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Outcomes in paediatric metastatic rhabdomyosarcoma: Results of The International Society of Paediatric Oncology (SIOP) study MMT-98 ☆

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ABSTRACT

Purpose: Results are presented of the SIOP study MMT-98 for paediatric metastatic rhabdomyosarcoma (RMS), which evaluated intensive chemotherapy followed by low intensity 'maintenance' chemotherapy in standard risk patients (SRG). For poor risk patients (PRG), the value of a therapeutic window study, sequential high dose monotherapy to achieve a complete response (CR) followed by low dose maintenance chemotherapy was examined.
Patients and methods: From November 1998 to 2005, 146 patients aged 6 months to 18 years with metastatic RMS were entered. Forty-five were SRG, i.e. age < 10 years and no bone marrow or bone involvement. Treatment was a 6-drug regimen with local therapy of surgery and/or radiotherapy followed by maintenance of 9 courses of vincristine, actinomycin D and cyclophosphamide (VAC). One hundred and one patients were PRG, i.e. >10 years, or with bone marrow or bone metastases. An upfront window study, high dose monotherapy, local treatment and then VAC maintenance therapy were given.
Results: With a median follow-up of 1.52 years, the 3-year event-free survival (EFS) and overall survival (OS) for SRG were 54.92% and 62.14%, respectively, whilst for the PRG 16.17% and 23.17%. The corresponding adverse hazard ratio (HR) for the PRG was HR = 2.65 (95% CI 1.63–4.31, p-value < 0.001) for EFS and HR = 2.51 (CI 1.53–4.11, p-value < 0.001) for OS.
Conclusion: SRG patients' EFS and OS were comparable to those of previous studies. For PRG patients there was no improvement in survival.

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1. Introduction

Metastatic rhabdomyosarcoma (RMS) remains a major challenge in paediatric oncology with little improvement in overall survival (OS) and event-free survival (EFS) in the last two decades. At best, estimated 3-year OS is 39%[1] contrasting with localised disease of 86%.[2] Specific prognostic factors at diagnosis predict a more favourable outcome including embryonal histology, less than two metastatic sites, 1 and genito-urinary non-bladder prostate primary sites.[3] For those categorised as having a very poor outlook,[3] experimental therapy as an 'upfront window study'[4] could be justified, with the addition of high dose chemotherapy. The International Society of Paediatric Oncology (SIOP) Malignant Mesenchymal Tissue (MMT) Working Group opened study MMT-98 to explore the incorporation of an upfront window study followed by high dose monotherapy and then by low intensity chemotherapy as maintenance treatment for poor risk patients to evaluate the CR, EFS and OS. Sequential high dose monotherapy without awaiting count recovery had been explored in a UKCCSG pilot study and found feasible. The hypothesis was that prolonged persistent high dose cytotoxic agent exposure feasible using one agent at a time would increase tumour cell death and hopefully OS.

2. Patients and methods

2.1. Patient population

Eligible patients were >6 months and <18-years-old with RMS. The patients were stratified into two risk groups, standard risk (SRG); <10 years and no bone or bone marrow involvement and poor risk (PRG); $\geqslant$10 years or with bone or bone marrow involvement. Institutional review boards of participating centres approved the study, and the patients or guardians gave written informed consent.

2.2. Treatment

For SRG patients induction treatment was a 6-drug regimen of ifosfamide, vincristine, actinomycin D, carboplatin etoposide and epirubicin, IVA/CbEV, over 26 weeks, followed by local therapy (surgery+/– radiotherapy) and then maintenance therapy of nine courses of VAC (Fig. 1a).

PRG patients entered into a single agent induction window study, dependent on which national group patients were registered under, of either doxorubicin 30 mg/m^2 days 1 and 2 and repeated 3 weeks later, or carboplatin AUC10 day 1 and repeated 3 weeks later. Sequential high dose therapy followed given at 14 day intervals irrespective of blood count, consisting of cyclophosphamide 2 g/m^2/d for 3 d, etoposide 800 mg/m^2/d continual 24 h infusion for 3 d, cyclophosphamide 2 g/m^2/d for 3 d and carboplatin AUC20 fractionated over 5 d (Fig. 1b). Centres unable to give either window or high dose therapy treated as for the SRG (SRG981, Fig. 1a). Another group of centres could not participate in the window study, but gave high dose therapy. These patients initially received one course of the 6-drug regimen, followed by high dose monotherapy (Fig. 1b). On completion of the doxorubicin window study, this was replaced with two courses of IVADo, ifosfamide 3 g/m^2/d for 2 d, vincristine 1.5 mg/m^2/d for 1 d and doxorubicin 30 mg/m^2/d for 2 d. Patients aged 6 months to 1 year or weight <10 kg received SRG treatment with dosage at 66% m^2 dose. Excluding the high dose monotherapy phase, count recovery to neutrophils 0.75×10^9/l and platelets $> 50 \times 10^9$/l was required before proceeding with the next course of chemotherapy.

2.3. Peripheral stem cell collection

Peripheral stem cell harvesting was undertaken when marrow was disease free. Harvesting was planned following the first course of cyclophosphamide or second if marrow remission had not been obtained. A target of at least 4×10^6/kg CD34 cells was obtained for infusion after carboplatin. The patients went off the protocol if they failed to clear the marrow. Re-infusion of stem cells was 72 h post completion of high dose carboplatin and at 5 d granulocyte colony-stimulating factor (G-CSF) 150 μg/m^2/d was commenced until neutrophils were $>0.75 \times 10^9$/l for 2 consecutive days.

2.4. Local treatment

Local treatment, either radiotherapy and/or surgery, was carried out at week 16 in the PRG intending to achieve CR prior to commencing VAC. For the SRG, para-meningeal primary sites were irradiated at week 9 while other sites at week 18, and surgery if needed prior to any irradiation. The aim was to give radiotherapy to the primary site unless a surgical CR was obtained after chemotherapy. However, all alveolar tumours were to receive radiotherapy at both primary and metastatic sites irrespective of whether CR had been obtained. The volume irradiated was the initial tumour volume with a margin of at least 2 cm, with the same approach applied to metastatic sites. Where feasible, all metastatic sites were irradiated, but this was left to the treating clinician's judgement.

2.5. Response definitions

Response was assessed at week 5 by physical examination, bone marrow examination and diagnostic imaging. Tumours were measured in two dimensions on cross-sectional imaging (Computed Tomography or Magnetic Resonance Imaging) with the product of these two measurements used to calculate a 2-dimensional surface area. Complete response (CR) was defined as disappearance of all tumour; partial response (PR) >50% decrease in surface area of all measurable lesions, mixed response (MR) a partial response at one site but no response at others; objective response (OR) >25% but <50% decrease in tumour area, without appearance of new disease; stable disease (SD) <25% increase or decrease of measurable disease; progressive disease (PD) >25% increase in size of measurable disease at any site, or the appearance of new lesions. Bone scan response was defined as CR if all sites of disease had resolved, PR as either complete response in some sites but others still present, or a general improvement at all sites, stable disease as no change in any sites and progres-

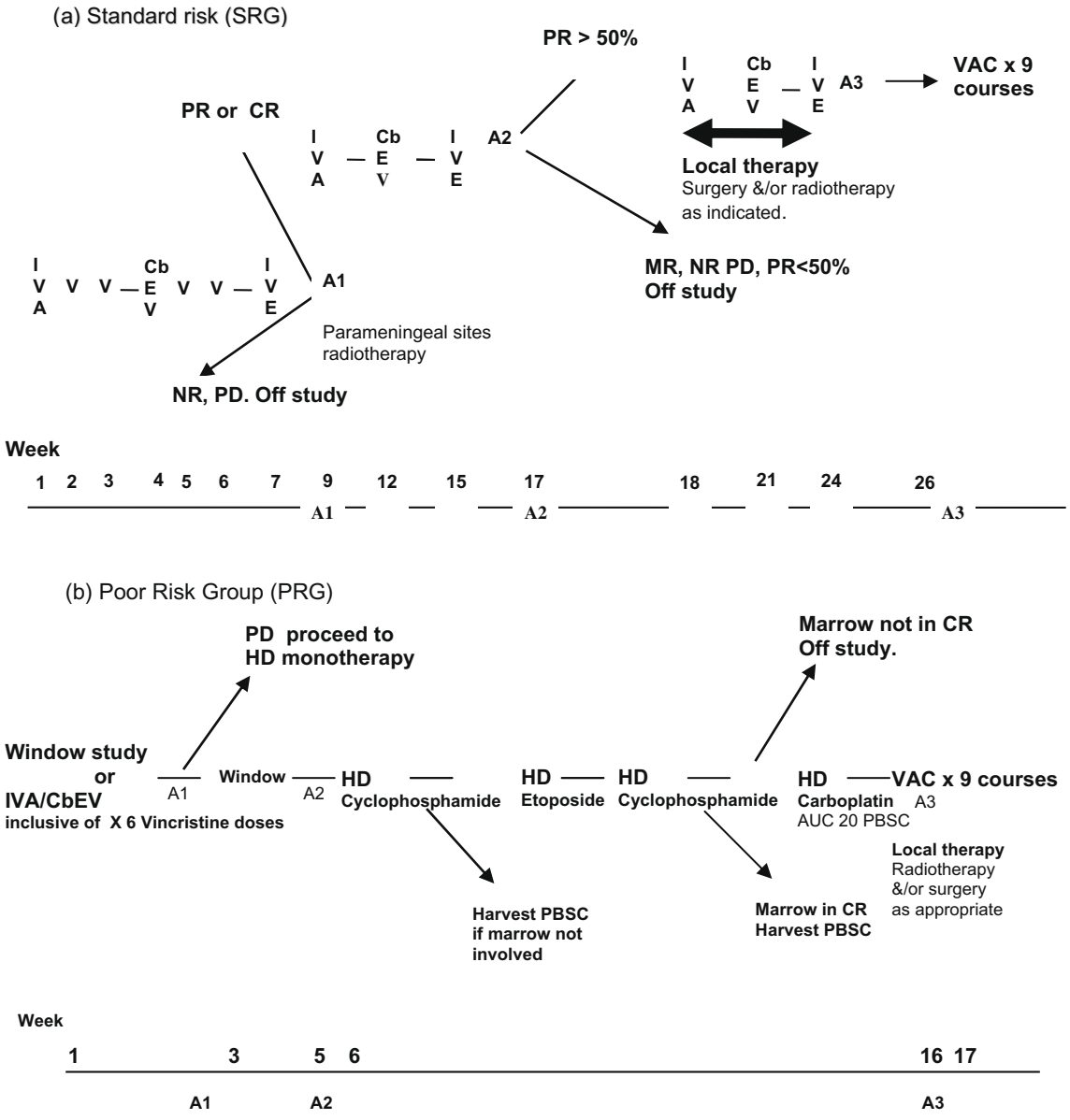

Fig. 1 – Trial design. IVA: I (ifosfamide) 3.0 g/m^2/d for 3 d, V (vincristine) 1.5 mg/m^2/d day 1 A (actinomycin) 1.5 mg/m^2/d day 1. CbEV: Cb (carboplatin) 500 mg/m^2 day 1, E (etoposide) 150 mg/m^2 day 1, V 1.5 mg/m^2 day 1. IVE: I 3.0 g/m^2/d for 3 d, V 1.5 mg/m^2 day 1, E 150 mg/m^2 day 1. VAC: V 1.5 mg/m^2 day 1, A 1.5 mg/m^2 day 1, C (cyclophosphamide) 1.0 g/m^2 day 1. HD – high dose: cyclophosphamide 2.0 g/m^2/d for 3 d, etoposide 800 mg/m^2/d for 3 d Carboplatin target dose AUC 20 over 5 d. CR: complete response, PR: partial response, MR: mixed response, NR: no response, PD: progressive disease. A: disease assessment. PBSC: peripheral blood stem cells.

sive disease if more sites were present or increase in volume and intensity of existing disease sites.

2.6. Toxicity

Toxicity data were collected and graded according to National Cancer Institute Common Toxicity Criteria (Version 2.0).[5]

2.7. Data monitoring committee

Regular reports on progress and safety issues were sent to an independent data monitoring committee.

2.8. Statistical methods

The study size was based on comparisons of 2-year OS with historical series of 70% and 20% for SRG and PRG, respectively (data not shown), and an anticipated recruitment period of 4–5 years with a minimum follow-up for survival of 2-years. Although no definitive target was set, the anticipated recruitment was 30 SRG and 75 PRG over this period, but with a recognition that recruitment rates within each subgroup might vary substantially. Where an improvement of 25% and 15% to be observed in 2-year OS, then the corresponding 95% confidence intervals (CI) would be approximately 77–98% and 25–46%, respectively.

Response rates (CR + PR) were calculated as a proportion of all patients recruited within the group concerned and the 95% CI calculated using the recommended procedure.[6] Overall survival (OS) was computed from the date of diagnosis to the date of death or the last date of contact if still alive. Similarly EFS was computed from the date of diagnosis but now to the date of the first event whether relapse, progression or death or the last date of contact for those who are still alive and believed to be free of disease. Progression through the window study was not considered an event. The Kaplan–Meier method was used to estimate the OS and EFS curves and the Cox model to estimate the relevant hazard ratios (HRs) and associated 95% CI.[7] The Cox model was also used to investigate the possible impact of known prognostic and other variables on outcome.

3. Results

3.1. Patient characteristics

From November 1998 to 2005, 168 patients, from 48 centres, with RMS were enrolled. The trial profile is summarised in Fig. 2 and 146/168 (86.9%) met the eligibility criteria, 3 were excluded by age: 2 >18, 1 <6 months; 1 was non-metastatic, while 18 (10.7%) received other protocols. Last data obtained were for June 2008 and the median follow-up for all patients is 1.52 years to a maximum of 8.78 years. The demographic and clinical characteristics of patients are shown in Table 1.

Registered RMS		168	
Ineligible Non-metastatic, Age< 6m, >18y Entered other protocols		1, 1, 2 18	
Risk Group		SRG 45	PRG 101
Surgery	At diagnosis Within 21 days	5 2	6 1
Initial Chemotherapy	As SRG IVA/CbEV	45	9 39
Window Chemotherapy	Carboplatin Doxorubicin IVADO		16 31 6
High Dose Therapy			79
Surgery		13	26
Primary RTX	Parameningeal Metastases Non-CR Other	9 6 6 1	10 21 11 8
Maintenance VAC cycles	1 — 3 4 — 6 7 — 9	3 2 26	6 14 49
Recurrence		16	64
RTX for Relapse		1	6
Alive		24	24

Fig. 2 – Patient flow through the study.

3.2. Treatment results

3.2.1. Chemotherapy – induction

Response rates are similar, approximately 40%, in those who receive the SR981 protocol irrespective of whether they are of the SRG or PRG (Table 2). The highest response rates (56.4% and 51.3% at weeks 5 and 17) were achieved by the PRG patients receiving IVA/CbEV. If a response occurs they are higher and more immediate (week 5, 43.9%) in PRG patients receiving carboplatin than those on doxorubicin (week 17, 35.5%).[8,9] There is little evidence of activity in those receiving IVADO although the numbers are small.

3.2.2. Intensification

In the PRG, 79/101 (78.2%) received high dose monotherapy after which 53/79 (67.1%) achieved a CR/PR, with no major delays in delivery.

3.2.3. Local treatment

In the SRG 32/45 (71.1%) received local treatment, 16 received radiotherapy alone, 9 surgery alone and 7 both modalities. Of the 9 patients who relapsed at the primary site, 6 then went on to receive radiotherapy. Although parameningeal primary site tumours were to routinely receive radiation therapy to the primary site, even if CR had been obtained with chemotherapy, 2 of 10 did not; 1 died at 8 weeks, the second relapsed at 33 months and died 5 months later without receiving radiotherapy.

In the PRG 67/101 (66.3%) received local treatment, 37 radiotherapy alone, 10 surgery alone and 20 both modalities. Of the 29 patients who relapsed at the primary site, 16 then went on to receive radiotherapy.

3.2.4. VAC

Thirty-one SRG patients commenced VAC, 12 in CR and 13 in PR, with 26/31 (83.9%) completing 7 or more courses (Fig. 2). In the PRG, 69 started VAC, 17 in CR and 32 in PR, with 49/69 (71.0%) completing 7 or more courses. Amongst those not commencing VAC, 11 were PR.

3.2.5. Toxicity

Serious adverse events (SAEs) involved 4 SRG patients all of whom subsequently died. Two were early at 21 and 34 d following IVA and CbEV, respectively; 1 at 248 d from fungal infection and 1 at 223, following encephalopathy and respiratory failure. For the PRG 8 patients had a SAE, 7 received IVA/CbEV (2 remain alive) and 1 window study carboplatin reported at 151 d post diagnosis with death at 19 months. None were outside the toxicities known and related to the drugs patients had received. High dose monotherapy was well tolerated.

3.2.6. Event-free and overall survival

For the SRG EFS was 54.92% at 3 years and 51.00% at 5 years, with corresponding rates of 16.53% and 14.88% for PRG. The corresponding adverse hazard ratio (HR) for the PRG was

Table 1 – Patient characteristics by pathology and risk group.

n	SRG	PRG
	45	101
Gender		
Male	27 (60.0%)	57 (56.4%)
Age (year)		
Median	4.28	10.64
Range	0.52–9.93	1.74–17.49
> 10 years	–	53 (52.5%)
Bone		
Neither	45	14
Bone alone	–	16
Marrow alone	–	24
Both involved	–	43
Unknown	–	4
Histology		
Embryonal	26	22
Alveolar	15	65
Not specified	2	8
Unknown	2	6
Primary site		
Orbit	–	1
Non-parameningeal	3	3
Parameningeal	10	23
GU BP	3	6
GU NBP male	–	5
Limb	6	30
Thorax	3	5
Retroperitoneal	6	3
Pelvis	14	16
Perianal	–	1
None apparent	–	7
Unknown	–	1
Tumour type		
T0	–	5
T1	11	28
T2	33	63
TX	1	5
Maximum tumour length > 5 cm		
Yes	35	78
No	10	20
Unknown	–	3
Nodal involvement		
N0	27	38
N1	14	51
NX	4	12
Metastatic sites		
Bone	–	59
Bone marrow	–	67
Lung	32	31
Pleura	7	11
CNS	1	10
CSF	4	7
Liver	1	3
Peri-omen	6	7
Distant nodes	7	29
Other	5	15
Metastases in multiple sites		
1	31	24
2	10	36
3	4	19
4	–	10
5 or more	–	8
Unknown	–	4
FU (month)		
Median	30.16	16.56
Range	0.69–105.40	0.76–101.39

2.68 (95% CI 1.64–4.37, p-value < 0.001). The relative performance of those on the PRG window studies gave a 3-year EFS for IVA/CbEV of 24.18%, carboplatin 6.25%, doxorubicin 8.36% and IVADO 33.3% (Fig. 3). Compared to IVA/CbEV, those receiving carboplatin (HR = 2.52, CI 1.35–4.71, p-value = 0.004) and doxorubicin (HR = 1.87, CI 1.09–3.20, p-value = 0.023) appear to have a worse outcome. In the 6 patients receiving IVADO there was no statistically significant difference (HR = .70, CI 0.21–2.29, p-value = 0.55).

For OS, the 3-year rate for the SRG is 62.14% and the 5-year 47.68%, with corresponding rates of 23.70% and 17.93% for those of the PRG (HR = 2.46: CI 1.51–4.03, p-value < 0.001). The relative performance of those on the different PRG window studies gave a 3-year OS for IVA/CbEV of 34.57%, for carboplatin 6.25%, doxorubicin of 16.44% and IVADO 27.78% (Fig. 3). Compared to IVA/CbEV those receiving carboplatin appeared to have a worse outcome (HR = 2.37, CI 1.26–4.46, p-value = 0.007), while for doxorubicin (HR = 1. 59, CI 0.91–2.77, p-value = 0.10) there was no statistically significant difference.

Seventy-nine patients (Fig. 2) of the PRG received HDT following initial chemotherapy or after a window study while 22 did not. The HDT patients comprised 35 IVA/CEV, 13 Cb, 25 Dox and 6 IVADO of whom 75.9% (60/79) received all four drugs. With HDT the 3-year EFS was 18.0% (CI 10.3–27.5) and without was 6.9% (CI 0.5–26.5). The corresponding OS was 26.1% (CI 16.7–36.4) and 13.3% (CI 2.3–34.2), respectively.

4. Discussion

In previous studies metastatic patients have been assigned the same treatment with 39% achieving an estimated 3-year overall survival after intensive multimodal treatment.[1] However, not all metastatic patients by virtue of one metastatic site have such a poor outcome. In IRS I study[10] the site of primary disease and number of metastatic sites influenced outcome, and for those treated on IRS-I and IRS-II genitourinary sites and age <11 years had improved survival.[11] A slightly better survival was also shown for patients without bone/bone marrow metastases and those <11 years in the German CWS-86 study.[12] Carli and colleagues[3] using multivariate analysis identified from the European Intergroup Studies MMT4-89 and MMT4-91 that unfavourable site, bone or bone marrow involvement and unfavourable age, >10 years or <1 year were independent unfavourable factors. Patients with fewer than two unfavourable factors had a 5-year EFS and OS of 40% and 47%, respectively, while those with more than two had 5-year EFS and OS of 7.5% and 9%. This was confirmed by

Table 2 – Response rates achieved at re assessment points in the protocol as outlines in Fig. 1a and b.

Treatment	SRG						PRG					
	SR981			SR981		IVA/CbEV	Carboplatin			Doxorubicin		IVADO
Schedule (week)	8	26	8	17	5	17	5	17	5	17	5	17
CR	–	–	–	1	1	1	–	–	2	1	–	–
PR	21	17	4	3	21	19	7	5	–	10	1	–
CR + PR (%)	21/45 (46.7%)	17/45 (37.8%)	4/9 (44.4%)	4/9 (44.4%)	22/39 (56.4%)	20/39 (51.3%)	7/16 (43.9%)	5/16 (31.3%)	2/31 (6.5%)	11/31 (35.5%)	1/6 (16.7%)	0/6 (0.0%)
95% CI	32.9–60.9%	25.1–52.4%	18.9–73.4%	18.9–73.4%	41.0–70.7%	36.2–66.1%	23.1–66.8%	14.2–55.6%	1.8–20.7%	21.1–53.1%	3.0–56.4%	0.0–39.0%

a pooled analysis from the United States and European Cooperative groups, identifying patients who could be candidates for experimental approaches.[13] Utilising this evidence, patients entering into MMT-98 were stratified into two groups, those with no unfavourable characteristics (SRG) received established chemotherapy regimens, whilst PRG received an upfront window agent and high dose mono-therapy. Previously reported therapeutic strategies aimed at improving outcome for PRG patients have included escalating doses of chemotherapy,[14] autologous stem cell rescue following myeloablative regimens[15–17] and a series of upfront window studies.[18] The latter sought to identify new agents in untreated patients who are less likely to have drug resistance, but nevertheless fail conventional treatment. This philosophy was based on the finding that while melphalan had very little efficacy in heavily pretreated patients in a phase II study, it was active in newly diagnosed high risk RMS patients.[19] On this basis, two window study agents were investigated, carboplatin, which has been included in SIOP studies MMT-95, MMT4-89 and MMT4-91, but for which there were little data for efficacy alone, and doxorubicin, important in adult sarcomas. The carboplatin window study of 16 patients showed a response rate of 31%,[8] while for doxorubicin 65% from the first 20 evaluable patients.[9] The corresponding and updated 3-year EFS which include all eligible patients are 6.25% and 8.36%. The lower response rate with carboplatin was reflected in an updated 3-year OS of 6.25% lower than that with doxorubicin, 16.44% and both inferior to 34.57% obtained in PRG patients who received the standard 6 drug arm. These results suggest that initial rapid disease response influences outcome, thus patients who received the window agents were compromised received carboplatin.

Concerns have been raised particularly if they that deferring standard treatment in order to carry out such window studies may compromise the final outcome. Single agent usage has been thought to pose a greater risk than combinations, but pooled analysis of several phase II window studies did not support this.[18] However, RMS can have intrinsic global drug resistance, failing to respond to window agents and to VAC, the gold standard RMS therapy. This study appears to support this drug resistance hypothesis.

Various studies have evaluated the role of high dose chemotherapy in paediatric solid tumours. Combinations of chemotherapy with or without total body irradiation or single chemotherapeutic agents[20,21] have provided some evidence of efficacy. MMT-98 sought to evaluate a sequence of high dose single agents, including myeloablative dosing of carboplatin, for PRG patients, given early in treatment when tumours were hoped to be relatively chemo sensitive. The use of etoposide and carboplatin was based on the good responses obtained in MMT4-89 and MMT4-91, with substitution for ifosfamide by cyclophosphamide to avoid renal toxicity.[3] The goal was that by administering single agents at high doses, continuous tumour exposure to cytotoxic killing could be achieved. Overall this treatment was well tolerated.

SRG patients received neither window study nor high dose chemotherapy based on evidence that they were at lower risk of standard treatment failure. On commencing VAC after local treatment, the higher CR rate in SRG supports the use of con-

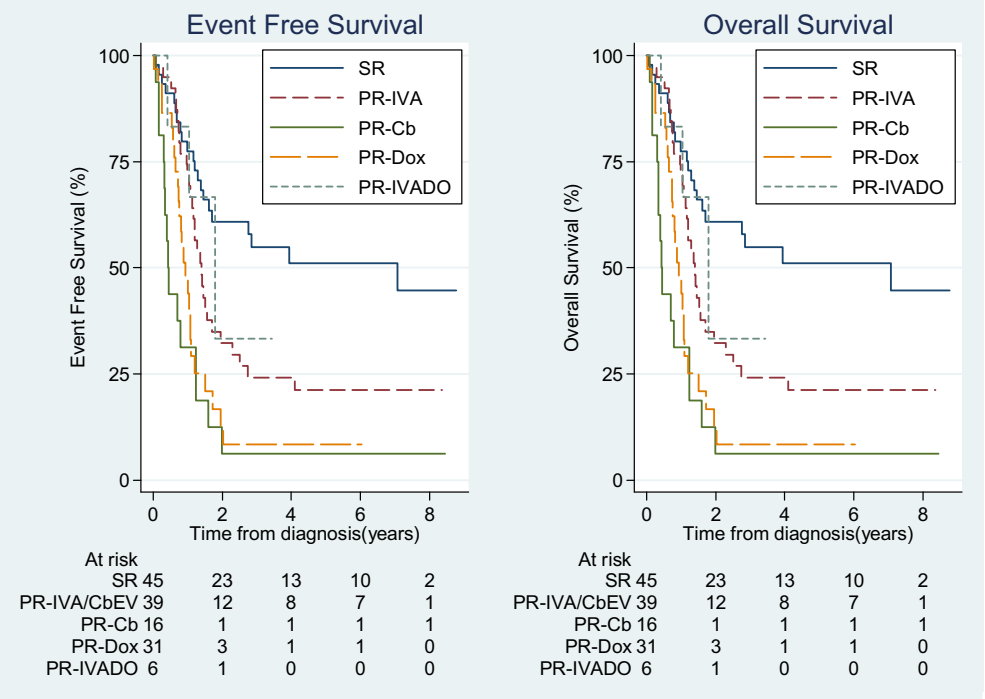

Fig. 3 – Event free and overall survival from diagnosis for SRG and each PRG receiving either IVA/CbEV, carboplatin (Cb), doxorubicin (Dox) or IVADO.

ventional treatment. Continuing VAC therapy sought to evaluate whether prolonging therapy would improve outcome. However, of the 96 patients commencing maintenance therapy, 5/31 SRG and 20/69 PRG received less than seven cycles: as progression and toxicity mainly haematological were common, limiting the feasibility of VAC as a maintenance therapy, following intensive therapy.

In this study two risk groups were identified and different treatment strategies applied: an intensive 6-drug multi-agent regimen for SRG,[3] with surgery and radiotherapy to improve local and metastatic control, and then prolongation of treatment with VAC. At the end of treatment 25 (55.6%) patients were free of disease translating into a 3-year EFS and OS of 54.92% and 62.14%, respectively. This is the first study to administer risk-adapted therapy according to defined adverse factors[1,3,22] and obtained a comparative outcome for SRG patients using conventional chemotherapy. Whilst 28 (28.3%) of PRG patients were free of disease at the end of treatment this translated into a 3-year EFS and OS of 16.17% and 23.17%: no improvement on previous studies.[1,3] Although obtaining an improved CR rate, this did not result in increased survival rates. This study also confirmed that myeloablative therapy does not confer a better outcome, as previously reported,[17] indeed oral maintenance therapy may be a more promising option.[23]

Phase II upfront window studies have demonstrated the predictive capacity of *in vivo* preclinical models[24] providing a rationale for including different agents into subsequent trials.[9,18] Whilst antitumour activity can give a clue to cross-resistance with VAC, response rate does not translate into long-term survival.[3,25] Phase II studies do however provide a safe platform for new agent evaluation.

New therapeutic approaches are required, based on better biological understanding of individual tumours. The PAX3-FKHR and PAX7-FKHR fusion proteins are useful in identifying unfavourable histology, but exploitation as a therapeutic strategy remains elusive.[26] Possible important pathogenic mechanisms have been identified including increased levels of PDGF receptors and insulin-like growth factor receptor (IGFR) associated with decreased survival,[27] drug resistance involving MDR1,[28] or receptor tyrosine kinases and ABCG2[29] Migratory and metastatic properties of RMS in respect to CXCR4 are also under review.[30]

Metastatic RMS patients with poor prognostic factors continue to do badly. New therapeutic agents are becoming available, but a deeper understanding of the pathogenic pathways is required for effective inclusion into treatment regimens. The future challenge will be to evaluate the best setting for these new agents to improve survival.

Conflict of interest statement

None declared.

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