



SHORT REPORT

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Comprehensive analysis of published phase I/II clinical trials between 1990-2010 in osteosarcoma and Ewing sarcoma confirms limited outcomes and need for translational investment

Annemiek M van Maldegem^{1†}, Aparna Bhosale^{1†}, Hans J Gelderblom³, Pancras CW Hogendoorn⁴ and Andrew B Hassan^{1,2*}

Abstract

Background: High grade primary bone sarcomas are rare cancers that affect mostly children and young adults. Osteosarcoma and Ewing sarcoma are the most common histological subtypes in this age group, with current multimodality treatment strategies achieving 55-70% overall survival. As there remains an urgent need to develop new therapeutic interventions, we have reviewed published phase I/II trials that have been reported for osteosarcoma and Ewing sarcoma in the last twenty years.

Results: We conducted a literature search for clinical trials between 1990 and 2010, either for trials enrolling bone sarcoma patients as part of a general sarcoma indication or trials specifically in osteosarcoma and Ewing sarcoma. We identified 42 clinical trials that fulfilled our search criteria for general sarcoma that enrolled these patient groups, and eight and twenty specific trials for Ewing and osteosarcoma patients, respectively. For the phase I trials which enrolled different tumour types our results were incomplete, because the sarcoma patients were not mentioned in the PubMed abstract. A total of 3,736 sarcoma patients were included in these trials over this period, 1,114 for osteosarcoma and 1,263 for Ewing sarcoma. As a proportion of the worldwide disease burden over this period, these numbers reflect a very small percentage of the potential patient recruitment, approximately 0.6% for Ewing sarcoma and 0.2% for osteosarcoma. However, these data show an increase in recent activity overall and suggest there is still much room for improvement in the current trial development structures.

Conclusion: Lack of resources and commercial investment will inevitably limit opportunity to develop sufficiently rapid improvements in clinical outcomes. International collaboration exists in many well founded co-operative groups for phase III trials, but progress may be more effective if there were also more investment of molecular and translational research into disease focused phase I/II clinical trials. Examples of new models for early translational and early phase trial collaboration include the European based EuroBoNeT network, the Sarcoma Alliance for Research through Collaboration network (SARC) and the new European collaborative translational trial network, EuroSarc.

Keywords: Ewing sarcoma, osteosarcoma, early phase trials, translational research

* Correspondence: bass.hassan@path.ox.ac.uk

† Contributed equally

¹Department of Oncology, Oxford Cancer and Haematology Centre, Churchill Hospital, University of Oxford, Oxford OX3 7LJ, UK

Full list of author information is available at the end of the article

Background

Primary bone sarcomas are rare, and account for approximately 6% of all childhood malignancies, with Ewing sarcoma and osteosarcoma accounting for approximately 3% of tumours arising in teenagers. Here we focus on osteosarcoma and Ewing sarcoma, the two most common bone sarcomas, whose treatments are similar as they involve multimodality treatment with dose intensive and toxic chemotherapy, combined with potentially mutilating surgery.

Osteosarcoma is the most common primary malignant tumour arising from bone. It is a pleiomorphic tumour of bone, and based on animal model systems, thought to arise in mesenchymal stem cells in which the mutant proliferating spindle cells produce osteoid or immature bones [1]. The EMEA published data in 2009 estimating approximately five people in 1,000,000 in the European Union (EU) are affected by osteosarcoma. Recently, data from the RARECARE surveillance network revealed an incidence of 0.23 per 100,000, amounting to approximately 1135 new cases per year in EU27 [2]. Osteosarcoma mostly affects children and young adults with the median age of diagnosis being fifteen. Seventy-five percent of patients are between eight and twenty-five years old. Osteosarcoma is often located in the extremities of long bones near metaphyseal growth plates. Current treatments for osteosarcoma achieve 60-70% event-free survival (EFS) for patients who present with localized disease and approximately 20% EFS for patients with clinically detectable metastatic disease [3]. Of all patients, 20% have clinically detectable metastatic disease at first presentation. Surgical resection of all clinically detectable sites of disease and systemic therapy to control microscopic metastatic disease is currently the therapy of choice for early stage osteosarcoma. Since the introduction of neo-adjuvant and adjuvant chemotherapy to surgery in the early 1980s, the long term survival of patients with osteosarcoma has remained stable at about 60-65%. In terms of chemotherapy, several agents have demonstrated activity in osteosarcoma including cisplatin, doxorubicin, high-dose methotrexate with leucovorin rescue (HDMTX) and ifosfamide. For current treatment options these agents are combined. Since the early 1980s, trials have been conducted in which the variations in doses and scheduling between these four agents were tested, but these have not result in improvement of EFS [4]. Since the introduction of ifosfamide, more than two decades ago, the only new agent that has been approved is muramyl tripeptide, a drug that activates the innate immune system [5]. Thus, despite surgical resection of the primary tumour and aggressive adjuvant chemotherapy, 30%-40% still die of metastases that are resistant to conventional therapies [6-8]. For

osteosarcoma patients with resectable pulmonary metastases it has become more standard to treat these patients with metastectomy. This has been shown to improve relapse free survival and a subgroup of patients may even be cured [9].

Ewing Sarcoma/Primitive Neuroectodermal (PNET) are the second most common bone malignancy after osteosarcoma in children and young adults with a peak incidence at age fifteen. Ewing sarcoma are diagnostically defined by a Ewing sarcoma EWS (Chromosome 22) translocation resulting in fusion with an ETS transcription factor, the commonest abnormality (85%) being EWS-FLI1 (Chromosome 11) or rarely with a non ETS family partner [10,11]. Although claimed in the past that the transcript type reflected a difference in prognoses [12] this proved not to be the case in prospective randomised trials [13]. RARECARE estimates an EU27 incidence rate for bone and soft tissue Ewing sarcoma of 0.13 per 100,000 and 0.05 per 100,000, respectively [2]. This translates to approximately 647 bone and 263 soft tissue new Ewing sarcoma diagnoses per year (EU27), with a predicted 65-75% 5 year survival for non-metastatic disease using conventional chemotherapy, radiotherapy, high dose chemotherapy and peripheral blood stem cell transplant (PBSCT). However, survival for the 25% of patients that present with metastatic disease is approximately 20% [14], and for those who develop relapsed and/or refractory disease, the survival is no more than 10%. To date, studies in the patient population requiring salvage treatment have been confined to chemotherapy combinations and high dose chemotherapy, with variable response rates and little or no impact on survival. During the last two decades, the outcome has improved in patients with localized disease. This has been achieved by dose intensification and standardisation of conventional therapeutics and radiotherapy. With the use of multidisciplinary treatments, such as chemotherapy (including vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide), surgery and radiation therapy, the five year overall survival probability exceeds 75% for patients with non metastatic low volume Ewing sarcoma. However, advances in the treatment of Ewing sarcoma have not impacted on the outcome of patients with large volume and metastatic disease [15].

In the last two decades the treatment outcome for these bone sarcomas has not improved greatly, even though some new treatment interventions have been successfully tested. Large scale phase III trials with long durations of recruitment have established material for prognostic and treatment related correlative studies with survival and toxicity outcomes, and importantly, have formed the basis of international collaboration.

However, the smaller phase I/II studies are also important in order to develop proof of principle single agent and combination treatments, particularly with newer molecular and biological based interventions that directly test disease specific molecular mechanisms.

We wished to establish the effective level of phase I/II activity that has been reported in peer reviewed publications in the last twenty years. We report an overview of the phase I/II trials that have been conducted for osteosarcoma and Ewing sarcoma, where we detail the kind of drugs that have been tested, what the published study outcomes were and what interventions have progressed to testing in phase III trials. The results show an improvement in overall activity, but that the number of studies and International collaborations in early phase trials remain at a low and limited level. We discuss potential routes to improve the number and quality of early phase trials in Ewing and osteosarcoma.

Methods

Search strategy

We report data available in the public domain only. Publications were identified from searches of PubMed, the Cochrane Controlled Trials Register, American Society of Clinical Oncology (ASCO) abstracts and ClinicalTrials.gov. databases for the period 1990-2010. The search strategies used terms for osteosarcoma; (osteosarcoma) AND (phase I OR phase II) AND (clinical trial), and was supplemented with a text word search. For Ewing sarcoma the search algorithm was; (Ewing sarcoma) AND (phase I OR phase II) AND (clinical trial). To validate the search we broadened the search algorithm to; (sarcoma) AND (phase I OR phase II) AND (clinical trial), and compared the results from the narrow search with the ones from the broad search. The latest search was performed in April 2010.

Whenever multiple reports from the same trial were published, we used only the report with the longest follow-up to avoid any duplication of information. Publications were eligible if they: (1) described (or cited a paper that described) osteosarcoma or Ewing sarcoma study of early phase clinical trials; (2) were published in English; and (3) came from industrialized countries. All types of evaluation were accepted (full papers, conference abstracts, reports) as long as results (including data) were presented.

Data extraction

Data extraction was conducted independently by two authors (A. B. and A.M. van M.). We used a systematic method for the search normally used for meta-analysis [16]. Differences in data extraction were resolved by consensus with a third author (A.B. H.). From each eligible trial we recorded authors' names, journal and year

of publication, number of patients enrolled, number of osteosarcoma or Ewing sarcoma patients, study phase and the outcome of the trial.

Results and discussion

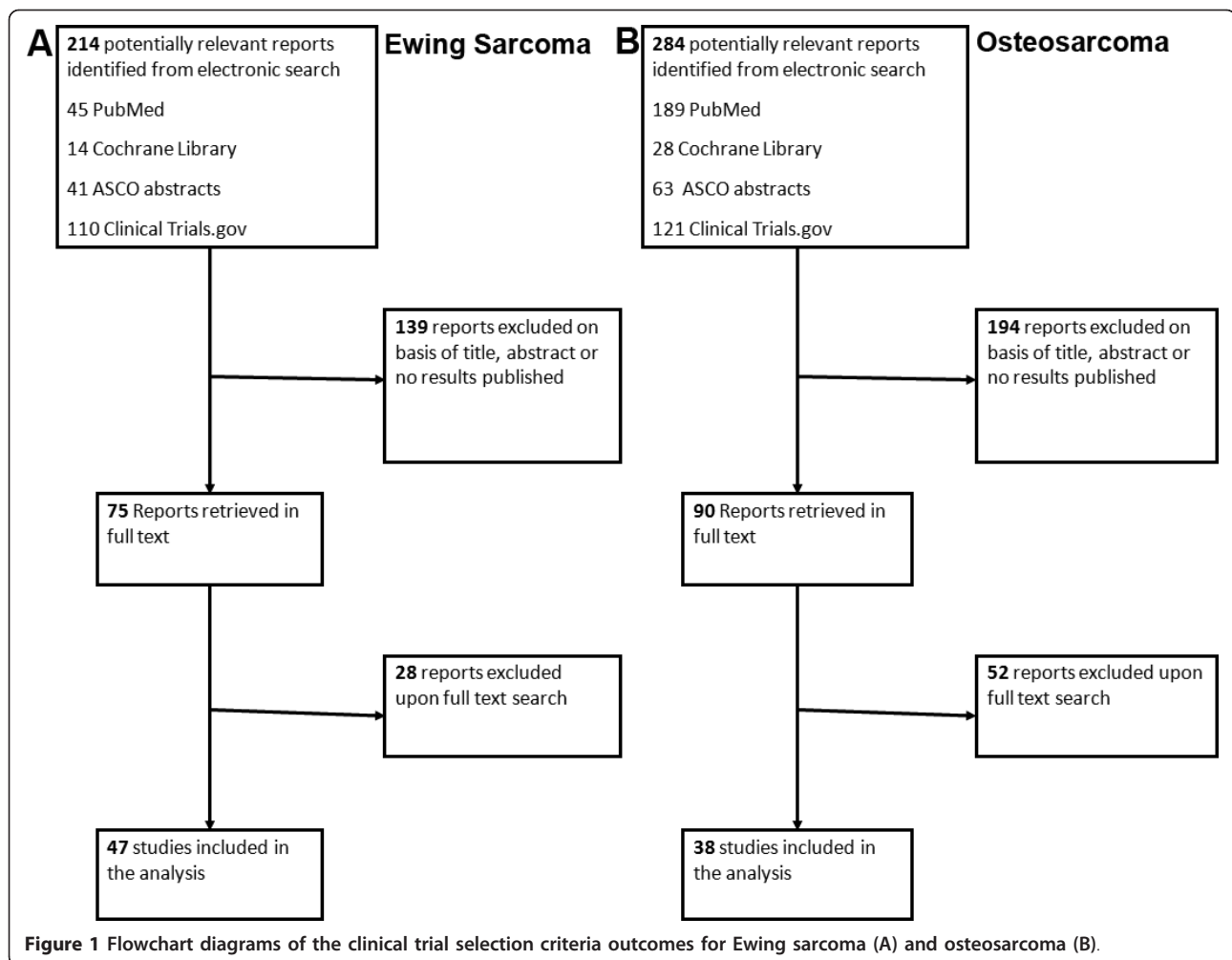
Eligible trials

A flow-chart indicating the identification of clinical trials for inclusion in the analysis is reported for Ewing sarcoma (Figure 1A) and osteosarcoma (Figure 1B). During the search many reports had to be excluded because no results were published. When we searched the reports using full text, we had to exclude some papers because neither osteosarcoma nor Ewing sarcoma patients were included in these studies. When we combined the results, we identified 42 trials enrolling patients with any histological diagnosis of sarcoma that were eligible for our study, in that they included osteosarcoma and Ewing sarcoma. Of the 42 clinical trials twenty-one were phase I, two were phase I/II and nineteen were phase II trials. We found eight clinical trials which included only Ewing sarcoma patients; of this group two were phase I and six were phase II trials. We identified twenty trials that included only osteosarcoma patients. There were two phase I, sixteen were phase II and two were phase I/II trials. A total of 3,736 patients were included in all the clinical trials, of which 1,263 were Ewing sarcoma and 1,114 were osteosarcoma patients.

Primary Outcome

Tables 1 and 2 show the search results for clinical trials conducted in patients with the wider diagnosis of general sarcoma, and specifically the trials that included either osteosarcoma (Table 3) or Ewing sarcoma patients only (Table 4). Table 1 and 2 are trials testing either chemotherapy or biological treatments, respectively. Analysis of the number of trials conducted which included only osteosarcoma or Ewing sarcoma patients from 1990 to the present, (Figure 2A) it was clear that the number of trials reported for osteosarcoma has been stable since 1995, with approximately five trials in five years. For Ewing sarcoma there has been an increase in the number of trials published, with the no early phase trials reported between 1990 and 1999, an increasing number of trials in the period 2000-2005 and even more between 2006-2010.

For the number of patients enrolled in the eligible trials the results were disappointing (Figure 2B), with an almost stable number of patients in osteosarcoma trials, except for 1999, 2005 and 2009 when the results from larger phase II trials were published (Table 3). For Ewing sarcoma there were increasing numbers of patients in early phase trials, especially in 2008 when the result of the largest trial in Ewing sarcoma patients was published (Table 4). Out of all the 780 osteosarcoma patients



enrolled in phase I/II trials including only osteosarcoma patients, 762 were evaluable and 58 patients (8%) achieved complete response (CR), 21 (2.8%) showed partial response (PR) and 30 (4%) developed stable disease (SD). For the trials enrolling only Ewing sarcoma patients, 869 were recruited and 840 were evaluable, 80 had CR (9.5%), 63 (7.5%) showed PR and 23 (3%) developed SD.

Looking at the trials subdivided for chemotherapy or biological treatment (Tables 1 and 2) in the past twenty years, there seems to have been a shift towards biologically based treatments instead of chemotherapy. Even so most of the phase III trials are still chemotherapy based treatments.

For current ongoing phase I and phase II studies we found 156 trials that are open and recruiting sarcoma patients. These trials recruit sarcoma patients in general or patients with solid tumours or soft tissue sarcoma. Studies enrolling only osteosarcoma or Ewing sarcoma patients are rare. For osteosarcoma we found four trials that are recruiting patients and two that are already

active but not yet recruiting patients (Table 5). Of the trials two were testing chemotherapy treatment, three biologically agents and one a combination of both. For Ewing sarcoma we found no trials that enrol only Ewing patients and two that are still active but not currently enrolling patients.

When searching for studies that are enrolling sarcoma patients we found a number of trials that were preliminary stopped. For example SARC011, this is a phase II trial of R1507, a recombinant human monoclonal antibody to the Insulin-like growth factor-1 receptor for the treatment of patients with recurrent or refractory Ewing sarcoma, osteosarcoma, synovial sarcoma, rhabdomyosarcoma and other sarcomas. In December 2009, Roche/Genentech decided to discontinue the development of their IGF-1R antibody although the drug had shown important clinical benefit <http://www.cancer.gov/ncicancerbulletin/111610/page5>. Roche said the decision was due to the available clinical data, the large number of molecules targeting the same pathway that are presently in development and the prioritization of the Roche

Table 1 Characteristics of eligible trials for general sarcoma with chemotherapy based treatment for phase I and phase II

Author	Year	Intervention	No Osteo patients	No Ewing Patients	Phase	Outcome
Pratt et al, <i>Cancer</i> , 74: 2593-8 [22]	1994	Leucovorin, 5-Fluorouracil	22	12	II	Ewing: 3 (25%) SD, Osteo: 1 (5%) SD
Kushner et al, <i>J Clin Oncol</i> , 13 (11): 2796-804 [23]	1995	Cyclo, Doxo, Etop, Ifos, Vin	Not mentioned	Not mentioned	II	6 (17%) CR, 2 (6%) PR, 34 (95%) CIR
Antman et al, <i>Cancer</i> , 82 (7): 1288-95 [24]	1998	Doxo, Dacarbazine, Ifos	31	13	II	10 (12%) CR, 34 (42%) PR
Blaney et al, <i>Clin Cancer Res</i> , 4 (2): 357-60 [25]	1998	Topotecan	18	25	II	1 (1%) CR, 1 (1%) PR, 8 (9%) SD
Lucidarme et al, <i>Bone Marrow Transplant</i> , 22 (6): 535-40 [26]	1998	Thiotepa combined with SCR	7	3	II	11 (50%) PR
Berg et al, <i>J Pediatric Hematol Oncol</i> , 22 (6): 506-9 [27]	2000	Pyrazoloacridine	8	10	II	0% response
Delaloge et al, <i>J Clin Oncol</i> , 19 (5): 1248-55 [28]	2001	Trabectedin	3	1	I	4 (14%) CR, 10 (35%) SD
Saylors et al, <i>J Clin Oncol</i> , 19 (15): 3463-9 [29]	2001	Cyclo and Topotecan	18	17	II	6 (35%) OR
Wagner et al, <i>Clin Cancer Res</i> , 10 (3): 840-8 [30]	2004	Temozolomide, Irinotecan	0	7	I	1 (8%) CR, 2 (17%) PR
Lau et al, <i>Clin Cancer Res</i> , 11: 672-7 [31]	2005	Trabectedin	4	3	I	1 (8%) CR
van Winkle et al, <i>Pediatr Blood Cancer</i> , 44 (4): 338-47 [32]	2005	Ifos, Carboplatin and Etop	35	22	I/II	Not mentioned
Hawkins et al, <i>Pediatr Blood Cancer</i> , 47 (6): 328-37 [33]	2006	Topotecan	11	20	II	2 (4%) PR
Navid et al, <i>Cancer</i> , 106 (8): 1846-56 [34]	2006	Vin, Doxo, Cyclo, Ifos and Etop	0	11	II	47 (66%) CR
Wagner-Bohn et al, <i>Cancer</i> , 46 (2): 262 [35]	2006	Gemcitabine	2	4	II	2 (10%) SD
Zaucha et al, <i>Int J Rad Oncol Biol Phys</i> , 64 (1): 227-34 [36]	2006	Total body radiation after high-dose chemotherapy	0	10	II	13 (25%) CR, 10 (19%) PR
Zwerdling et al, <i>Cancer</i> , 106 (8): 1821-8 [37]	2006	Docetaxel	23	21	II	2 (1%) CR, 6 (3%) PR, 17 (10%) SD
Geoerger et al, <i>J Clin Oncol</i> , 26: 4394-400 [38]	2008	Oxaliplatin	6	2	I	2 (4%) PR, 17 (6%) SD
Geler et al, <i>Pediatr Blood Cancer</i> , 52	2009	Paclitaxel, Ifos	1	3	I	3 (20%) PD, 5 (33%) SD
Wagner et al, ASCO abstract	2009	Vin, Irinotecan, Temozolomide	3	5	I	1 (3%) PR, 2 (6%) OR
McGregor et al, <i>Cancer</i> , 115 (8): 1765-75 [39]	2009	Oxaliplatin, Irinotecan	6	1	I	1 (8%) CR, 1 (8%) SD

Abbreviations: CIR = Clinical Response; CR = Complete Response; Cyclo = cyclophosphamide; Doxo = doxorubicine; EFS = Event Free Survival; Etop = etoposide; Ewing = Ewing Sarcoma; Ifos = ifosfamide; No = number; OR = Objective Response; Osteo = Osteosarcoma; PD = Progressive Disease; PR = Partial Response; RR = Response Rate; SCR = Stem Cell Rescue; SD = Stable Disease; TMR = Total Marrow Radiation; Vin = vincristine

Table 2 Characteristics of eligible trials for general sarcoma with biologically based treatment for phase I and phase II

Author	Year	Intervention	No Osteo Patients	No Ewing Patients	Phase	Outcome
Daw et al, J Clin Oncol, 23 (25): 6172-80 [40]	2005	Gefitinib	6	3	I	1 (4%) PR, 4 (16%) SD
Maki et al, Cancer, 103 (7): 1431-8 [41]	2005	Bortezomib	1	2	II	1 (4%) OR
Villablanca et al, J Clin Oncol, 24 (21): 3423-30 [42]	2006	Fenretinide	2	5	I	1 (2%) CR, 13 (24%) SD
Biron et al, ASCO abstract	2007	Gimatecan	0	Not mentioned	II	3 (8%) SD
Bagatell et al, Clin Cancer Res, 13 (6): 1783-8 [43]	2007	Tanespimycin	6	2	I	0% OR
Jimeno et al, Pediatr Blood Cancer, 49 (3): 352-7 [44]	2007	Gefitinib	3	1	I	1 (7%) PR, 3 (20%) SD
Kramer et al, J Clin Oncol, 25 (34): 5465-70 [45]	2007	Monoclonal antibody(131-I-3F8)	0	2	I	3 (23%) CIR
Bond et al, Pediatr Blood Cancer, 50 (2): 254-8 [46]	2008	Imatinib mesylate	10	24	II	1 (1%) PR
Chao et al, ASCO abstract	2008	Imatinib mesylate	0	7	II	1 (14%) PR
Fox et al, Clin Cancer Res, 14 (4): 1111-5 [47]	2008	Tubulin Inhibitor (ABT-751)	3	3	I	0% OR
Jakacki et al, J Clin Oncol, 26 (30): 4921-7 [48]	2008	Erlotinib, Temozolomide	1	0	I	1 (2%) SD
Langevin et al, Pediatr Blood Cancer, 50 (3): 577-80 [49]	2008	Rebeccamycin	16	14	II	% OR
Mita et al, J Clin Oncol, 26 (3): 361-7 [50]	2008	Deforolimus	1	1	I	4 (13%) PR, 18 (56%) SD
Olmos et al, ASCO abstract	2008	Figitumumab	0	9	I	1 (5%) PR, 6 (27%) SD
Chawla et al, Mol Ther, 17 (9): 1651-7 [51]	2009	Rexin-G	3	1	I/II	13 (65%) SD
Chugh et al, J Clin Oncol, 27 (19): 3148-53 [52]	2009	Imatinib	27	13	II	1 (0.5%) CR, 3 (2%) PR
Malempati et al, ASCO abstract	2009	Cixutumumab	Not mentioned	10	I	1 (4%) PR
Patel et al, ASCO abstract	2009	IGF-1R antibody (R1507)	43	71	II	Not mentioned
Widemann et al, J Clin Oncol, 27 (4): 550-6 [53]	2009	Ixabepilone	3	2	I	4 (21%) SD
Jacobs et al, Clin Cancer Res, 16 (2): 750-4 [54]	2010	Ixabepilone	11	9	II	0% OR
Kurzrock et al, Clin Cancer Res, 16 (8): 2458-65 [55]	2010	IGF-1R antibody (R1507)	0	9	I	2 (5%) PR, 13 (35%) SD
Olmos et al, Lancet Oncol, 11: 129-35 [56]	2010	Figitumumab	0	16	I	1 (3%) CR, 1 (3%) PR, 8 (28%) SD

Abbreviations: CIR = Clinical Response; CR = Complete Response; Cyclo = cyclophosphamide; Doxo = doxorubicin; EFS = Event Free Survival; Etop = etoposide; Ewing = Ewing Sarcoma; Ifos = ifosfamide; No = number; OR = Objective Response; Osteo = Osteosarcoma; PR = Partial Response; RR = Response Rate; SCR = Stem Cell Rescue; SD = Stable Disease; TMR = Total Marrow Radiation; Vin = vincristine

Table 3 Characteristics of eligible trials for osteosarcoma only

Author	Year	Intervention	Phase	No of Patients	Outcome
Salesh RA, et al. <i>Cancer</i> 65:861-5. [56]	1990	Etoposide 72-h i.v 600 mg/m ² . Cyclophosphamide 300 mg/m ² every 12 hours for a total dose of 1800 mg/m ² .	II	17	15 (88%) CR or PR
Kleinerman ES, et al <i>J. Clin. Oncol.</i> 10, 1310-6. [57]	1992	L-MTP-PE 2 mg/m ² infused during a 1-h period twice a wk for 12 wks, then once a wk for 12 wks.	II	16	Not mentioned
Kleinerman ES, et al <i>Am J Clin Oncol.</i> 18(2):93-9. [58]	1995	L-MTP-PE, 2 mg/m ² , i.v over a 1-h twice a wk for 12 wks in 12 pts (Group 1). 16 pts (Group 2) had 2 mg/m ² L-MTP-PE twice a wk for 12 wks, then once a wk for 12 wks, for a total of 24 wks.	II	36	2 (6%) SD
Kleinerman ES, et al <i>J. Immunother. Emphasis Tumor Immunol.</i> , 17, 181-93. [59]	1995	IFO 1.8 g/m ² for 5 days every 21 days for up to 8 cycles. L-MTP-PE twice weekly for 12 weeks, then once weekly for 12 weeks	IIb	9	Not mentioned
Harris MB, et al <i>Med Ped Oncol</i> 24, 87-92. [60]	1995	Two courses of ifosfamide (2400 mg/m ² × 5 days) administered 3 wks apart	II	33	Stratum 1: 1 (11%) CR, 8 (24%) PR Stratum 2: 1 (3%) CR, 2 (7%) PR
Patel SR, et al <i>Cancer</i> ; 78:741-4. [61]	1996	Paclitaxel 175 mg/m ² 24-h i.v	II	15	0% OR
Gentet JC, et al <i>Eur J Cancer</i> , Vol. 33, No. 2, 232-7 [62]	1997	Two courses of IFO 3 g/m ² /day and etoposide 75 mg/m ² /day for 4 days.	II	27	6 (23%) CR, 7 (25%) PR, 5 (23%) SD
Worth LL, et al <i>Clin Cancer Res.</i> 3 (10):1721-9. [63]	1997	IL-1alpha followed by ICE daily for 5 days/3 wks.	II	9	3 (34%) PR, 1 (11%) SD
Voûte PA, et al <i>Annals of Oncology</i> 10: 1211-8. [64]	1999	IFO 3 g/m ² /dl-2, DOX 25 mg/m ² /dl-3 i.v. bolus and CDDP 100 mg/m ² /dl.	II	103	5 year survival was 62% in limb-non-metastatic, 41% in axial skeletal and 16% in limb metastatic patients.
Fagioli F, et al <i>Journal of Clinical Oncology</i> , Vol 20, Issue 8:2150-6 [65]	2002	High-dose chemotherapy consisted of carboplatin and etoposide followed by stem-cell rescue.	I	32	25 (78%) CR, 6 (19%) PD, 3 year OS 20% 3 year DFS 12%
Laverdiere C, et al <i>Cancer</i> ; 98:832-40. [66]	2003	Trabectedin 1500 micro g/m ² as a 24-h i.v every 3 wks.	II	25	0% OR
McTiernan A, et al. <i>Sarcoma</i> , Vol. 8, No. 2/3, 71-6. [67]	2004	Docetaxel 100 mg/m ² 1-h i.v every 3 wks	II	14	1 (7%) PR, 2 (14%) SD

Table 3 Characteristics of eligible trials for osteosarcoma only (Continued)

Ferrari S et al J Clin Oncol 23:8845-52. [68]	2005	Two blocks of high-dose IFO (15 g/m ²), MTX (12 g/m ²), CDDP (120 m g/m ²), and DOX (75 m g/m ²)	II	182	5-year EFS 64% and OS 77%
Arpaci F, et al Cancer; 104:1058-65. [69]	2005	2 cycles of CDDP, DOX, and IFO followed by HDC and APBSCT.	II	22	3 year: OS was 83% & 70% DFS
McTiernan A, et al Pediatr Blood Cancer. 46(3):345-50. [70]	2006	IFO 2.5 g/m ² etoposide 150 mg/m ² and DOX 20 mg/m ² on days 1-3, every 21 days, with interval MTX 12 g/m ² given on day 14, for a maximum of 8 cycles.	I/II	13	0% OR
Seibel NL, et al Cancer 2007; 109:1646-53. [71]	2007	Topotecan daily x5 followed by chemotherapy (IFO, carboplatin, ICE, alternating with CDDP and CD.	I	28	1 (6.6%) PR, 1 (6.6%) CLR 2- and 5-year EFS rates 7% & 4%, resp, 2- and 5-year OS rates 44% and 22%, resp.
Basaran M, et al Oncology;72:255-60 [72]	2007	Epirubicin 90 mg/m ² cisplatin 100 mg/m ² on day 1 and IFO 2.0 g/m ² day with an equivalent dose of mesna on days 2-4, repeated every 21 days	II	38	10 (26%) CR, 5 year DFS 41.9%, OS 48.2%.
Iwamoto Y, et al J Orthop Sci 14:397-04. [73]	2009	Preoperative chemotherapy: HD-MTX, CDDP, and ADR.	II	113	5 year OS 77.9% 5 year EFS 65.5%
Berger M, et al Cancer 115: 2980-7. [74]	2009	Cyclophosphamide 4 g/m ² on Day 1 followed by etoposide at 200 mg/m ² on Days 2, 3, and 4.	II	26	9 (35%) SD, OS at 1 yr 50%, PFS 42%
Chawla S P, et al Mol Ther. 17:1651-7. [51]	2009	Escalating doses of Rixin-G i.v from 8 × 10 ¹¹ to 24 × 10 ¹¹ colony forming units (cfu)/ cycle.	II I/II	Osteo = 10 (58.8%) SD 22 3 (50%) SD(lowest dose) Sar = 20 10 (71%) SD(higher dose) Osteo = 0	

Abbreviations- ADR = adriamycin; APBSCT = autologous peripheral blood stem cell support transplantation; CDDP = cisplatin; Cfu = colony forming units; CR = complete response; DOX = doxorubicin; EFS = event free survival; GCSF = Granulocyte colony-stimulating factor; HD-MTX = High-dose Methotrexate; ICE = etoposide; IFO = ifosfamide; IL-6 = interleukin -6; IL-8 = interleukin-8; L-MTP-PE = liposomal muramyl tripeptide phosphatidyl ethanolamine; MTX = methotrexate; OR = objective response; PD = progressive disease; PFS = progression free survival; OS = overall survival; RDI = relative dose intensity; resp = respectively; Sar = sarcoma; TNF = tumour necrosis factor

Table 4 Characteristics of eligible trials for Ewing sarcoma only

Author	Year	Intervention	Phase	No of Patients	Outcome
Hawkins et al, <i>Med Pediatric Oncol</i> , 34 (5): 328-37 [33]	2000	Myeloablative therapy followed by HSCT.	I	16	3-year EFS 36%
Kolb et al, <i>J Clin Oncol</i> , 21 (18): 3423-30 [75]	2003	7 cycles of chemotherapy consisted of Cyclo, Doxo, Vin, Ifos and Etop	II	68	29 (43%) CR, 13 (19%) PD or SD
Meyer et al, <i>Sarcoma</i> , 7 (1): 13-7 [76]	2003	Doc thrice weekly for a maximum of six cycles.	II	14	1 (14%) PR, 2 (28%) SD
Bernstein et al, <i>J Clin Oncol</i> , 24 (1): 152-9 [77]	2006	High-dose induction therapy followed by window period. Randomization between topo, topo + cyclo or no treatment. No window treatment patients received Amifostine	II	117	45 (43%) CR, 41 (39%) PR, 14 (14%) SD
Womer et al, ASCO abstract	2008	Vin, Doxo and Cyclo alternating with Ifos and Etop, for 14 cycles. Regimen A: 3 weeks cycle, regimen B: 2 week cycle. Primary tumor treatment was scheduled to begin week 13.	II	587	EFS at a median of 3 years was 65% in Regimen A and 76% in Regimen B.
Rosenthal et al, <i>Bone Marrow Transplantation</i> , 42: 311-8 [78]	2008	HDT followed by HSCT.	I	22	3-year EFS 47%, 3-year OS 45%
DuBois et al, <i>Pediatric Blood Cancer</i> , 52 (3): 324-7 [79]	2009	Cytarabine.	II	10	1 (10%) SD
Casey et al, <i>Pediatric Blood Cancer</i> , 53 (6): 1029-34 [80]	2009	Irinotecan and Temozolomide.	II	20	5 (25%) CR, 7 (36%) PR
Olmos et al, <i>Lancet Oncol</i> , 11: 129-35 [56]	2010	A subgroup of Ewing Sarcoma patients were treated with Figitumumab	I	15	1 (6%) CR, 1 (6%) PR, 6 (37%) SD

Abbreviations: CR = complete response; Cyclo = cyclophosphamide; Doc = docetaxel; Doxo = doxorubicine; EFS = event free survival; Etop = etoposide; G-CSF = granulocyte-colony stimulating factor; HDT = high-dose chemotherapy; HSCT = hematopoietic stem cell transplantation; Ifos = ifosfamide; OR = overall response; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease; Topo = topotecan; Vin = vincristine

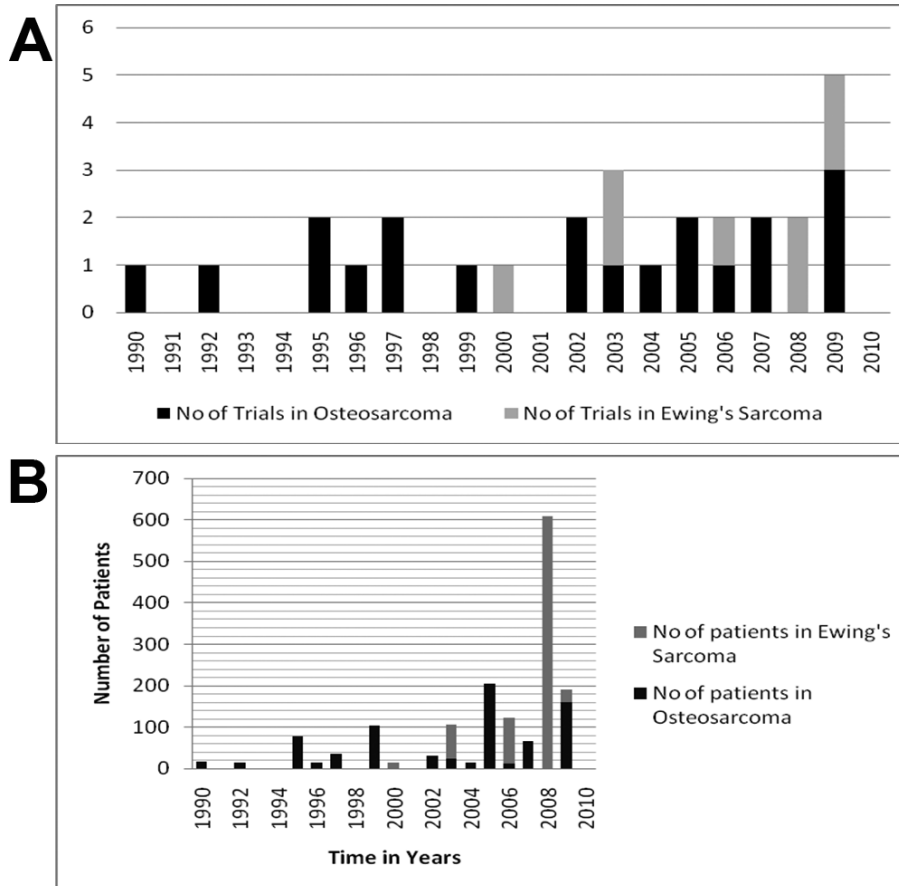


Figure 2 Distribution of the number of trials published that have recruited either osteosarcoma or Ewing sarcoma patients between 1990-2010 (A). The total number of either osteosarcoma or Ewing Sarcoma patients entered in phase I/II trials published between 1990-2010 (B).

portfolio. The decision was not as a result of safety concerns. Both this study, and a Phase I/II with figitumumab (Pfizer) have been published since completing this survey, and show low but durable response rates in a subset of relapsed Ewing patients (10-20%) [17,18].

Bone sarcoma is fatal in approximately one third of the children and young adults in whom it is diagnosed. This mortality rate has not changed greatly in the two decades since the initial introduction of surgery and chemotherapy. The primary cause of death in treated

Table 5 Ongoing phase I or II trials in osteosarcoma (Assessed from www.ClinicalTrials.gov)

ClinicalTrials.gov Identifier	Sponsors	Title	Status
NCT00102531	Transave	Phase Ib/Ia non-randomised study of SLIT Cisplatin by inhalation in the treatment of patients with relapsed/progressive osteosarcoma metastatic to the lung	Recruiting
NCT01002092	Shandong Simcere-Medgenn Bio-pharmaceutical Co., Ltd	A randomized, controlled multicenter trial of Endostar combined with chemotherapy for treatment of osteosarcoma (phase II)	Recruiting
NCT00889057	Italian Sarcoma Group	Phase II, open label, non-randomized study of second or third line treatment with Sorafenib (BAY 43-9006) in patients affected by relapsed high-grade osteosarcoma	Recruiting
NCT00752206 NCT00923286	Sarcoma Alliance for Research through Collaboration (SARC)	A randomized, double-blinded, placebo-controlled, multi-institutional, phase II study of AZD0530, a selective Src kinase inhibitor, in patients with recurrent osteosarcoma localized to the lung	Recruiting
NCT01005043	University of Heidelberg	Phase I/II therapy non-randomised trial to determine the safety and efficacy of heavy ion radiotherapy in patients with osteosarcoma	Not yet recruiting
NCT00902044	Baylor College of Medicine	Administration of Her2 Chimeric antigen receptor expressing T Cells for subjects with advanced osteosarcoma (HEROS) (phase I)	Not yet recruiting

patients is recurrent metastatic disease often to the lung. In the group of patients who present either with metastatic or relapsed disease, it is especially important to conduct biologically based trials with small groups of patients from which quantitative and quick answers of whether a treatment intervention is either working or not can be obtained. Importantly, tumour material obtained may provide informative clues for future studies especially if analysed with genomic technologies.

It is difficult to do trials in an orphan disease, mainly because of the problems of recruiting enough eligible patients for the trial. In our literature search, we identified 42 phase I/II trials for sarcoma patients which were published between 1990 and 2010. However the phase I trials for general sarcoma (Table 1) are not complete, this is because of our search criteria. With a PubMed search you only search the abstract of the article, so if sarcoma is not mentioned there we didn't find the article. In phase I trials quite a few different tumour types are sometimes enrolled and only the one who show results are mentioned in the abstract. Some of these articles we found in the Cochrane Controlled Trial Register or the ClinicalTrials.gov database, but not all trials are registered in these databases. Except with a very wide PubMed search using (phase 1) as only search criteria we don't think that it is possible to find all phase I trials enrolling sarcoma patients.

Of the trials we did find with our search criteria twenty-one were phase I, two phase I/II and nineteen phase II trials. Only eight clinical trials included only Ewing sarcoma patients; of this group two were phase I and six were phase II trials. We found only twenty trials which included only osteosarcoma patients. There were two phase I, sixteen phase II, and two phase I/II trials. A total of 3,736 patients were included in the clinical trials, of which 1,263 were Ewing sarcoma and 1,114 were osteosarcoma patients. From the identified trials, the results are not convincing for benefit and most of the time even disappointing, from osteosarcoma trials we found 8% CR, 2.8% PR and 4% SD. For Ewing sarcoma the results are 9.5% CR, 7.5% PR and 3% SD. And if the drugs seem to be effective, a lot of toxicity is reported (Tables 1, 2, 3, 4). Looking at the number of trials we found for sarcoma patients, the results seem encouraging as a high number of patients were included. However, if we make a calculation of the number of new Ewing sarcoma patients expected in the last twenty years, assuming a world population of five billion and an incidence of 2 in 1,000,000, approximately 200,000 new cases would be expected in twenty years worldwide. Of these patients, we could only find 1,263 reported and included in published clinical trials. For osteosarcoma the number is even worse, with 500,000

new cases expected in twenty years and only 1,114 reported in trials.

To improve these results changes in conducting trials for orphan state diseases have to be made. It is important to collaborate between nations; the Sarcoma Alliance for Research through Collaboration (SARC) is a good example based principally in North America. SARC is a non-profit organization started in 2003. Funding is provided by generous donations, sponsors and grants. SARC works with healthcare professionals as part of a collaborative multidisciplinary team from over 35 institutions in the USA. It works with a number of international institutions and provides the infrastructure for collaboration between physicians, researchers, and medical institutions from across the worlds who are engaged in clinical research for development of new standards of sarcoma patient treatment, education, and prevention. This organization facilitates dialogue and collaboration among sarcoma researchers and clinicians, assists in the development and dissemination of protocols for clinical trials and information relating to sarcoma research and the results of clinical trials, administers research grants and funding for clinical trials, and acts as a primary resource for those treating patients with sarcoma. The EORTC Soft Tissue and Bone Sarcoma Group is one of SARC's European counterpart, conducting multicenter academic studies in sarcoma, including some early stage translational studies, although it's main contribution in the past has been in the field of larger phase III trials soft tissue sarcoma. The European Osteosarcoma Intergroup, EURAMOS and EuroEwing consortium are examples of groups acting primarily as platforms for phase III studies in bone sarcomas.

The EC-granted European network, EuroBoNeT <http://www.eurobonet.eu>, was the first central organized network of excellence for integrated bone sarcoma research and staff exchange, in order to increase and disseminate knowledge of primary bone tumours at the molecular level for development of new tools for patient care. This integration, exchange of material (virtual Bio-Bank), standard operating protocols and the use of technology platforms enabled researchers to obtain statistically significant datasets, otherwise not achievable due to the rareness of the condition and the large number of sub-entities. Without these kinds of collaborations, the development of new treatment strategies in osteosarcoma and Ewing sarcoma is going to be very difficult. But perhaps most importantly is that phase I/II clinical trials have to be conducted. To achieve this funding needs to be established from industry and governments to feed through these collaborative structures over time frames that might result in enduring progress.

Recent progress has also been made with the FP7 funding of EuroSarc, European trials in rare sarcomas within an integrated translational trial network (2011-2016). In this new translational trial network, the challenges of combining high quality disease research into clinical trials in being addressed, and progresses the field beyond conventional trials and the existing clinical trial networks.

In addition to the challenge of identifying the most promising agents for clinical trials in bone sarcoma, obstacles inherent to this disease further complicate the successful design and completion of trials of novel agents. In evaluating the efficacy of novel agents, the standard approach is to use objective response criteria, such as Response Evaluation Criteria in Solid Tumours (RECIST) [19], to compare the size and/or volume of lesions pre-treatment and at regular intervals during and post-treatment. New methods for tumour response which may be more precise are radiological response based on new criteria, e.g. ¹⁸FDG-PET-CT and contrast enhanced MRI. For a patient to be eligible for a trial using this approach, he or she must have measurable disease. The traditional approach for patients with relapsed bone sarcoma, in particular pulmonary relapse, has been surgical resection, which at least temporarily renders a patient free of radiographic measurable disease and thus, ineligible for most trials of novel agents. Unfortunately novel targeted therapies may be most effective in the setting of minimal residual disease. The use of creative surrogate end points to estimate response and perhaps render the combination of surgical resection and treatment on trials of new agents not mutually exclusive would allow for better evaluation of new therapies in patients with bone sarcoma [20].

When conducting the literature search we found that the results of many trials are not published. We can only guess what the reason for this is, but it seems logical that the trial results were disappointing. From the phase I/II trials only a very limited number of treatments proceeded to phase III trial. For Ewing sarcoma we found three clinical trials conducted in the last twenty years and two trials which are being recruiting at this moment and for osteosarcoma we found twenty-two phase III clinical trials and four active trials currently recruiting patients and one is ongoing trial but not recruiting.

Most of the phase I/II trials that have been conducted recruited patients with general sarcoma or solid tumours. In these trials it is very difficult to say anything about disease specific response and it is therefore almost impossible to translate the results to clinical practise and patients with a specific sort of cancer. Of course it is understandable why researchers test a drug in

different patient populations in the same trial, especially in rare cancers like bone sarcoma, but it makes it more difficult to proceed to a disease specific phase II or even phase III trial.

While the current standard of care continues to be multi-agent chemotherapy and surgical resection, it is clear that further intensification of traditional chemotherapy regimens is limited by toxicity, and new approaches are needed. Some promising novel agents are currently in or are entering into phase II trials in children with relapsed bone sarcoma. For example, Muramyl Tripeptide Phosphatidylethanolamine (MTP-PE) is the first drug to be approved for osteosarcoma in Europe for ten years [21]. In Ewing sarcoma the identification of the Insulin-like Growth Factor 1 Receptor (IGF1R) pathway deregulation, as a consequence of the EWS-FLI1 translocation seems to be a new treatment strategy to be explored. The incorporation of these new treatments into the up-front therapy for bone sarcoma in the near future holds promise for improving outcomes.

Lists of abbreviations

EMA: European Medicines (Evaluation) Agency; EFS: Event free survival; IGF1R: Insulin-like Growth Factor 1 Receptor; MTP-PE: Muramyl Tripeptide Phosphatidylethanolamine; OS: Overall survival; PET: Positron emission tomography; PFS: Progression free survival; RECIST: Response Evaluation Criteria in Solid Tumours; SARC: Sarcoma Alliance for Research through Collaboration network.

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Author details

¹Department of Oncology, Oxford Cancer and Haematology Centre, Churchill Hospital, University of Oxford, Oxford OX3 7LJ, UK. ²Sir William Dunn School of Pathology, South Parks Road, University of Oxford, Oxford OX1 3RE, UK. ³Department of Clinical Oncology, Leiden University Medical Center, Leiden, PO Box 9600, 2600 RC Leiden, The Netherlands. ⁴Department of Pathology, Leiden University Medical Center, Leiden, PO Box 9600, 2600 RC Leiden, The Netherlands.

Authors' contributions

ABH conceived the study. AVM and AP collected data with ABH. Data extraction was conducted independently by two authors (AB and AVM). Differences in data extraction were resolved by consensus with a third author (ABH). AVM and ABH wrote the paper and AP, PC and AG made comments. All authors have read and approved the final manuscript.

Competing interests

All authors have read and approved the final manuscript, and have no competing financial interests in the publication of this manuscript. No organisation is funding or implicated in the manuscripts analysis and interpretation. Academic interests of the authors are to improve the

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