinal	3/1	3/3	4/1
- Hepatic	-/-	-/1	-/-
- Pulmonary	-/-	-/1	-/-
- Neurologic (central)	1	2	0
- Neurologic (peripheral)	0	1	0
- Renal	-/-	1/-	-/-
- Skin	1/-	-/-	2/-
- Electrolytes	-/-	-/1	-/-

Abbreviations: CEVAIE = carboplatin, epirubicin, vincristine, actinomycin-D, ifosfamide, etoposide; IVADo = ifosfamide, vincristine, actinomycin-D, doxorubicin; SHD = sequential high dose.

[a] Some patients received more than three CEVAIE cycles for different reasons.

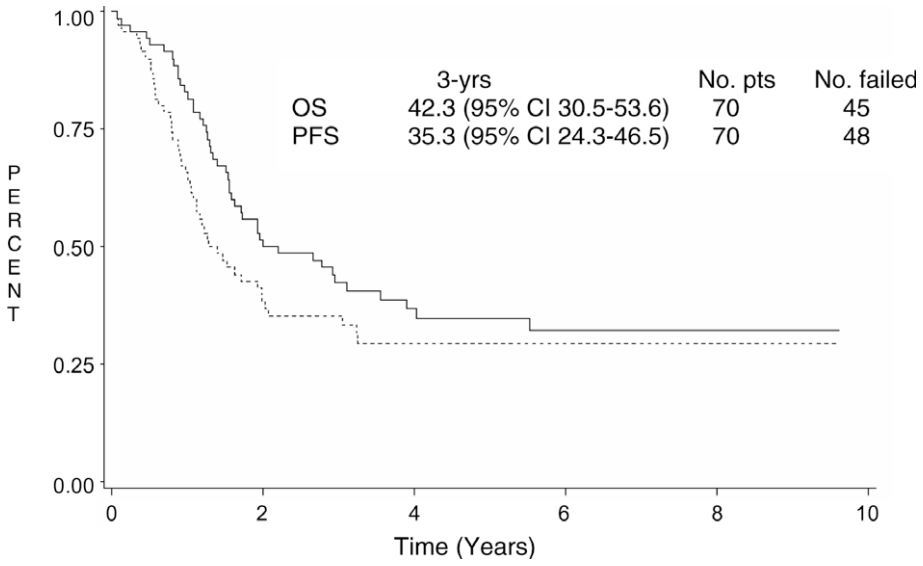

Fig. 2 – Overall and progression free survival of the whole population enrolled in the RMS4.99 study.

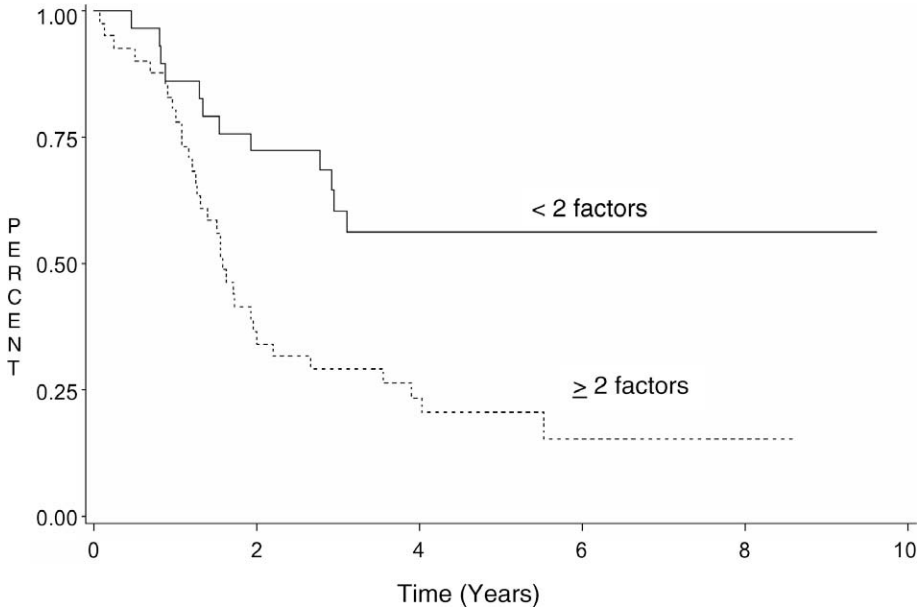

Fig. 3 – Survival of patients according to risk score (negative prognostic factors are age >10 years, unfavourable site of the primary tumour, bone or bone marrow involvement, number of metastatic sites >2).

Multivariate analysis only confirmed the role of age as a prognostic factor for survival, with a relative risk of 2.59 (1.3–5.1) for children over 10 years of age.

We analysed the outcome according to the prognostic scoring system proposed by Oberlin et al.[9] which identified four negative prognostic factors (age, site of the primary tumour, bone or bone marrow involvement, and more than two metastatic sites). The OS and PFS were 60.5% and 54%, respectively, for the 29 children with less than two negative prognostic factors, in comparison to 29.3% and 22% in the other cases (p=0.001) (Fig. 3).

4. Discussion

The prognosis for patients with metastatic RMS has improved very little over the years, despite investigators' attempts to use different therapeutic approaches. Strategies to improve the outcome for these patients have included adding active agents, such as anthracyclines, platinum derivatives and etoposide,[7,10] to standard chemotherapy, but to no apparent benefit.

The search for new drugs or more effective multidrug combinations has been conducted systematically by the

Intergroup Rhabdomyosarcoma Study Group including high-risk metastatic patients in a series of window studies based mainly on the use of alkylating agents (ifosfamide-doxorubicin, ifosfamide-etoposide, vincristine-melphalan) or topoisomerase I poisons (topotecan, topotecan-cyclophosphamide, irinotecan). Despite satisfactory response rates, ranging from 41% to 55%, the inclusion of these combinations in the standard treatment was unable to improve the failure-free survival rate (25% at 4 years).[11] It is worth noting that children with favourable characteristics, i.e. embryonal histology and age under 10 years at diagnosis, were not included in these studies.

A different approach was used by other cooperative groups and institutions which tested dose intensification strategies in an attempt to overcome drug resistance. In general, high-dose chemotherapy followed by hematopoietic stem cell rescue was used as consolidation therapy in children achieving a CR with standard chemotherapy. In the initial studies, the use of different high-dose regimens, such as combinations of melphalan, etoposide and carboplatin, or thiotepa, cyclophosphamide and carboplatin, or melphalan and etoposide, produced 3- or 2-year EFS rates ranging from 19% to 44%.[12–15]

The MMT4 study represents the largest study to date to have compared megatherapy with standard intensive chemotherapy for metastatic RMS. Four identical cycles of CEVAIE were initially used in this European protocol, but after 2 years the fourth CEVAIE cycle was replaced with high-dose melphalan in patients achieving a CR. There was no difference in 3-year EFS when these latter patients were compared with the earlier cases (29.7% versus 19.2%).[5] The early onset of drug resistance and/or the ineffectiveness of a single, high dose of chemotherapy in eradicating any residual disease have been suggested as possible explanations for the unsatisfactory results.

The MMT4 protocol provided the foundations for the RMS4.99 study. We originally chose to adopt the CEVAIE regimen for the initial chemotherapy because of the high response rate previously demonstrated.[7] Initial chemotherapy was also needed to 'clear' the bone marrow of tumour cells before harvesting PBSC. We then decided to begin dose intensification earlier in the treatment and to assess the potential value of sequential high-dose chemotherapy. In addition to melphalan, we used etoposide and thiotepa, as they are well-known agents that have already been tested in high-dose regimens against STS.[15–17] Doses were kept lower than the maximum tolerated to allow for the administration of multiple cycles without excessively long intervals between them, and to avoid having to postpone local treatment measures for too long. The feasibility of this approach was tested in a pilot study.[18] The acute toxicity of the SHD phase seems acceptable and the number of patients in CR increased from 20% after initial chemotherapy to 43%. A considerable number of patients developed tumour progression during or after the SHD phase, however, which showed that this strategy was unable to prevent drug resistance. Implementing local control measures late in the treatment (after the SHD phase) may have contributed to this increase in PD. The survival rate achieved in this study was only marginally better than in the European MMT-4 study[1] or in series treated with more standard approaches.[2,10,11]

Most of the prognostic factors identified in previous studies were confirmed in our analysis, the patient's age proving the strongest outcome predictor. Recent cooperative analyses[1,9] have identified other variables correlating with a worse outcome, including: unfavourable tumour site, bone or bone marrow involvement, age (< 1 year or > 10 years), three or more metastatic sites. Patients with none or only one of these factors have a significant chance of cure with a 3-year EFS of 44%.[9] In our study, patients with these characteristics had a 54% 3-year PFS, but the limited number of patients prevents us from concluding that they may have gained from our strategy.

However, when patients had more than one risk factor, the survival rate remained low. There are several potential reasons for these unsatisfactory results. Metastatic RMS is an aggressive disease that rapidly becomes resistant to chemotherapy, and this was not prevented by anticipating the administration of high-dose chemotherapy. The SHD phase may have interfered with the optimal administration of the most active drugs (anthracyclines or ifosfamide), leading to a reduction of their dose intensity, although the IVADo regimen (in which anthracyclines were used intensively) did not improve the results.

The role of high-dose chemotherapy in metastatic RMS should also be analysed in the light of two recent experiences. The SIOP Group recently reported the preliminary results of a multicentre study on 70 patients with high-risk RMS (i.e. with bone/bone marrow metastases or alveolar histology). At each centre's discretion, standard CEVAIE treatment was administered to 28 patients, while 46 received sequential high-dose monotherapy with cyclophosphamide, etoposide and carboplatin, early in the treatment. The EFS was much lower among patients given high-dose monotherapy (12% versus 42% for those given standard chemotherapy).[19] The German Cooperative Group recently identified a survival advantage for metastatic patients when low-dose 'maintenance' oral chemotherapy (four cycles of trofosfamide + etoposide alternated with four cycles trofosfamide + idarubicin) was administered instead of two courses of high-dose chemotherapy (thiotepa + cyclophosphamide and melphalan + etoposide). The results were very promising in 62 patients, with a 5-year OS above 50% for patients taking oral treatment, as opposed to 27% after high-dose chemotherapy.[20]

Both studies seem to indicate a negative role of high-dose chemotherapy but since the comparisons were not randomised these results need to be confirmed.

In conclusion, the role of high-dose chemotherapy has been explored in several studies using different strategies. Previously published trials were unable to find any significant benefit. Our experience shows that patients with favourable characteristics had a better survival but the use of SHD chemotherapy did not produce convincingly better results when compared with other experiences.[9–21]

Unfortunately, no randomised trials have been performed so far, and the relative rarity of metastatic patients makes it very difficult to attempt such a trial, even at the international level. This becomes even more difficult because the unsatisfactory results obtained to date may induce clinicians to give priority to other, possibly more promising approaches, such as low-dose chemotherapy or experimental drugs with a novel antineoplastic action, such as antiangiogenic agents or drugs active against specific molecular targets.

Conflict of interest statement

None declared.

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