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Review

Chemotherapeutic adjuvant treatment for osteosarcoma: Where do we stand?

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ABSTRACT

Aim: Since the introduction of chemotherapy, survival in localised high-grade osteosarcoma has improved considerably. However, there is still no worldwide consensus on a standard chemotherapy approach. In this systematic review evidence for effectiveness of each single drug and the role of response guided salvage treatment of adjuvant chemotherapy are addressed, whereas in a meta-analysis the number of drugs in current protocols is considered.

Methods: A systematic literature search for clinical studies in localised high-grade osteosarcoma was undertaken, including both randomised and non-randomised trials. Historical clinical studies from the pre-chemotherapy era were included for comparison purposes.

Results: Nine historical studies showed a long-term survival of 16% after only local treatment. Fifty single agent phase II studies showed high response rates for adriamycin (A, 43%), ifosfamide (Ifo, 33%), methotrexate (M, 32%), cisplatin (P, 26%) but only 4% for etposide (E). In 19 neo-adjuvant studies the mean 5-year event free survival (EFS) was 48% for 2-drug regimens and 58% for $\geqslant$3 drug regimens, with a 5-year overall survival (OAS) of 62% and 70%, respectively. Meta-analysis showed that $\geqslant$3 drug regimens including methotrexate plus adriamycin plus cisplatin (plus ifosfamide) (MAP(Ifo)) had significant better outcome (EFS: HR = 0.701 (95% confidence interval [95% CI]: 0.615–0.799); OAS: HR = 0.792 (95% CI:

Abbreviations: A, adriamycin, doxorubicin; M, methotrexate; Ifo, ifosfamide; P, cisplatin; E, etoposide; MAP(Ifo), methotrexate plus adriamycin plus cisplatin (plus ifosfamide); BCD, bleomycin, cyclofosfamide and actinomycin-D; MTP, liposomal muramyl tripeptide fosfatidylethanolamine or mifamurtide; OSS, high-grade osteosarcoma; CR, complete remission; PR, partial remission; RR, response rate (CR + PR); COSS, Cooperative Osteosarcoma Studygroup; IOR, Istituto Ortopedico Rizzoli; IOR/OS, Istituto Ortopedico Rizzoli Osteosarcoma Study; SSG, Scandinavian Sarcoma Group; EOI, European Osteosarcoma Intergroup; FU, follow-up; OAS, overall survival; EFS, event free survival; pGR, pathologic good response; pPR, pathologic poor respon.

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0.677–0.926) than 2-drug regimens, but there was no significant difference between MAP and MAPIfo (or plus etoposide). Salvage of poor responders by changing drugs, or intensifying treatment postoperatively has not proven to be useful in this analysis.
Conclusion: Meta-analysis in patients with localised high-grade osteosarcoma shows that 3-drug regimens, for example MAP are the most efficacious drug regimens.

1. Introduction

High-grade osteosarcoma (OSS) is the most frequent primary malignant bone tumour[1] and occurs predominantly during puberty with a second peak in the elderly.[2–4] The annual incidence rate is on average 4.4 per 10^6 people aged 0–24 years, 1.7 per 10^6 people aged 25–59 years and 4.2 per 10^6 in people $\geqslant$60 years. OSS typically is a tumour of the extremities: 78% is localised in the lower extremity, with 64% around the knee and 10% localised in the humerus.[5–10] Long term survival in localised OSS has increased substantially from 10–20% when surgery as single treatment was given before the 1980's up to 50–60% from 1985 onwards. However, since then no substantial further improvement of survival is observed[4,11–16] (Fig. 1). Children have a 5–10% better survival rate than patients up to 50 years, while patients older than 60 years have a survival rate of only 24%.[4–16] The improvement in survival has been attributed to the use of intensive multi-agent chemotherapy given in combination with advanced surgery. In modern treatment schedules, usually a combination of doxorubicine (adriamycin (A)) and cisplatin (P), with or without high-dose methotrexate (M) and/or ifosfamide (Ifo) and/or etoposide (E) are being used.

Our aim is to address several questions. What is the evidence for the effectiveness of each of these drugs as single agent? How many drugs should at least be given to accomplish the most effective treatment regimen? What is the value of increased dose intensity or salvage treatment after a poor pathological response on preoperative chemotherapy?

Due to the presence of heterogeneous studies including the design, regimen, follow-up or definitions of histological response, a random effects meta-analysis was employed on a number of selected studies.[17] The ultimate goal of the analysis was to define the most efficacious treatment in localised OSS.

2. Materials and methods

2.1. Literature search strategy

To assess the efficacy of the different chemotherapy regimens a Pubmed and EMBASE search was performed in January 2010, with osteosarcoma, osteogenic sarcoma, bone sarcoma and the drug names methotrexate, doxorubicin, adriamycin, cisplatin, ifosfamide and etoposide as search terms. Only papers in the English language were accepted for this review. Letters, abstracts or review papers were not included for reason of incomplete data of the studies or follow-up or duplication (Fig. 2). If reports were published more than once on the same patient population, the most mature data were used.

Phase II studies on the aforementioned 5 drugs were included. For the historical pre-chemotherapy era studies additional studies were retrieved from the references. Only studies with an appropriate definition of OSS and non-metastatic stage were used. Phase III studies of patients with localised disease only, were selected to have included at least 50 patients and with at least 5 years of follow-up. For the included studies, the following data were collected: study period, patient number and characteristics, chemotherapeutic regimens (drugs, dose, frequency) as well as type of surgery, histological response, duration of follow-up (FU), event free (EFS) and overall survival (OAS).

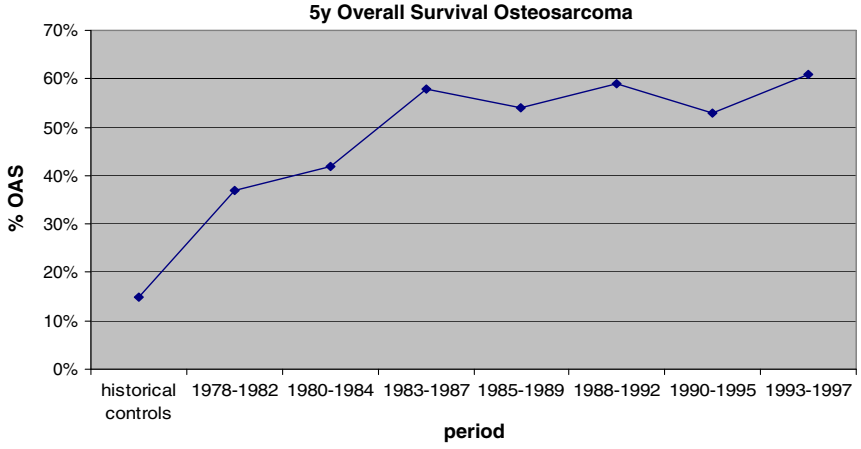

Fig. 1 – Reported 5y-overall survival (% OAS) during subsequent periods. Data from Magnani (*n*=3502).[14] and Stiller (*n* = 1324).[15] Overall survival since 1970, when chemotherapy was introduced in addition to surgery (historical controls). This curve demonstrates clearly that OAS reaches a plateau phase from 1985 onwards.

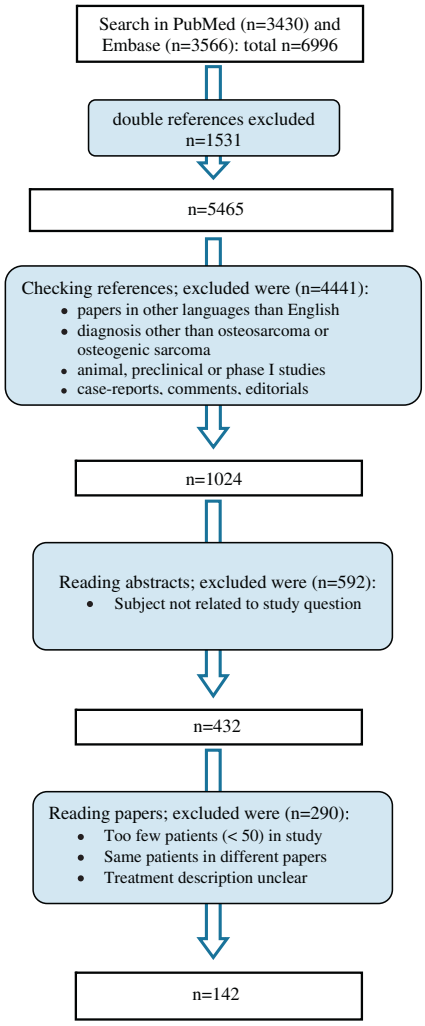

Fig. 2 – Search strategy for papers in this review.

2.2. *Definition of results and outcome*

Histological response was defined according to the proportion of viable tumour cells after induction chemotherapy: good pathological response (pGR) was defined if <10% is viable and poor pathological response (pPR) if ⩾10% of the tumour cells is viable. Response rate, event free survival (EFS) and overall survival (OAS) were taken from the original publications. In phase II studies, a drug was considered effective when the response rate was ⩾20%.

2.3. *Statistical analysis: meta-analysis*

The meta-analysis performed here is based on a new methodology for pairs of survival curves under heterogeneity and cannot be casted in the classical meta-analysis where the well-known forest plot is used to illustrate the results of the meta-analysis. A multivariate random-effects model for a joint analysis of survival proportions reported at different times in the different studies has been used in this manuscript in order to be able to use all information available in each paper included in the meta-analysis. For each study included in the meta-analysis where the same two treatments are compared, published EFS and OAS at a predetermined set of time points during follow-up and accrual information are known. Data in each study consist of disease free survival and overall survival probabilities every 6 months for the first 5 years after treatment. Two separate meta-analyses are performed. First the survival rates of patients who received a 2-drug regimen are compared with those who received a 3-drug regimen. Then the survival rates of patients, treated with 3-drug versus 4-drugs were compared. The techniques described by Parmar[18] and Fiocco[19] were used to reconstruct the number of patients at risk, the number of deaths and the number of censored patients during the time intervals in each arm and each trial. Using these aggregate data, the treatment effect and the overall survival curves for the two arms were estimated by applying a Poisson correlated gamma frailty model as described in Fiocco.[17] Using this model, we were able to incorporate also studies with only one arm, while the traditional approach can be applied only when information concerning both treatment arms are given. This adds more efficiency to the results based on the statistical model.

3. Results

3.1. *Pre-chemotherapy era studies*

Nine historical studies were retrieved from 43 papers on treatment of localised OSS before the chemotherapy era (Table 1).

Long term survival of the combined 1555 patients after local tumour control without chemotherapy was 16% (9–23%). The typical course of the disease in these patients is reflected by the pattern of metastases, with 85% of patients developing pulmonary metastases, half of these within 6–8 months after local treatment (Fig. 3). With (neo) adjuvant chemotherapy, survival was higher, time to metastases was on average 1.5–2× longer, less pulmonary metastases but more extra-pulmonary metastases were observed compared with the historical group.[14,20–26]

3.2. *Single drug phase II studies*

In order to get evidence for responsiveness of drugs, which are commonly used in OSS, phase II studies of M, A, P, Ifo and E as single drugs in pre-treated, relapsed or refractory patients were retrieved from literature. Among 140 papers, 50 were selected for this review (Table 2). Patients, entered in these studies, had relapsed or refractory disease. The data from studies showed high response rates of 43% for A, 33% for Ifo, 32% for M and 26% for P, all well above the predefined 20% threshold. E was included because some modern trials included this drug. However, E had a response rate of only 4%.

4. Description of neo-adjuvant chemotherapy studies

4.1. *American OSS studies (Table 3)*

4.1.1. *Memorial Sloan Kettering Cancer Center (MSKKC)*

The first neoadjuvant (Rosen's) T-5 protocol enabled limb salvage after shrinkage of the tumour by pre-operative MA.[83] The M-dose was escalated when no clinical or biochemical

Table 1 – Selected studies from treatment of localised osteosarcoma patients before the chemotherapy era. Nine papers with the total of 1555 patients with surgery or/and radiotherapy and follow-up of at least 5 year or more were selected out of more than 40 papers.

Institute	Study-period	Number of patients	Overall survival ⩾5 year (%)	References
Karolinska Hospital Sweden	<1956	86	17	[27]
Westminster Hospital London	1951–1962	92	22	[28]
MSKCC New York	1949–1966	145	17	[29]
Mayo Clinics Rochester	1900–1966	465	18	[30]
Radium Hospital Oslo	1938–1964	102	18	[31]
Bristol Bone Tumour Register	1946–1972	149	17	[32]
Rizzoli Bologna	1959–1979	127	10	[21]
MD Anderson Cancer Center	1950–1974	213	9	[6]
Netherlands Bone Tumour Registry	1962–1969	176	23	[7]

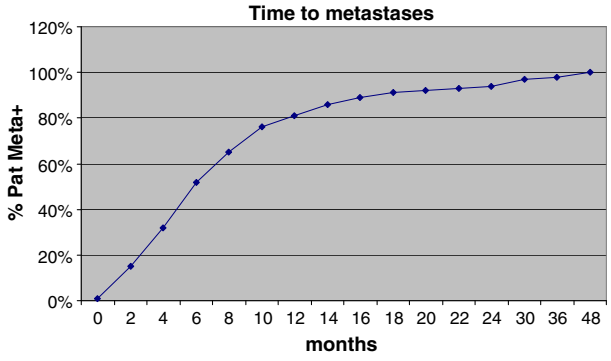

Fig. 3 – Pattern of clinical detectable metastases in patients with local treatment only (historical data). In 80–90% of all patients with OSS metastases develop in the lungs, other bones and rarely in lymph nodes and other organs. Half of the metastases develop between 6 and 8 months after local therapy, 75–90% occur within 1 year, and after 2–2.5 year the curve of development of metastases flattens.

response were present[84] and based on the excellent results after 2 years, chemotherapy was further intensified in T-7[84,85] and T-10[86] by giving M at weekly intervals and replacement of cyclophosphamide by bleomycin, cyclofosfamide and actinomycin-D (BCD). To salvage pPR in the T-10 protocol, drugs post-operatively differed from those used preoperatively.[86,87] The response rate in T-10 was lower than in the previous trial, due to early planning of surgery, but the EFS was similar as in T-7.[88] In the last randomised study (T-12), a higher response rate in the more intensified arm resulted in a similar EFS (78%) to the control arm (73%) and to the previous (T-10) trial.[89] Again, despite an increased response rate, no improvement in EFS was achieved.

4.1.2. *MD Anderson Cancer Center*

In three subsequent studies (TIOS I–III), the response of preoperative chemotherapy was used to design postoperative treatment in 98 patients.[90] Sixty seven patients were treated with M,A and P containing regimens, depending on the response on preoperative chemotherapy, but 31 patients refused surgery and were treated with chemotherapy only. These patients had a significant lower 5y-EFS (23%) compared to those who were treated with surgery and chemotherapy (5y-EFS 62%),[90,91] confirming that patients with localised OSS cannot be treated with chemotherapy alone.[91] Intra-arterial P was more effective than M in a subgroup of these patients.[90,92]

4.1.3. *Children's Cancer Group CCG782*

The objectives of CCG-782 were to improve EFS compared to the adjuvant protocol CCG 741 and to evaluate the value of a grading system for histological response, using a T-10 based regimen.[93,94] Although the outcome was significantly better than in CCG 741, the response rate and survival were lower than in Rosen's T-10 study.[86] However, because CCG-741 was less intensive, the conclusion that the neo-adjuvant approach was better than adjuvant chemotherapy could not be generalised. pPR was a significant higher risk for an adverse event than pGR (relative risk 0.23, $p < 0.0001$).

Table 2 – Drugs with a response rate (CR plus PR) of ⩾20%. Etoposide is included to demonstrate the response rate in a small number of studies.

Drug	Dose range (mg/m^2/course)	Number of patients	Number responding patients		Response rate (%)	References
			Complete remission (CR)	Partial remission (PR)		
Adriamycin	35–90	108	14	32	43	[33–44]
Ifosfamide	5.000–15.000	246	30	50	33	[45–59]
Methotrexate	80–15.000	164	26	26	32	[60–70]
Cisplatin	60–150	174	18	28	26	[69,71–78]
Etoposide	120–625	27	0	1	4	[79–82]

Table 3 – American OSS groups. In this table are included only studies with more than 50 patients (for drug names see list of abbreviations). BOTG: Brazilian Osteosarcoma Treatment Group. In addition: Ctx: Cyclophosphamide, Vc: Vincristin, Epi: Epirubicin, Ca: Carboplatin. LR and HR represent low risk (patients without HR criteria) and high risk (patients requiring an amputation or tumours >12 cm), respectively.

Study period	Number of patients	Drug regimen		GR (%)	EFS (%)	OAS (%)
		Pre-operative	Post-operative			
MSKCC T10 1978–1981	153	M_{x4}	*pGR*:$[M_{x4} + A + BCD]_{x4}$; *pPR*: $M_{x4} + A + BCD + [AP_{x2} - BCD]_{x3}$	34	77^{3y}	82^{3y}
MSKCC T12	Pilot ($n = 51$)	$M_{x6} + BCD_{x2}$	*GR*:M-BCD; *PR*:AP_{x6}	41	75^{2y}	76^{2y}
1986–1993	MBCD ($n = 26$)	$M_{x4} + BCD$	*pGR*:$[M_{x2} + A + BCD]_{x4}$; *pPR*:$[M_{x2} + AP + BCD]_{x2} + [AP_{x2} + BCD]_{x2}$	39	73^{5y}	78^{5y}
	MAPBCD($n = 26$)	$M_{x2} + AP_{x2} + BCD$	*All*: $[M_{x2} + A + BCD]_{x3} + BCD$	44	67^{5y}	73^{5y}
MD-Anderson	65	All		43	62^{5y}	–
1979–1989	TIOS-1 TIOS-3	M_{x12} versus P_{iartx7} P_{iartx7}	Resp: MAP_{x6}; non-Resp: MA or MAP A_{450} or A_{450} – Cycl or A_{450} – VAC			
CCG 782 1983–1986	231	$M_{x4} + BCD$	*pGR*:$[M_{x4} + A + BCD]_{x4}$; *pPR*: $M_{x4} + ABCD + [AP_{x2} - BCD]x3$	28	53^{8y}	60^{8y}
POG 8651	100	ALL			65^{5y}	78^{5y}
1986–1993	*neoadjuvant* ($n = 45$)	$M_{x4} + AP_{x2}$	$M_{x8} + A + AP_{x2} + BCD_{x5}$	62	61	76
	adjuvant ($n = 55$)	–	$M_{x12} + A + AP_{x4} + A + BCD_{x5}$		69	79
SWOG 9139 1992–1996	63	$AP_{x2} + AI_{x2}$	$AP_{x2} + AI_{x2}$	48	41^{5y}	58^{5y}
INT 0133	677	ALL		45	64^{6y}	74^{6y}
1993–1997	MAP ($n = 340$)	$M_{x4}AP_{x2}$	$M_{x8} + AP_{x2} + A_{x2} \pm$ L-MTP	43	63	73
	MAPIfo ($n = 337$)	$M_{x4}AI_{x2}$	$M_{x8} + AP_{x2} + AIfo_{x2} + P_{x2} + Ifo_{x2} \pm$ L-MTP	48	64	75
			MAP(Ifo) – MTP		61	70
			MAP(Ifo) + MTP		67	78
BOTG	225			29	39^{10y}	47^{10y}
1991–1996 (study III)	96/105	IfoEpiCax2	LR: IfoEpix3 + IfoCa + EpiCa; HR: LR + Mx6	47	40	50
1996–1999 (study IV)	113/120	APCax3	IPx2 + IAx2 + ACa + ICa	18	38	44

4.1.4. *Pediatric Oncology Group POG 8561*

This randomised study compared immediate and delayed surgery after an induction of 2 cycles MAP.[95] Outcome was not significantly different between both arms. Patients, who had <10% viable tumour after induction, had a significant better EFS (73%) than patients with pPR. It was concluded that timing of surgery did not influence outcome and that a better response was not translated into a survival benefit.

4.1.5. *South West Oncology Group SWOG 9139*

In order to assess the efficacy of additional Ifo, 63 patients were treated with a regimen consisting of A and P, alternated with Ifo.[96] With a response rate of nearly 50% and 5y-OAS of 58%, the authors concluded that this 3-drug regimen did not improve outcome compared with prior regimens of A and P alone and that the value of increasing dose intensity by adding drugs in OSS is limited.

4.1.6. *Children's Oncology Group Intergroup study INT0133*

In a randomised 2×2 factorial study INT0133 the value of Ifo as a 4th drug compared with MAP and the addition of the immune modulating agent liposomal muramyl tripeptide (MTP) to chemotherapy were investigated.[97,98] Analysis after 4 year follow-up suggested an interaction between Ifo and MTP but re-analysis after 6 years FU showed no evidence of interaction.[98] A significant ($p = 0.03$) improvement of OAS when MTP was added to chemotherapy (6y-OAS 78% versus 70% in chemotherapy alone) was observed while outcome of MA-PIfo versus MAP were similar. Due to the complex design and interaction concerns of this study, the relevance of these conclusions have been challenged.[99]

4.1.7. *Brazilian studies*

Both the EFS and OAS were lower in a regimen that did not contain M, but Ifo and Epirubicin plus Carboplatin (study III),[100] both were considered less active drugs in OSS. In Study IV, A was added to the regimen of study III, without better results.

4.2. *European OSS study groups*

4.2.1. *Cooperative Osteosarcoma Study Group (COSS) studies (Table 4)*

The first neoadjuvant study of the COSS (COSS-80) demonstrated a significant better survival compared with the COSS-77 adjuvant study.[101,102] Randomisation in this study did not show any difference between P and BCD and Interferon-β was of no additional benefit.[102] The following trial, COSS-82, investigated the reduction of intensity of pre-operative chemotherapy and salvage of poor responders. The overall results were worse than the previous trial and M-BCD not only showed a significant lower response rate compared with AP, but the pPR had also a significant worse survival.[103] It was concluded from this randomised trial that salvage by changing drugs failed.[104] Therefore, in COSS-86, chemotherapy was intensified by adding Ifo to an already aggressive regimen of MAP for high risk (definition risk groups: see Table 4) patients.[105] Furthermore, in a controlled way the question was addressed whether intra-arterial administration of P would yield a higher response rate, hence a better outcome. With a

Table 4 – COSS results. Overview COSS-studies from 1979 until 1988. The first 2 studies were randomised. The subscript figures in the rows with chemotherapy indicate the number of courses of the particular drug or drug combinations (drug names see list of abbreviations). pGR is pathologic good response, pPR is pathologic poor response. GR is proportion of good responders, in most cases ⩾90% TCN (tumour cell necrosis). The superscript figures in the survival rows indicate follow-up period in years.

Study period	Number of patients	Drug regimen		pGR (%)	EFS (%)	OAS (%)
		Pre-operative	Post-operative			
COSS 80	116			53	58^{10y}	67^{10y}
1979–1982		$M_{x4} + A + BCD$	$M_{x10} + A + BCD_{x3} \pm Ifn$		59	69
		$M_{x4} + A + P$	$M_{x10} + A + P_{x3} \pm Ifn$		56	65
COSS 82	125			43	50^{10y}	64^{10y}
1982–1984		$M_{x4} + BCD_{x2}$	$pGR{:}M_{x4} + BCD_{x2}$; $pPR{:}AP_{x6}$	26	46	59
		$M_{x4} + AP_{x2}$	$pGR{:}M_{x4} + AP_{x2}$; $pPR{:}IfoP_{x3} + BCD_{x3}$	60	55	68
COSS 86	171			69	66^{10y}	71^{10y}
1986–1988		LR: $A + M_{x2} + P_{x2}$	$pGR{:}A_{x3} + M_{x10} + P_{x2}$; $pPR{:}A_{x4} + M_{x12} + PIfo_{x3}$	68	66	75
		HR: $AMx2PIfo_{x2}$	$A_{x4} + M_{x12} + PIfo_{x3}$	69	67	72

long term EFS of 66%, these results were the best published so far by COSS.[104,105] In both high and low risk patients, the response rate was nearly similar, and like the previous studies, pGR had a significant better survival than pPR. No benefit of the intra-arterial use of P on tumour response or survival was seen.[105,106]

4.2.2. *Istituto Ortopedico Rizzoli (IOR/OS) studies (Table 5)*
In the first IOR/OS study it was shown that high-dose M regimens had a significantly better outcome than low-dose M and that salvage of pPR by changing drugs failed.[107,108] Subsequently, a greater response rate and better salvage therapy by more intensive pre-operative chemotherapy and the addition of Ifo and E for pPR, respectively, resulted in a significant better EFS in the next trial, IOR/OS-2.[109,110] The following trial demonstrated that the cumulative dose of A safely could be reduced to 390 mg/m^2, and Ifo alone instead of Ifo plus E could be used to salvage for pPR.[111] IOR/OS-4 succeeded in increasing the response rate to 77% by further intensifying pre-operative chemotherapy, which was not translated into a better outcome.[112] Finally the effect of giving all four effective drugs at maximum dosages was feasible but did not yield a superior outcome compared with standard Ifo dose.[113,114] The value of the intra-arterial administration of P was investigated in the IOR-studies as well, but despite a higher response rate in the less intensive IOR-OS-3 study, no effect on the EFS or surgical procedure was present.[115] In the more intensive IOR-OS-4 both administration routes were equally efficient.

4.2.3. *Scandinavian Sarcoma Group (SSG) studies (Table 6)*
In study SSG-II, the results of Rosen's T-10 protocol could not be confirmed.[116,117] The modest response rate (17%) and low outcome of pPR patients indicated an insufficient effect of single agent M as induction treatment and the salvage of pPR by changing drugs. The next study SSG-VIII was a MAP based induction, with change to IfoE to salvage pPR.[117,118] The response rate increased to 57%, but long term survival and EFS for pPR were not different compared to SSG-II, indicating that a better response rate was not translated into a survival advantage and salvage for pPR by changing drugs failed.

4.2.4. *European Osteosarcoma Intergroup (EOI) trials (Table 7)*
The EOI compared, in 2 randomised trials, the role of AP based regimens with multidrug regimens.[119,120] EFS in the AP-arm of study 80831 was significantly better (HR=0.63;95% CI(0.42–0.94)) than in the MAP arm, but no difference in OAS was observed (HR=0.69;95% CI(0.43–1.09)).[119] In the next trial (80861) outcome was similar in the AP and multi-drug arm and the AP-regimen was preferred because of the better tolerability.[120] However, in the 80831 trial, the total dose intensity of AP in the MAP-arm was reduced to 2/3 of AP in the 2-drug arm.[119] In study 80861 the received dose intensity of P and A in the multidrug arm were 52% and 62%, respectively, whereas in the 2-drug arm this was 78% for both drugs.[120] In the 80931 study it was possible to increase the dose intensity by shortening the interval between subsequent cycles of chemotherapy, using G-CSF, by 30%.[121] This resulted in a significant ($p = 0.003$) higher proportion of pGR. However, outcome was

Table 5 – Istituto Orthopedica Rizzoli (IOR) results. Successive chemotherapeutic protocols of IOR (drug names see list of abbreviations). The first study randomised between low dose M (0.75 g/m^2) and high dose M (7.5 g/m^2). M-doses are noted by superscript in pre-operative column, and are post-operatively the same. TN is total necrosis, No-TN is group without TN.

Study period	Number of patients	Drug regimen		pGR (%)	EFS (%)	OAS (%)
		Pre-operative	Post-operative			
IOR/OS 1 1983–1986	127			52	46^{12y}	53^{12y}
	MDMTX (n = 60)	$M^{0.75}P_{x2}$	*pGR*: A + MAP_{x3}; *pPR*: A-BCD_{x5}	42	38^{12y}	45^{12y}
	HDMTX (n = 67)	$M^{7.5}P_{x2}$		62	52^{12y}	61^{12y}
IOR/OS-2 1986–1989	164	$M^{8}AP_{x2}$	*pGR*: A + MAP_{x3}; *pPR* A + $MAPIfoE_{x3}$	71	63^{5y}	75^{5y}
IOR/OS-3 1990–1991	95	$M^{10}AP_{x2}$	*pGR*: A + MAP_{x3}; *pPR*: A + $MAPIfo_{x3}$	56	54^{7y}	69^{7y}
IOR/OS-4 1993–1995	162	$M^{12}APIfo_{x2}$	No-TN: $MAPIfo_{x3}$ + AM; TN: $MAPIfo_{x2}$ + AM	77	56^{7y}	71^{7y}
ISG/SSG-pilot 1995–1997	68	$M^{12}APIfo_{x2}$	*pGR*: $MAPIfo_{x2}$; *pPR*:$MAPIfo_{x2}$ + MIfoP	56	73^{4y}	87^{4y}
ISG/SSG-1 1997–2000	182	$M^{12}APIfo_{x2}$	*pGR*: $MAPIfo_{x2}$; *pPR*: $MAPIfo_{x3}$	60	64^{5y}	77^{5y}

Table 6 – Scandinavian Sarcoma Group (SSG) results. Summary of the results of the SSG since 1982 (drug names see list of abbreviations).

Study period	Number of patients	Drug regimen		GR (%)	EFS (%)	OAS (%)
		Pre-operative	Post-operative			
SSG-II 1982–1989	97	$M_{x4}^{12/8}$	*pGR*:M_{x16} + BCD_{x4}; *pPR*:M_{x4} + $AP_{x6}BCD_{x4}$	17	56^{5y}	66^{5y}
SSGVIII 1990–1997	113	$M_{x4}^{12}AP_{x2}$	*pGR*:$M_{x2}AP_{x3}$; *pPR*:$IfoE_{x5}$	58	61^{5y}	74^{5y}
ISG/SSG-1 1997–2000	182	$M_{x2}^{12}AP_{x2}Ifo_{x2}$	*pGR*:$MAPIfo]_{x2}$; *pPR*:$[MAPIfo]_{x2}$ + [MIfoP]	60	64^{5y}	77^{5y}

Table 7 – EOI results. Summary of results of the 3 randomised EOI trials since 1983 (drug names see list of abbreviations). The number of patients in each arm is given between brackets. In the column "Patient number" arms C and DI represent the conventional dose and the dose intensive regimen respectively. All M doses are 12 g/m^2, the number of courses are indicated by the subscript figures.

Study period	Number of patients	Drug Regimen		GR (%)	EFS (%)	OAS (%)
		Pre-operative	Post-operative			
EORTC 80831 1983-1986	179					
	AP (*n* = 99)	AP_{x3}	AP_{x3}	41	57^{5y}	64^{5y}
	MAP (*n* = 99)	MAP_{x2}	MAP_{x2}	22	41^{5y}	50^{5y}
EORTC 80861 1986-1991	391					
	AP (*n* = 199)	AP_{x3}	AP_{x3}	30	44^{5y}	55^{5y}
	multidrug (*n* = 192)	$M_{x4}A$	$M_{x4}A$ + $BCP_{x4}AP_{x6}$	29	44^{5y}	55^{5y}
EORTC 80931 1993-2002	504					
	C (250)	AP_{x2}	AP_{x4}	36	39^{5y}	55^{5y}
	DI (254)	AP_{x3}	AP_{x3}	51	41^{5y}	58^{5y}

Table 8 – Other European study groups. Studies from France and (former Eastern) Germany (for drug names see list of abbreviations). IGR: Institute Gustave Roussy, SFOP: Société Française d'Oncologie Pédiatrique, HELP: Holoxan (Ifo), Eldesine (Vindesine, V), Cisplatin (P) with A.

Study group period	Number of patients	Drug regimen		GR (%)	EFS (%)	OS (%)
		Pre-operative	Post-operative			
T-10 IGR-Paris 1981–1986	70	M_{x7} + BCD + A	pGR: $[M_{x4}A\text{-}BCD]_{x3}$; pPR:$[AP_{x2}\text{-}BCD]_{x3}$	56	68^{7y}	74^{7y}
SFOP-HELP 1989–1993	62	M_{x7} + Ifo_{x2} + V_{x2} + AP_{x2}	M_{x6} + Ifo_{x2} + V_{x2} + AP_{x2}	64	59^{5y}	77^{5y}
SFOP 1994–2001	234				62^{5y}	76^{5y}
	MA (n = 116)	M_{x7} + A_{x2}	pGR: M_{x12} + A_{x3}; pPR: $IfoE_{x5}$	43	58	75
	MIfoE (n = 118)	M_{x7} + $IfoE_{x2}$	pGR: M_{x12} + $IfoE_{x3}$; pPR: AP_{x5}	64	66	76
Berlin 1986–1992	53	$[APCtxVc]_{x3}$	$[APCtxVc]_{x6}$	45	59^{10y}	67^{10y}

similar in both arms, suggesting that the increased histological response rate was reflecting the given pre-operative dose and not translated into better survival.

4.2.5. *French OSS studies (Table 8)*

The first single centre study aimed to reproduce the findings of Rosen's T-10 protocol and showed similar results.[122] The next study was MAPIfo based, resulting in a better response rate, but no improved survival.[123] The last trial SFOP-94, was a randomised comparison between MIfoE and MA[124] and showed a better response rate in the IfoE arm, but the outcome was not statistically different.

4.2.6. *Berlin study (Table 8)*

Tunn et al. demonstrated in a small cohort of 53 patients that a multidrug regimen without M achieves similar survival rates to M-based schedules.[125]

5. Statistical results and meta-analysis

Two drug, 3-drug and 4-drug regimens as listed in table 9 were used for meta-analysis, according to Parmar[18] and Fiocco.[17,19] For each study-arm multiple EFS and OAS corresponding to a predetermined set of time points (0.5,1,1.5,2,2.5,3,3.5,4,4.5,5,10 years) were known. The meta-analysis on EFS shows an improvement in survival by employing a three instead of two-drug regimen, which is significant (HR: 0.701, 95% CI: 0.615–0.799; Fig. 4). The same was demonstrated for the OAS as is shown in Fig. 5 (HR: 0.792, 95% CI: 0.677–0.926). Treatment effect was not significantly different between regimens with 3 drugs and 4 drugs with respect to either EFS (HR: 0.956; 95% CI: 0.779–1.177) or OAS (HR: 1.043; 95% CI: 0.851–1.280). Figs. 6 and 7 illustrate the estimated means survival for EFS and OAS, respectively.

6. Discussion

Data from single agent phase II studies in OSS patients for M, A, P and Ifo show response rates $\geqslant$20%, indicating the effectiveness of these drugs. Several investigators confirmed the importance of A in a sufficient dose, for example 390–450 mg/m^2, to be included in regimens for OSS.[103,104,107,111,126–128] A number of studies addressed the question whether or not high-dose M is essential for adequate treatment of OSS.[96,100,119,120,125] Survival outcomes of the SWOG, the Brazilian Osteosarcoma Study group and the EOI without M all are around 40–55%,[96,100,119–121] lagging behind the results of the M containing regimens of the COSS, IOR/OS, SSG and INT0133. The conclusion of the EOI that AP was superior[119] or equal[120] to M-based regimes must be interpreted with caution because of the inequalities in total dose intensity.[119,120,129]

To cope with heterogeneity between studies a Poisson correlated gamma frailty model has been used in this analysis. The results show a significant (p = 0.03) different 5y-EFS in 2-drug regimens (46%) compared with 3-drug regimens (54%) (Fig. 4). The five year-OAS of the 2- versus 3 drug regimens were 60% and 66%, respectively, (p = 0.04; Fig. 5), justifying 3-drug regimens in current OSS protocols.

Table 9 – Studies included in the meta-analysis to estimate survival (EFS and OS) at different time points. From these aggregate survival data, the difference between 2-drug and 3-drug regimens was estimated by employing a Poisson correlated frailty model (see text for details and references). Two drug regimens used for analysis were AP from the EOI-80831, EOI-80861, both AP-arms from study EOI-80931 and the MA-arm from SFOP-OS94. Three drug regimens used in the analysis were the MAP regimens from the randomised EOI-80831, COSS-80, COSS-82, INT-0133 and SFOP-OS94 studies, as well as the non-randomised IOR/OS-2 and -3 and SSG-VIII studies. The four-drug regimens which were used in the meta-analysis were the multi-drug arm of EOI-80861, the high-risk patients of COSS-86, the IOR/OS-4, ISG-SSG studies, the 4-drug arms of the randomised INT-0133 study and the POG-8651 multidrug study.

2-drug regimens	3-drug regimens	4-drug regimens
EOI-80831	EOI-80831	EOI-80861
EOI-80861	COSS-80	COSS-86
EOI-80931	COSS-82	IOR/OS-4
SFOP-OS94	IOR/OS-2	ISG-SSG-I
	IOR/OS-3	INT 0133
	SSG-VIII	POG 8651
	INT 0133	
	SFOP-OS94	

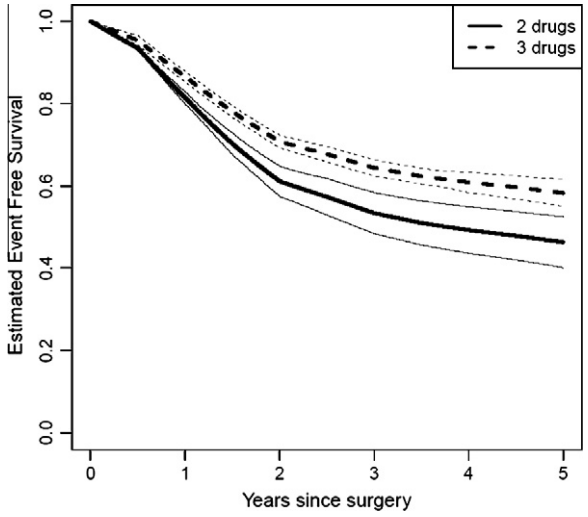

Fig. 4 – Estimated events free survival (EFS) based on meta-analysis of 5 two-drug regimens versus 8 three-drug regimens. Mean values of EFS are estimated along with their confidence intervals: HR = 0.701; 95% CI (0.615–0.799).

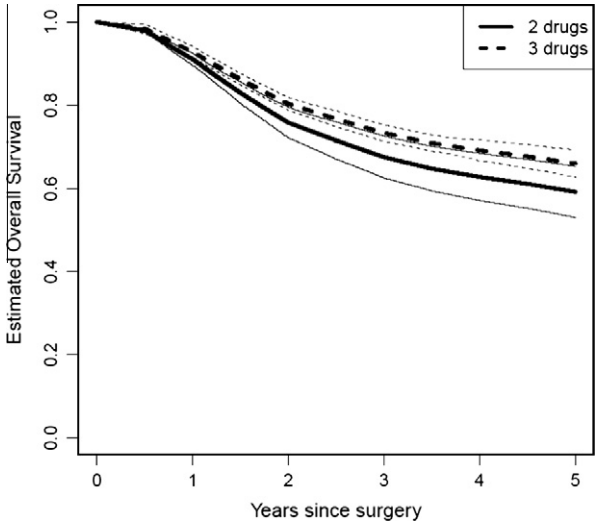

Fig. 5 – Estimated overall survival (OAS) based on meta-analysis of 5 two-drug regimens versus vs 8 three-drug regimens. Mean value of OAS are estimated along with their confidence intervals: HR = 0.792; 95% CI (0.677–0.926).

Whether or not a fourth drug has to be added to MAP remains an unsolved question. The meta-analysis comparing 3-drug regimens ($n = 9$) with 4-drug regimens ($n = 6$) did not show a difference in EFS and OAS between the 2 arms (Figs. 6 and 7). This indicates that there is no benefit of a fourth drug in treatment regimens.

The question how to salvage patients who respond poorly on preoperative treatment cannot simply be answered. Using different drugs and/or intensification after surgery has not shown to been beneficial.[88,103,104,107,117] Because in many studies histological response has been an highly important prognostic factor, intensifying pre-operative chemotherapy not only increases the response rate,[104,105,107,118] but also leads to better survival in most studies.[105,111,130] Although getting a higher intratumoural drug concentration by intra-arterial infusions in possible, resulting in a high fraction of tumour cell necrosis,[69,78,106,115,131–133] this route of administration does not result in a better survival than when given intravenously.[78,105,106,115,134] Therefore, intensifying chemotherapy beyond a certain level does not improve outcome, neither for pGR nor for salvage pPR.[89,95,113,114,118,121] Probably the results of the EURAMOS-1 study will give an answer whether or not patients with a pPR benefit from Ifo and E, added to MAP (www.euramos.org). As was suggested by Meyers in 1992,[88] intensive upfront treatment to increase the proportion of pGR has shown that the response rate improves, but this is not necessarily accompanied with better survival, which has been shown in other studies as well.[89,105,112,114,118,121,123,130,135,136] Limitations of treatment due to toxicity[114,123] and lack of efficacy despite maximal dosages[105,114,121,123,137] prevent further improvement in outcome. Therefore, new approaches have to be investigated, such as immune modulating agents as MTP[97,98,138,139] or inter-

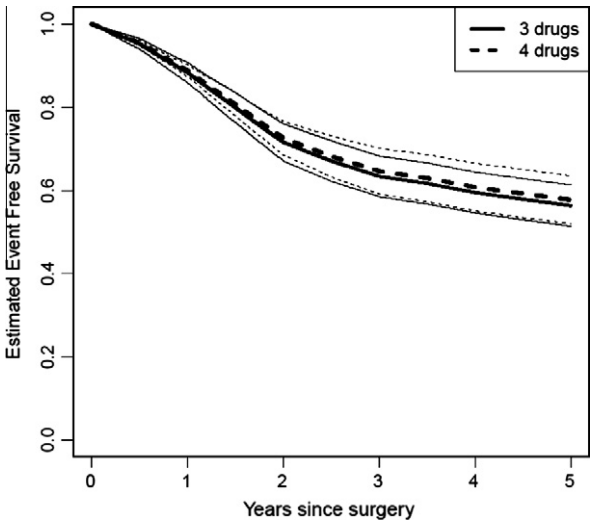

Fig. 6 – Estimated EFS curve based on the meta-analysis of 8 three-drug regimens versus 7 four-drug regimens. As illustrated, the survival curves are completely overlapping. HR = 0.956; 95% CI (0.779–1.177).

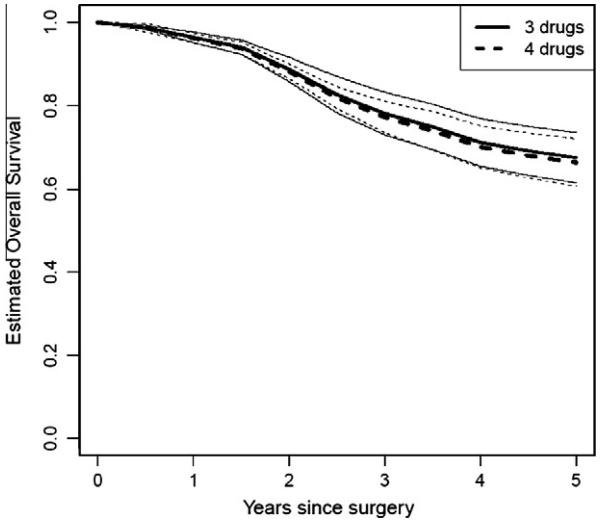

Fig. 7 – Estimated OAS curve based on meta-analysis of eight 3-drug regimens versus seven 4-drug regimens. Similar as in , the survival curves are overlapping, indicating no difference between both arms. HR = 1.043; 95% CI (0.851–1.280).

feron[140,141] as well as molecular approaches.[142] International large collaborative randomised studies in the last decennia, did regrettably not result in further improved survival. Our opinion is that Bayesian designed rapid turnover trials with biological end-points should be encouraged to explore the field of new ways of treatment of this resistant disease. It is emphasised here that this kind of studies only can be successful in international collaboration.

In summary: early phase-II trials demonstrated that A, M, P and Ifo have a proven single agent efficacy against OSS. Meta-analysis showed a significant advantage of 3-drug over 2-drug regimens, but the use of a fourth drug is not better than 3 drugs. Whether or not dose intensification after a poor response to preoperative chemotherapy improves survival remains an open question.

Conflict of interest statement

None of the authors of this manuscript, entitled: "Chemotherapeutic adjuvant treatment for osteosarcoma: where do we stand", has a conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.05.030.

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