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Efficacy of carboplatin given in a phase II window study to children and adolescents with newly diagnosed metastatic soft tissue sarcoma

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ABSTRACT

Aim: The activity of carboplatin was evaluated in a phase II window study in previously untreated children with metastatic soft tissue sarcoma.

Methods: Children with poor-risk metastatic disease (over 10 years and/or with bone/bone marrow involvement) treated in the SIOP MMT 98 study were scheduled to receive two courses of intravenous carboplatin (area under curve [AUC] of 10), 21 days apart.

Results: Sixteen eligible patients were entered into the rhabdomyosarcoma (RMS) group. Response (complete remission or partial remission) was seen in five children (31%, 95% confidence interval (CI) 14–56%). Ten eligible patients with other soft tissue sarcomas were recruited into the non-RMS group. Two responses (20%, 95% CI 6–51%) were seen. Toxicity in both groups was predictable nausea, vomiting and marrow suppression and there were no toxic deaths.

Conclusion: Single-agent carboplatin at AUC of 10 has an acceptable toxicity profile but only moderate efficacy in poor-risk metastatic soft tissue sarcoma.

1. Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma (STS) in children and adolescents, accounting for 5–8% of all childhood malignancies. The prognosis for non-metastatic RMS has improved considerably over the last 30–40 years using combination chemotherapy together with local therapy.[1–3] However, the outcome for patients with metastatic disease remains very poor, despite intensification of treatment with agents known to be active, and attempts at introducing novel therapies.[4–6]

The mainstay of chemotherapy for rhabdomyosarcoma continues to be vincristine and actinomycin D in combination with an alkylator (cyclophosphamide or ifosfamide). Other

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drugs such as doxorubicin, etoposide and cisplatin have been added to this combination in higher risk patients but to date there is no definitive evidence of improved outcome with the addition of these drugs, despite evidence of response in the relapse setting.[2,6]

Carboplatin has been used in the treatment of high-risk RMS despite a paucity of preclinical data on its efficacy in STS. In classical phase II studies in relapsed and refractory patients, a response rate to carboplatin of 12% (6/50) was noted in adults with recurrent STS.[7] The only previous single-agent data in children with relapsed STS gave a response of 6% (1/16).[8] By contrast, 61% of children with relapsed/refractory STS responded to the combination of carboplatin with etoposide.[9] A response rate of 53% was noted in previously untreated patients with metastatic RMS receiving carboplatin combined with etoposide and epirubicin.[10] Based on the latter finding, a 'six-drug' combination including the addition of carboplatin, etoposide and epirubicin to vincristine, actinomycin D and ifosfamide was utilised in Europe in the late 1980–1990's in high-risk RMS in studies conducted by the Malignant Mesenchymal Tumours Group of the International Society of Paediatric Oncology (SIOP MMT).[11,12] Carboplatin has also been used at myeloablative levels with stem cell support in RMS[5,9,13,14] and it remains the subject of clinical trials in RMS.[15] However, the precise contribution of carboplatin in the treatment of STS remains uncertain.

Phase II window studies have been undertaken in chemotherapy-naïve, newly diagnosed patients with high-risk RMS on the assumption that these give a more accurate model of drug activity than classical phase II studies. Single-agent melphalan[16] and ifosfamide[17] both showed good response in newly diagnosed patients with RMS. The Intergroup Rhabdomyosarcoma Study Group, now part of the Children's Oncology Group, subsequently undertook a series of window studies using single agents and combinations of drugs in children with metastatic RMS.[18–22] The combination of vincristine and irinotecan gave the best response rates in high-risk metastatic RMS (70%).[6,22]

SIOP MMT set out to investigate carboplatin and doxorubicin as single agents in two up-front phase II window studies in poor-risk patients with metastatic STS, as part of the main MMT 98 study. This paper reports on the efficacy and toxicity of carboplatin window therapy in children with RMS and other STS.

2. Patients and methods

2.1. Patients

The MMT 98 study included children aged 6 months to 18 years with metastatic STS who were previously untreated except for primary surgery performed within 8 weeks prior to registration. Patients with metastatic STS were classified as 'standard risk' if aged <10 years and without bone or bone marrow metastases. Patients were classified as 'poor risk' if they were aged 1 year and above, and/or had either bone or bone marrow metastases, whether or not they had involvement of other metastatic sites.[5] Only 'poor-risk' patients were eligible for the window study. MMT 98 centres were able to elect whether or not to participate in the window study, and so the window study was undertaken in a limited number of centres.

MMT 98 opened in May 1999 and following interim analysis of the window study in January 2002, only patients with RMS and peripheral primitive neuroectodermal tumour (pPNET) meeting the above criteria remained eligible for inclusion in the window study. Wherever possible the diagnosis was confirmed by central pathology review.

For all patients, the primary tumour site was imaged by Computed Tomograpy (CT) or Magnetic Resonance Imaging (MRI), the chest was imaged by CT, bone marrow was assessed by bilateral aspirates and trephine biopsies and distant bone metastases by bone scan at diagnosis with more detailed imaging (plain X-ray, CT or MRI) of involved bony sites. Other involved metastatic sites were assessed with CT or MRI as appropriate.

The multicentre, European, MMT 98 study, including the window study, was approved by the local or national research ethics committees of the centres concerned as appropriate. Patients from centres in Czech Republic, Denmark, Ireland, Norway, The Netherlands and the UK took part in the window study. Informed, written consent was obtained from the parent or legal guardian of the child before study entry, including specific consent for the window study.

2.2. Protocol treatment

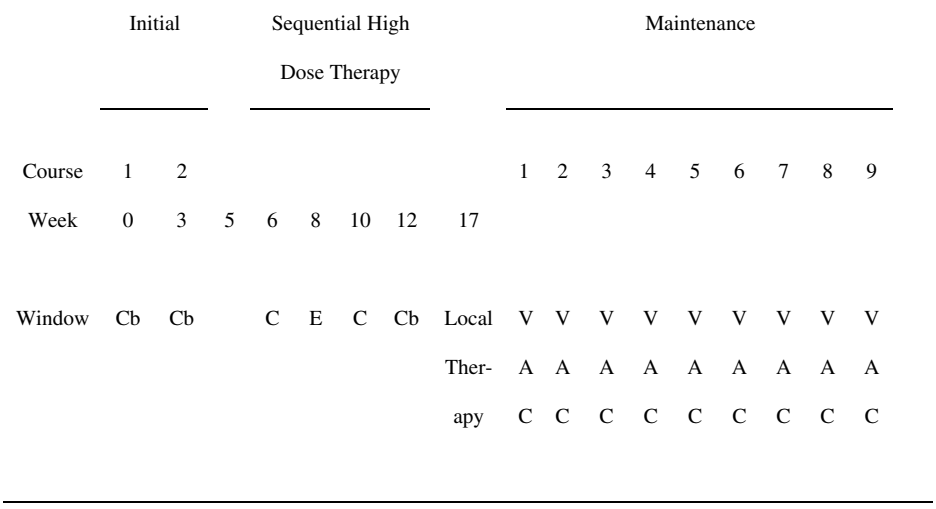
Newly diagnosed patients were scheduled to receive intravenous carboplatin (AUC of 10 based on the Glomerular Filtration Rate (GFR) estimated by chromium ethylenediamine tetraacetic acid (EDTA) clearance and calculated according to the following formula):

$$\text{Dose} \times (\text{mg}) = 10 \times (\text{uncorrected GFR mls/min} + [15 \times \text{surface area}])^{23}$$

The total dose was fractionated over 5 days (as a 1 h infusion daily), with two courses planned at 21-day intervals in the absence of progressive disease or excessive toxicity. Patients required an ANC $>1 \times 10^9$/l and platelets $>100 \times 10^9$/l to proceed with the second course. Granulocyte colony stimulating factor (GCSF) was not routinely used. Full response assessment of primary and metastatic sites was performed at week 5. Patients then proceeded on treatment schema MMT-982 with sequential high dose chemotherapy and autologous peripheral blood stem cell rescue (see Fig. 1). Patients who were eligible for the window study but did not receive window therapy were recommended to receive two cycles of standard chemotherapy (vincristine, actinomycin D, ifosfamide followed by vincristine, carboplatin, epirubicin) in place of window therapy and then to proceed to sequential high dose chemotherapy following the MMT-982 schema (Fig. 1).

2.3. Response definitions

Response was assessed at week 5 by physical examination, bone marrow examination and diagnostic imaging. Bone marrow and bone scan results were not included in the formal response assessment as they give measurable but not evaluable results, but negative results were required to substantiate



Key: A (Actinomycin); C (Cyclophosphamide); Cb (Carboplatin); E (Etoposide); V (Vincristine)

Fig. 1 – Carboplatin window for 'poor-risk' patients preceding protocol MMT 982.

complete response (CR) in patients with a previously positive test result. Central radiological review was performed wherever possible for RMS patients. Tumours were measured in two dimensions on cross-sectional imaging (CT or MRI) with the product of these two measurements used to calculate a surface area. Complete response (CR) was defined as the disappearance of all tumour. Partial response (PR) was defined as a decrease in surface area of all measurable lesions by 50% or more. Mixed response (MR) was a partial response of a measurable lesion at one site but no response at others. Objective response (OR) was defined as >25% but <50% decrease in measurable disease surface area, without the appearance of new disease. Stable disease (SD) was <25% increase or decrease of measurable lesions. Progressive disease (PD) was defined as >25% increase in surface area of measurable lesion at any site, or the appearance of new lesions.

2.4. *Toxicity*

Toxicity data were collected following each course of carboplatin. Toxicities were graded according to National Cancer Institute Common Toxicity Criteria (Version 2.0).

2.5. *Statistical methods*

Formal assessment of planned study size was not made as the whole MMT 98 study was monitored collectively and decisions concerning closure or otherwise were made at that level. Nevertheless it was anticipated that approximately 30 patients would be recruited to this window study during the anticipated 5-year lifetime of the larger study. There was no formal data monitoring committee; data were reviewed at national review meetings.

Response rates (CR + PR) were calculated as a proportion of all eligible patients recruited within the group concerned and 95% confidence intervals (CI) calculated using exact procedures.[24] 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 event-free survival (EFS) was computed from the date of diagnosis 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. The Kaplan–Meier method was used to estimate the OS and EFS curves.

3. Results

Sixteen of 48 MMT 98 centres entered patients into the window study and over the period from May 1999 to June 2004, 27 patients with metastatic STS were recruited. This included 17 patients reported to have RMS and 10 patients with non-RMS. One patient with metastatic RMS had no poor-risk features (i.e. he was aged less than 10 years without bone or bone marrow metastases) and so is excluded from the analysis. Patient flow through the study is shown in Fig. 2 and characteristics of the 26 eligible patients are shown in Table 1. Pathology review was available in 12 patients reported to have RMS and 9 patients reported to have other STS.

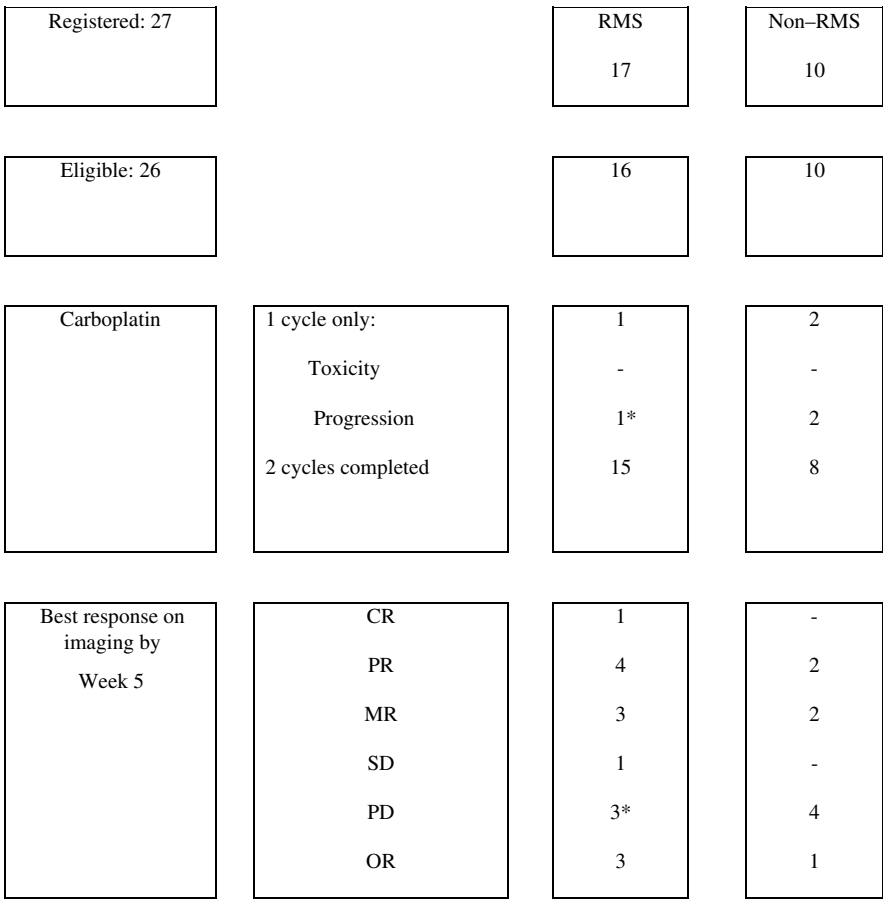
3.1. *RMS patients*

3.1.1. *Chemotherapy*

The median dose of carboplatin given in Cycle 1 in 16 patients with RMS was 1099 mg (range 460–1650); in Cycle 2 in 15, median 1087 mg (range 480–1650). The median total dose given over a maximum of two cycles was 2132 mg (range 940–3300). The median time between courses was 22 days (range 14–33).

3.1.2. *Toxicity*

Following the first cycle of carboplatin, 26 grades 3 and 4 toxicities were reported in 12/16 patients. After the second cycle, 34 grades 3 and 4 toxicities were reported in 11/15 patients. The commonest grades 3 and 4 toxicities reported were



*The RMS patient in whom there was no response evaluation was reported as clinical PD after 1 cycle.

Fig. 2 – Patient flow through the study.

nausea (6), vomiting (3), anaemia (9), neutropaenia (16), leukopaenia (5) and thrombocytopaenia (11). Grade 3 or 4 neutropaenia was slightly more common after the second course than after the first course of carboplatin (nine reported events compared to seven after first course) and a similar pattern was reported for thrombocytopenia (seven reported events compared to four after first course). Thrombocytopenia and neutropenia were prolonged ($\geqslant$7 days) in three and six episodes, respectively. No grade 3 or 4 infection or fever was reported and there were no unexpected serious adverse events. Other significant toxicities were uncommon but included mood changes (1, grade 3); diarrhoea (1, grade 3) and constipation (2, grade 3). Three patients had mild elevations of alanine transferase or alkaline phosphatase (1 grade 1 and 2 grade 2 on both occasions) after both cycles.

3.1.3. *Response*

One patient had no response evaluation. Central radiology review was available for 11, while in those for whom it proved difficult to access imaging for central review the local investigator assessment report was used (1 PR, 1 SD, 1 MR, 1 PD). At week 5 the response was 5/16 (1 CR and 4 PRs) or 31% (95% confidence interval (CI) 14–56%). Three patients showed documented PD and a further patient with no response evaluation was reported as clinical PD after 1 cycle.

3.2. *Non-RMS patients*

Details of the non-RMS patients are shown in Table 1. Among nine patients entered during the initial phase of the study, only two responses (PR), were reported, both in pPNET, and there were four reports of PD. From January 2002 recruitment was restricted to pPNET only for as long as the RMS component remained open, and one further patient with pPNET was entered. Imaging for the non-RMS patients has not been reviewed centrally. One patient had inadequate response evaluation.

3.3. *Chemotherapy*

The median dose of carboplatin given in Cycle 1 in 10 patients was 1253 mg (range 600–1750); in Cycle 2 in 8, median 1378 mg (range 600–1750). The median total dose given over a maximum of two cycles was 1843 mg (range 920–3500). The median time between courses was 26 days (range 17–29).

3.3.1. *Toxicity*

Following the first cycle of carboplatin, 19 grades 3 and 4 toxicities were reported in eight patients and after the second cycle, 6 grades 3 and 4 toxicities were reported in four of these. The commonest grades 3 and 4 toxicities reported were nau-

Table 1 – Patient characteristics of eligible patients

	RMS	Non-RMS
Gender		
Male	7	4
Female	9	6
Age (year)		
Median	12.1	14.3
Range	3.7 – 17.5	5.1 – 17.3
⩾10	12	9
Bone involvement		
Neither	3	2
Bone	1	2
Bone marrow	3	–
Both	9	6
RMS type		
Embryonal[a]	3	–
Alveolar	11	–
Not Otherwise Specified (NOS)	2	–
Non-RMS		
pPNET	–	5
DSRCT[b]	–	2
Rhabdoid	–	1
Spindle cell sarcoma	–	1
Clear cell sarcoma		1
Site		
PM	7	–
GU BP	1	–
GU NBP Female	–	1
GU NBP Male	–	1
Limb	4	2
Retroperitoneal	1	1
Perianal	1	–
Chest wall/thorax	–	1
Pelvis	1	2
None apparent	1	2
Tumour		
T0	1	1
T1	3	–
T2	12	8
TX	–	1
Nodal status		
N0	6	6
N1	7	3
NX	3	1
FU (months)		
Median	9.91	18.51
Range	0.95–82.27	0.72–69.62

PM, parameningeal; GU, genitourinary; GU NBP, genitourinary, non-bladder, non-prostate.
a Pathology review classified one case as undifferentiated.
b Desmoplastic small round cell tumour.

sea (2), vomiting (2), unspecified haematological (2), anaemia (4), neutropaenia (4), granulocytopaenia (3) and thrombocytopaenia (6). Only two patients had prolonged neutropaenia or granulocytopaenia (grade 3; 7 days); thrombocytopaenia was prolonged in one patient (grade 3). No grade 3 or 4 fevers was reported and there were no unexpected serious adverse events. Other significant toxicities were uncommon but included neurological (1, grade 3); central venous catheter infection (1, grade 4); elevated bilirubin (1, grade 4) and elevated aspartate transaminase (1, grade 3). The latter patient did not receive Cycle 2.

3.3.2. *Response*

At week 5, PR was documented in 2/10 or 20% (CI 6–51%) patients (both with pPNET) although a further patient with pPNET who had inadequate response evaluation showed some clinical response following two cycles of carboplatin. Response rate in pPNET was 2/5.

4. Survival

The estimated 2-year EFS was 25% for RMS and 20% for non-RMS patients with corresponding overall survival of 25% and 23% (Fig. 3).

5. Discussion

Previous standard phase II studies reported a response rate of 12% (6/50) in adults with recurrent STS[7] using carboplatin 400 mg/m^2, and 6% (1/16) in children with STS given carboplatin at 560 mg/m^2.[8] Limited available data on the efficacy of single-agent carboplatin in the Ewing's family of tumours (EFT) showed only one response (CR) in 15 evaluable patients (7%).[7] Despite this lack of data, carboplatin-containing regimens have found favour for high-risk RMS patients or patients with RMS or EFT in the relapse setting.

This phase II window study demonstrates that carboplatin does have some efficacy in RMS, with responses documented in about a third of the patients. The study in non-RMS patients was aborted early in view of poor response but there was the suggestion of activity in pPNET (2/5), a member of EFT, although the numbers are small.

In retrospect there are some limitations to the design of this trial. In particular a two-stage design, in which a minimum response rate to carboplatin is set before continuation to the second stage is implemented, would have been preferable. Further guidelines for early termination in the event of a high rate of progressive disease would have been useful as would the advice of an independent data monitoring committee.

Phase II studies have been useful tools in identifying agents to take forward into phase III trials. However, these studies are typically performed in patients who have already failed standard treatment approaches, where response rates may be complicated by acquired drug resistance. Such studies may not give a true estimation of the activity of the drug in the treatment-naïve setting. Phase II window studies allow the assessment of activity in the newly diagnosed patient and may accrue patients more quickly than classic phase II trials in the relapse setting. Window studies in children with RMS show superior results when compared with standard phase II response rates for single-agent ifosfamide (86% versus 18%)[17] topotecan (46% versus 0%)[19] and irinotecan (42% versus 11%).[22,25] However, there is no clear consensus of what response rate to an agent is needed in the treatment-naïve patient before it is taken forward into combination therapy.

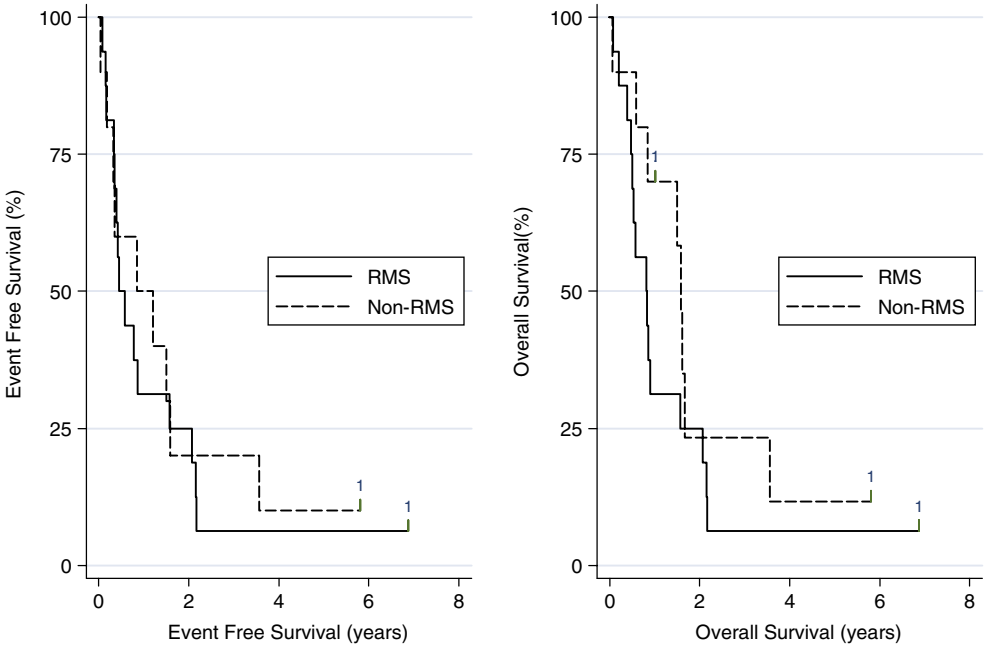


Fig. 3 – Event-free and overall survival for RMS and non-RMS eligible patients.

The response rate to carboplatin in metastatic RMS may appear somewhat disappointing. However, patients in this study were selected as belonging to a particularly poor-risk group[5] which may skew results as compared with previous window studies in metastatic RMS. Also accrual to the study was slower than expected for reasons that we cannot identify and we do not know whether patient selection may have influenced response rates. Central radiology review of some cases did not affect the reported response rate but for better overall accuracy it seems sensible to incorporate central review by a radiologist who is entirely familiar with the response criteria being utilised in the specific window study.

Carboplatin response and toxicity are dependent on the AUC achieved, with greater uniformity in AUC achieved by renal function based dosing than by surface area based dosing.[26] In this study, carboplatin was given at a planned AUC of 10. This intermediate dose of carboplatin was chosen as the maximum dose tolerable without the need for stem cell support. Similar intermediate range doses have been used as salvage therapy in the treatment of germ cell tumours and osteosarcomas.[27,28] Such a strategy might minimise the risk of losing control of disease following the application of single-agent therapy. A similar strategy was adopted with the evaluation of topotecan in RMS, using approximately three times the dose in the single-agent study as compared with that used in the combination study.[19]

Carboplatin was associated with tolerable and predictable toxicity. Excluding bone marrow suppression, the toxicities encountered were similar to previous studies, and no grade 3 or 4 infectious episodes was encountered. Some significant delays in administration of the second course were encountered and it is not known whether the routine administration of GCSF might have prevented these.

Potential ethical dilemmas exist when utilising window therapy. Despite the potential benefits of assessing drugs in chemotherapy-naïve patients, the drug(s) chosen for the window study may potentiate development of resistance and, if not very active, may permit escape of disease. Thus there is a theoretical risk of a poorer patient outcome by inclusion in a window study. In this study, 3 of the 15 evaluable patients with RMS experienced progressive disease (PD) during the window study (20%). In the IRS series, progressive disease was more common in window studies utilising the single agents irinotecan or topotecan (30–31%) than in studies of combinations of agents (7–19%) suggesting that single-agent window studies place patients at increased risk of initial treatment failure.[6] In some window studies, failure free survival was poorer than among patients receiving 'standard' therapy in the IRS III study but differences were not confirmed statistically and patients who participated in window studies had similar (poor) overall outcomes. Thus, there is no evidence at present that a window approach is unsafe in this patient group although it is possible that the lack of statistical significance in outcome between window studies and standard therapy relates to sample size.[6]

In view of the very poor prognosis with conventional therapy the concept of window therapy remains justified in these children. However, it is important that agents chosen for window studies show good evidence of activity in preclinical or xenograft models and/or in the classical phase II setting and are used in doses and schedules that are compatible with inclusion with standard therapies in the phase III setting. We suggest that it would be wise to avoid single-agent window therapy in metastatic RMS in the future because of the risk of early disease progression. It remains to be seen whether agents such as irinotecan that have been identified as active in window studies contribute to improved outcome when utilised in the phase III setting in paediatric RMS.

Two-year event-free survival in both RMS and non-RMS patients was poor, reflecting the high-risk patient groups

included in the study. Some events were noted beyond 2 years (Fig. 3). Our data appear similar to previous European data suggesting a 5-year EFS of around 7.5% for the poorest risk group of children with metastatic RMS.[5] There is no evidence that the use of carboplatin window therapy adversely affected outcome in this patient group, although no improvement in EFS was apparent.

In conclusion, we have shown moderate response rates with single-agent carboplatin given at an AUC of 10 in chemotherapy-naïve patients with high-risk metastatic RMS and other metastatic soft tissue sarcomas. Carboplatin has some activity in these tumours and was tolerable at this dose. However, there is an urgent need to find other agents that, when utilised as part of multimodality therapy, will contribute to improved EFS in these very poor-risk patients.

The following investigators and institutions participated in this study:

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Coordinating centre: UK Children's Cancer and Leukaemia Group (CCLG) Data Centre, University of Leicester, Leicester, UK.

Clinical Centres participating (the number of patients enrolled from each centre is given in parenthesis):

Czech Republic:	Motol Hospital, Prague (1);
Denmark:	Odense University Hospital, Odense (1).
Ireland:	Our Lady's Hospital for Sick Children, Dublin (2).
Norway:	University Hospital, Tromsø (1).
The Netherlands:	Academic Medical Center, Amsterdam (1).
United Kingdom:	Birmingham Children's Hospital (2), Addenbrooke's Hospital, Cambridge (2), Bristol Royal Hospital for Sick Children (1), Children's Hospital for Wales, Cardiff (2), Royal Hospital for Sick Children, Glasgow (1), St James's University Hospital, Leeds (2), Royal Liverpool Children's Hospital (2), Great Ormond Street Hospital, London (2), Middlesex Hospital, London (2), Southampton General Hospital (3), Royal Marsden Hospital, Sutton (2).

Conflicts of interest statement

None declared.

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