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Review

Treatment strategies for metastatic Ewing's sarcoma

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Abstract

Therapy in metastatic Ewing's sarcoma is reviewed using the methodology recommended by the guidelines project of the Federation of French Cancer Centres (FNCLCC) Standards, Options and Recommendation (SOR) Group. Twelve articles relating to conventional dose therapy and seven articles related to high-dose therapy were judged suitable for detailed appraisal. Rates of complete response (CR) at metastatic sites and local control were high using combinations of vincristine, actinomycin, cyclophosphamide and doxorubicin with radiation or surgery. With more recent regimens, including increased doses of alkylating agents and anthracyclines the relapse-free survival has increased from <15 to 20–30%. 'Megatherapy' regimens with haematopoietic stem cell rescue are tolerable in this patient group, but to date there is little evidence of any benefit. It appears that patients with isolated lung metastases do significantly better (approximately 40% EFS) than those presenting with combined sites such as bone, bone marrow and lung. The use of lung irradiation in children with lung metastases is associated with a reduced incidence of subsequent lung recurrence and a consistently better overall relapse-free survival (RFS).

Keywords: Metastatic Ewing's sarcoma; Chemotherapy; Radiotherapy; Children

1. Metastatic Ewing's sarcoma

With improved cure rates in most localised children's cancers, attention is now focused on those tumours in which the outcome remains poor. One example is metastatic Ewing's sarcoma. There are a group of tumours which are appropriately combined under the single term 'Ewing's family of tumours' (EFT) [1]. These share histological, immunohistochemical and cytogenetic characteristics and in the past have been called Ewing's sarcoma of the bone or soft tissue, malignant peripheral primitive neuroectodermal tumour, primitive neuroepithelioma and Askins tumour [2]. Although there is some debate about the management of soft tissue compared with bone Ewing's it is clear that the behaviour of metastatic disease is shared by all members of the family.

20–30% of EFT are metastatic at presentation [3]. The commonest sites are lung, which are bilateral in approximately 60% of patients, bone and bone marrow. In the largest study reported to date [3], 30% of those with metastases had lung metastases alone, 30% had bone or bone marrow and 20% had lung combined with bone metastases. The incidence of sites varies between series due to differences in the techniques used to detect metastases, particularly in bone marrow. Compared with localised disease, patients tend to have primary tumours of the pelvis or femur rather than the more favourable peripheral bones [3].

The main questions in the management of this disease are whether intensification of induction chemotherapy either by dose escalation or the addition of drugs such as etoposide improves response and outcome and if consolidation of first complete response (CR1) with megatherapy and haematopoietic stem cell rescue prolongs relapse-free survival. The role of radiotherapy to sites of initial metastases is also debated.

This review addressed these issues by a detailed evaluation of the published data over the past 15 years.

The selection of articles for the detailed review followed the guidelines drawn up by the National Federation of French Cancer Centres (FNCLCC) Standards,

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Options and Recommendation (SOR) Group [4,5]. Literature searches were carried out centrally by FNCLCC librarians using Medline, Cancerlit from the years 1985–1999, by searching reference lists at the end of retrieved articles and also the authors' personal reference lists. The data search was less extensive than that used by Cochrane groups and only published data were reviewed. Direct contact or follow-up from authors was not sought. A standard grid was used to screen the quality of each study and for the critical appraisal on the basis of patient number, whether it was prospective or retrospective, randomised or single arm, the methods of inclusion and evaluation, and the end-point definition and analysis.

Proceedings abstracts were not included. For studies relating to conventional dose chemotherapy, any paper that included less than 10 children with metastatic disease was excluded and for high-dose therapy studies a minimum of 5 patients in first complete response (CR) had to be described. The few papers containing only adults with Ewing's tumour (ET) were excluded, but where there was a mixed population, all were included.

2. Results of conventional therapy

From a total of 28 articles which contained some information on conventional dose therapy for children with metastatic ET, 12 suitable publications were identified, describing 16 studies in which 12 different regimens were used [3,6–16] (Table 1). Data were collected prospectively in all these studies. Data derived from five national or international collaborative group studies were included; The United Kingdom Children's Cancer Study Group (UKCCSG), the American Ewing's Intergroup (IESS), the German Ewing's Study Group (CESS), the American Pediatric Oncology Group (POG) and the European collaboration (EICESS). There were a number of publications which included an overlap of patients, and interpretation of the data regarding site distribution and outcome should take this into account. In particular, studies 3 and 5, 6 and 10.

Numbers of patients described in the articles ranged from 12 to 171 (median 37). Ages ranged from 1 to 45 years with the median for each study ranging from 11 to 17 years (Table 2). The pelvis was the primary site in 32% (range 17–59%), long bone in 32% (range 17–35%). The lungs were the only site of disease in 56%, bone/bone marrow in 50% (these figures are derived from the nine studies in which details were provided).

Lung metastases were detected with computed tomography (CT) scan in 11 publications. To assess bone disease, Technetium bone scan was used in nine, various methods in one and not specified in two.

The method of marrow assessment varied widely: aspirate alone in two, aspirate + trephine in three, trephine alone in one and method not specified in six.

3. Local therapy strategies

3.1. Surgery

The use of surgery was not specified in eight studies (Table 3). In the four studies where details were given between 8 and 31% had surgery with or without irradiation.

Table 1
Regimens used in metastatic Ewing's tumour (ET)

St Jude regimen EW1-79, 81, POG [6,10,13]	Cyclophosphamide 150 mg/m^2 orally daily $\times$7, doxorubicin 35 mg/m^2, then vincristine 1.5 mg/m^2 weekly, actinomycin 1.5 mg/m^2 every 2 weeks
ET2 regimen IVAAd [16]	Ifosfamide 9 g/m^2, vincristine 2 mg/m^2, doxorubicin 60 mg/m^2 then alternate doxorubicin with actinomycin 2 mg/m^2
EICESS 92, CESS 81, CESS 86 [3,15]	Cyclophosphamide 1200 mg/m^2 or ifosfamide 6 g/m^2, doxorubicin 60 mg/m^2, vincristine 1.5–2 mg/m^2, actinomycin 1.5–2 mg/m^2, (VAIA) $\pm$etoposide 150 mg/m^2
IESS VACA [8]	MD1 weekly vincristine 1.5 mg/m^2 and cyclophosphamide 500 mg/m^2, pulses of actinomycin 2.25 mg/m^2 or doxorubicin 60 mg/m^2. MD2 above plus 5-fluorouracil (5-FU) 300 mg/m^2 with early doxorubicin (75 mg/m^2) and delayed irradiation
UKCCSG VACA ET1 [12]	Vincristine 2 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 1000 mg/m^2 then alternate actinomycin 1.4 mg/m^2 with doxorubicin
HD cyclo [9]	Cyclophosphamide 4200 mg/m^2, doxorubicin 75 mg/m^2, vincristine 2 mg/m^2, followed by ifosfamide 9 g/m^2, etoposide 500 mg/m^2
St Jude IfVP [10] EW1-87	Ifosfamide 8 g/m^2, etoposide 500 mg/m^2.
VAC IfVP [11]	Vincristine 2 mg/m^2, doxorubicin 50–90 mg/m^2, cyclophosphamide 1200–1800 mg/m^2, alternate with ifosfamide 5 g/m^2, etoposide 500 mg/m^2
St Jude intensive [16]	Ifosfamide 6 g/m^2, etoposide 450 mg/m^2, doxorubicin 45 mg/m^2 then alternate ifosfamide/etoposide with cyclophosphamide (2 or 3000 mg/m^2) doxorubicin 60 mg/m^2
SFOP IVAAd [7]	Ifosfamide (6 g/m^2), vincristine (1.5 mg/m^2), doxorubicin (60 mg/m^2), alternate actinomycin 2.2 mg/m^2

3.2. Radiotherapy

No details of irradiation were given in eight reports. Where specified, its use ranged from 54 to 100%. The dose ranged from 30 to 66 Gy depending on the completeness of excision or response to chemotherapy. Lung irradiation was used in 10 regimens (Table 3) and not given in six in the event of a chemotherapy-induced CR. The dose ranged from 12 to 18 Gy depending on the patient's age.

4. Outcome of combined modality therapy

The event-free survival (EFS) was documented at between 30 months and 10 years follow-up. In the St Jude pre-1979 series there were no long-term survivors. In the later studies, the EFS ranged from 9% in the ETI study to 55% at 30 months in the original Hayes publication of the St Jude 79 regimen and 30% at 5 years in the IESS studies MD1 and 2. EFS was not documented in three reports. Overall survival (OS) at 5 years ranged from 14% in ETI to 61% with the St Jude 79 regimen. (Table 3). Details of survival were not provided in five studies [6,7,9,11,16]. Relapse sites were not specified in the majority of reports.

5. Prognostic factors identified in studies

Most studies were too small to permit any meaningful univariate or multivariate analysis. Only five reports contained 40 or more patients (UKCCSG ET2, St Jude, IESS, EICESS, CESS) which described 42, 43, 121, 171 and 114 cases, respectively. In the IESS studies, outcome was age-dependent ($\leqslant$10 years 40% OS; $>$10

Table 2
Details of patients included in studies using conventional chemotherapy and the methods of detecting metastases

Author, year [Ref.]	Year of study	Patient number age range years (median)	Isolated lung metastases	Method of detection of metastases
Hayes (1987) [6]	78–85	18 4–18 (12)	6	CT Tc Aspirate
Demeocq (1989) [7]	84–89	22 3–18 (11)	NS	CT Tc BM NS
Cangir (1990) [8]	75–77 80–83	122 NS	65	CT Tc BM NS
Kuschner (1995) [9]	NS	12 1–36 (17)	6	CT Tc Multiple asp/treph
Sandoval (1996) [10]	62–92	43 3–22 (12)	18	Varied with time
Wexler (1996) [11]	86–92	23 7–24	23	CT Tc 2 asp/2 treph
Craft (1997) [12]	78–86	22 1–33 (12)	10	Tomo/CT Tc BM NS
Donaldson (1998) [13]	83–88	37 2–30 (14)	NS	CT Bone NS BM asp
Paulussen (1998) [15]	81–97	114 2–45	All lung or pleura	CT Bone NS BM NS
Craft (1998) [16]	87–93	42 1–27 (13)	22	CT Tc Asp/treph
Paulussen (1998) [3]	90–95	171 0–44 (15)	61	CT Tc Treph
Marino (1999) [14]	92–96	19 4–25 (13)	NS	CT Tc BM NS

NS, not specified; B/bm, bone±bone marrow; Asp, aspirate; Treph, trephine biopsy; Tomo, tomography; Tc, technetium bone scan; CT, computed tomography.

Table 3
Treatment details and outcome with standard dose therapies

Chemotherapy regimen [Ref.]	Duration (month)	Time of local treatment	XRT lung dose	XRT bone	Event-free	Overall survival
St Jude EWI 79 [6]	12	15 week	No	Yes	55% (median FU 30 months)	NS
SFOP IVAAd [7]	9	10 weeks	No	No	NS	NS
IESS MD1 [8]	24	XRT week 1	Yes 15 Gy <1 year	Yes	MDI 30%	31% at 5 years
					MD2 30%	28%
MD2 [8]	24	XRT week 10	Yes 18 Gy >1 year			
High dose cyclophosphamide [9]	6	Surgery Week 9 XRT at end	Yes 12 Gy	No	NS	NS
St Jude VACAd [10]	NS	NS	No	Yes	NS	10% (0–27) at 3 years
EWI 79 [10]	12	Week 15	No	No	NS	61% (39–84)
EWI 87 [10]	12	Week 18	No	No	NS	51% (19–83)
VAC If VP [11]	12	Week 15	No	No	13% (5–32) at 5 years	NS
ET1 [12]	24 reduced to 12	Week 6	Yes 15 Gy	NS	9% (0–21) at 5 and 10 years	14% (0–25 at 5 years, 9% at 10 years
POG [13]	12	Week 14	Yes	Yes	23% (±7) at 5 years	31% (±8) at 5 years
CESS 81 [15]	18	NS	Yes 14–18 Gy	NS	36% (26–46) at 5 years[a]	46% (35–57) at 5 years[a]
CESS 86 [15]	10	NS	Yes 14–18 Gy	NS	30% at 10 years[a]	31% at 10 years[a]
ET2 [16]	12	Week 12	Yes 15 Gy	NS	23% (8–38) at 5 years	NS
EICESS 92 [3]	10	Week 20	Yes 15–18 Gy	NS	27% (20–34) at 4 years	32% (25–39) at 4 years
St Jude intensive [14]	10	Week 9	Yes if No CR 12 Gy	Yes	27%±13 at 3 years	35%±13% at 3 years

NS, not specified; XRT, radiotherapy; CR, complete response; b/R, bone/bone metastases.
[a] Including EICESS 92.

years 20% OS), although rib primaries were more common in the younger patients (39% versus 16%). Only 4/29 with pelvic primary and 5/19 with marrow disease survived. In the St Jude studies, no feature was of prognostic value and in particular neither the primary site or site of metastases were of significance. In the ET2 study, the outcome was similar with either bone or lung disease, but no patient with multiple sites of disease survived.

Only the detailed analyses of the CESS and EICESS data throw light on prognostic factors. In the first analysis [15], the outcome and prognostic factors were considered in patients with isolated lung or pleural metastases treated on three consecutive studies run by the CESS group — CESS 81, CESS 86 and EICESS. In the second report [3], a similar analysis is made for all metastatic patients in the most recent European collaborative EICESS study. The conclusion by these authors was that, in the study with lung metastases, multivariate analysis revealed bilaterality of lung metastases and poor chemotherapy response at the primary site to be the only independent poor risk factors. The EICESS data showed age >15 years and combined sites to be adverse factors.

Table 4
Influence of whether or not lung irradiation was given in CESS and EICESS series

Author, year [Ref.]	Analysis	Population	Criteria	Lung irradiation	
				Yes	No
Paulussen (1998) [15]	Univariate (actuarial survival)	Lung metastatses at diagnosis ($n=100$)			
		Older studies	EFS at 5 years	38%	27%
		Recent studies	EFS at 5 years	42%	22%
	Multivariate Cox model	Lung metastases at diagnosis	EFS at 5 years	OR 2.2	$P=0.04$
	Logistical regression		Probability of relapse	OR 2.1	NS
Paulussen (1998) [3]	Univariate (actuarial survival)	Isolated lung 2° ($n=59$)	EFS at 4 years	40%	19%
		Lung + bone ($n=36$)		30%	5%
	Multivariate Cox model	Lung + bone ($n=36$)	EFS at 5 years	OR 3.9	$P<0.005$

OR, odds ratio; EFS, event-free survival; 2°, secondary; NS, non significant.

Table 5
Details of patients receiving high dose treatment strategies and the regimens used

Author, year [Ref.]	Number	Stage	Site of metastases	High dose regimen	Outcome	Toxic mortality
Prete (1998) [17]	17 14 metastatic	3 and 4	NS	Bu Thio Etop	63% EFS, 70% OS (including St 3) at 2 years	0/17
Burdach (1993) [18]	17 including 10 relapsed	4	Multifocal 6 BM 1	Etop Melph TBI ±Carbo, IL2	3/7 EFS follow-up NS	0/7
Atra (1997) [19]	18 11 metastatic	3 and 4	Lung 10 BM 1	Bu Melph	65% EFS at 3 years	1/18
Miser (1988) [20]	23 13 metastatic	3 and 4	Lung 2 B/BM 7	VCR, Dox, CP TB1	32% EFS at 30 months	0/23
Ladenstein (1995) [21]	63 32 CR1 31 CR2	4 or relapsed	Lung 5 Bone 7 Multiple 9	Chemotherapy based; Melph ±Carbo, Cis, BCNU, VM26, VCR Bu CP TBI-based ± VCR, Carbo,VP, Cis, BU CP	21% EFS at 5 years, TBI 19% non-TBI 34% Bu-Mel 51%	8/63
Hartmann (1990) [23]	32 12 CR1	4 or relapsed	NS	BCNU, procarb melph×2 or BCNU, melph then Bu/melph	3/12 DF at 30–68 months	2/32
Horowitz (1993) [22]	65 49 metastatic grouped with RMS	3 and 4	BM 47% Lung 45% Bone 41% Multiple 50%	VDoxCP/TBI	EFS 10% at 6 year 14% OS no difference RMS or ET	6/65

Bu, busulphan; Dox, doxorubicin; Melp, melphalan; Cis, cisplatin; VCR, vincristine; Mets, metastases; Carbo, carboplatin; Etop, etoposide; RMS, rhabdomyosarcoma; CP, cyclophosphamide; Thio, thiotepa; Procarb, procarbazine; TBI, total body irradiation; NS, not specified; CR1, complete response 1; VM26, teniposide; DF, disease-free; IL2, interleuken 2; B, bone, BM, bone marrow.

In both studies, univariate analysis showed a benefit from whole lung irradiation on EFS for those irradiated (Table 4). In the CESS study of patients with lung/pleural metastases alone multivariate analysis using logistic regression failed to show lung radiotherapy as a significant independent factor (odds ratio (OR) 2.1 compared with 4.2 and 3.7 for laterality of lesions and response to chemotherapy respectively). In the EICESS study, multivariate analysis showed lung irradiation to be of benefit both in isolated lung metastases (EFS 40% versus 19%) and those with combined lung and bone metastases (risk ratio 3.9 if radiotherapy not given). In the latter study, results were somewhat confounded by the use of megatherapy as consolidation with or without lung radiotherapy. 'Intensification', i.e. high-dose therapy or lung irradiation, both appeared to improve outcome in patients with combined site disease (risk ratio 5.4 if no intensification given).

6. Results using high-dose therapy with stem cell rescue

Twenty-five articles relating to high-dose therapy were considered and seven were included [17–23]. A total of 123 patients who received high-dose therapy in CR1 were described out of a total of 235 high risk patients i.e. bulky primaries and relapsed disease. Only two studies [21,22] contained more than 15 children with initially metastatic ET (Table 5).

Details of the methods used for the initial reassessment were rarely provided and the distribution of metastatic sites varied between studies reflecting either the small numbers or patient selection. In the Burdach study [18], all were poor risk with multifocal disease, whereas most of the patients in Atra's report had lung metastases only [19]. High-dose regimens were predominantly melphalan-based, invariably combined with other agents such as busulphan, etoposide or 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU). In four studies, TBI was used combined with a variety of other drugs.

The treatment-related mortality was 7% overall (17/250). Data were not provided separately for those with initial metastases.

Most of the studies contained too few patients to draw conclusions about effectiveness. The two largest studies were Ladenstein's review of data from the European Bone Transplant Register (EBMT) [21] and the NCI series that combined both ET and rhabdomyosarcoma [22]. The EBMT data were limited by the heterogeneity of the regimens used and the inevitable selection of patients. The EFS for those in CR1 after initial metastases was 21% at 5 years. In an analysis of outcome in the whole series i.e. including relapsed and non-metastatic cases, there appeared to be some benefit for non-TBI regimens; EFS were respectively 19, 51 and 34% for TBI, busulphan-melphalan and other chemotherapy. In the Horowitz series, the EFS at 6 years for those with initially metastatic ET was 10%.

7. Lessons from published data

In this review, it was striking that few firm conclusions could be drawn from the various publications

other than that the regimens used carried certain early and late toxicities. The confidence intervals for EFS and OS were invariably very wide due to the small numbers involved and therefore any comparison with previous regimens is difficult. In the case of megatherapy, no single study was large enough for any conclusions to be drawn about the effectiveness and for conventional dose regimens, only the IESS and CESS/IECESS studies contain sufficient numbers to be reasonably confident about the outcome measures. There is no level A or B1 evidence that any particular regimen is superior and only the CESS/EICESS analysis of prognostic factors provides level B2 evidence [4].

The induction chemotherapy regimens used in these studies can be divided into three groups; those using standard doses of doxorubicin, vincristine, cyclophosphamide (AdVAC), those incorporating higher doses of alkylating agent, and more intensive multiagent combinations.

Results with a conventional dose and schedule (1 g/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin given every 21 days) in the ET1 regimen produced very poor results — 9% EFS at 5 years and this was the case with other earlier reports of this type of regimen. The encouraging results from the St Jude group (50% EFS at 8 years) using a 7 day oral cyclophosphamide schedule (150 mg/m^2 with only 35 mg/m^2 doxorubicin) must be seen in the context of the small number of patients [6]. A subsequent multicentre POG study using the same chemotherapy regimen failed to reproduce these results in 37 patients — EFS 23% at 5 years. This study used irradiation to treat all sites of metastases except marrow and it is possible that by giving this at an early stage, chemotherapy may have been compromised. Irradiation was not used in the St Jude study.

The results from the larger IESS studies appear to be superior to ET1 and one difference was the use of weekly cyclophosphamide (500 mg/m^2) rather than every 3 weeks, raising the possibility that more protracted scheduling of cyclophosphamide may be superior in this disease. The dose of anthracycline was also rather higher than in ET1 (60 and 75 mg/m^2 for studies MD1, MD2 respectively). 5-FU did not influence outcome.

Both the CESS (CESS 86 and EICESS) and UKCCSG (ET2) groups have escalated doses, but used conventional scheduling (ifosfamide 6–9 g/m^2 and doxorubicin 60 mg/m^2). The results with these regimens are the best reported to date, particularly in those with only lung metastases where around 40% are EFS at 5 years. Lung irradiation was used in most patients in these regimens.

Further intensification with the use of high doses of cyclophosphamide, e.g. up to 4.2 g/m^2 or the use of ifosfamide-etoposide has had no obvious impact on outcome. The results of the addition of etoposide in the randomised EICESS study for localised disease will be of interest.

The timing and nature of local therapy is of importance. As in other metastatic tumours, it is desirable to sustain dose intensity during the first few weeks of treatment and if radiotherapy or surgery are used too early this may either cause delays in chemotherapy or the omission of certain drugs. Moreover, it is preferable to leave any surgery until it is clear that there has been a good response to treatment at metastatic sites. There is little point subjecting the child to surgery if it is likely that residual distant disease will progress shortly afterwards. Timing of local treatment ranged from week 1 in MD1 to week 20 in the EICESS trial. In most studies it was around 10–15 weeks.

It appears that in many series radiotherapy was used electively — perhaps to avoid mutilating surgery in patients where the long-term prognosis appeared to be very poor. With the best regimens, the outlook for those with lung metastases only is now such that these patients should undergo the same radical but limb-sparing surgery as is used in localised disease, guided by response and tumour site.

The value of lung irradiation remains unproven. In the detailed analyses by the CESS group this does appear to improve outcome but the authors have advised caution, as there has been no randomised comparison. However, at the present time it seems appropriate to follow the strategy recommended by this group which has analysed in considerable detail a large group of patients treated within national studies and to include bilateral lung irradiation in all patients presenting with lung metastases. It is possible that this is not independent of chemotherapy response or age and that these two independent adverse prognostic factors could be used to guide more aggressive strategies. Perhaps in the younger child who has had a good chemotherapy response at the primary site lung irradiation could be omitted. In the current European trial, patients who are randomised to receive high-dose therapy with busulphan/melphalan will not receive lung irradiation in contrast to those randomised to standard chemotherapy. It is to be hoped that sufficient numbers are recruited to this study to allow subsequent analysis of outcome on the basis of both the treatment received and prognostic factors.

The latter study will address the question of megatherapy as consolidation of CR1, but excludes those with bone/bone marrow disease who are planned to have more investigational treatments. The role of megatherapy has remained unclear for many years, but despite this has continued to be practised outside any formal trials. The data from the EBMT suggest that TBI is not necessary and whether the use of double graft or even more intensive multiagent consolidation regimens will improve outcome remains to be seen. It is

clear that for patients with bone/bone marrow metastases most of the combinations used to date have had little beneficial effect.

Much remains to be done to improve the outcome in children with metastatic Ewing's. Progress will only come from carefully designed multicentre, international trials asking specific questions and which are likely to recruit sufficient numbers to answer these questions in a realistic period of time. Small limited centre pilot studies have an important place in defining the questions to ask, but have failed in the past decade to provide any real answers.

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