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Point of View

On the Current Management of Osteosarcoma. A Critical Evaluation and a Proposal for a Modified Treatment Strategy

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The current management of osteosarcoma (OS) is critically reviewed and a modified treatment strategy is put forward for discussion. The overall treatment results in high-grade OS are less impressive than widely assumed. Whereas in 'classical OS' survival has indeed increased during the past decades from approximately 20% to at least 60%, in other subgroups, comprising more than 40% of the entire OS population, the prognosis has been only modestly improved. Today still more than half of an unselected OS population eventually succumbs to the disease despite the current multimodal primary treatments as well as second-line chemotherapy and surgical metastasectomy(ies). Analysis of the reported results indicates that a survival plateau of approximately 60% can be achieved by several different drug combinations. The inclusion of additional drugs and treatment with complex combinations to all patients has not yielded a convincing survival benefit. These expensive regimens overtreat a large number of patients, namely those who could have been cured by the previous less drastic regimens, and it increases the acute and delayed side-effect. Toxic deaths occur and life-threatening side-effects are not infrequent, necessitating interruption of the treatment or reduction in the dose intensity. A possible marginal early survival benefit may well be offset by late side-effects. For the above reasons, we propose an alternative, risk-adapted, treatment strategy, to retain the present results at a lower price in terms of acute toxicity and late morbidity. It is suggested that all patients with classical OS should be treated pre-operatively with optimal doses of only the two most active agents, methotrexate and doxorubicin. This presumably is sufficient in the majority of these patients. The most toxic treatment involving additional anticancer agents should be reserved for high-risk and relapsing patients, i.e. for situations where drastic measures are necessary and warranted. An important consideration is that relapsing patients are likely to benefit in particular from drugs to which they have not been previously exposed. © **1997 Elsevier Science Ltd.**

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THE CURRENT MANAGEMENT OF OSTEOSARCOMA

TREATMENT OF osteogenic sarcoma (OS) is fraught with difficult predicaments. The literature contains several apparent contradictions and inconsistencies rendering the evaluation of drug regimens and treatment results problematic. This may partly be due to confounding factors that are often not appreciated, some of which will be discussed below.

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The development of curative multimodality treatment in osteosarcoma is covered in detail in several recent reviews [1–4]. What is attempted here is to give a critical update with special focus on the question of whether the current trend to treat all patients initially with increasingly more toxic multidrug regimens is justified.

Although significant treatment progress in OS has been made over the past two decades, the overall survival benefit is considerably less dramatic than widely assumed. Thus, less than half of the patients showed long-term survival in a complete cohort of OS patients treated at our institution from 1981 onwards (Figure 1).

OS appears in distinct clinical forms having different degrees of malignancy and prognoses [5–7]. The most favourable group with high-grade histology is 'classical OS', i.e. young patients with tumours localised to the extremities and absence of recognisable metastases at diagnosis. Even today at least 30% of such patients eventually succumb to the disease [8–13], most due to lung metastases [14]. A previous study from our institution on classical OS has yielded treatment results comparable to those in the literature [9].

Classical OS, however, represents less than 60% of the entire high-grade OS population [5–7]. Several other subgroups have a much poorer prognosis. These include patients with primary tumours located in the axial skeleton (27% in our material; Figure 1). Many of these patients may die without detectable metastatic disease due to failure to obtain local tumour control [16]. Patients with radiation-induced OS, and OS developing from Paget's disease also respond poorly to current multimodal treatment. The latter two groups, often denoted secondary OS, comprise 5–8% of the entire OS population [5–7]. Older patients (14% of our patients > 40 years) usually do not tolerate high-dose chemotherapy well and outcome is poor. Another group carrying a dismal prognosis comprises those 15–20% who present with overt metastases (19% in our material). While previously all these patients rapidly succumbed, currently approximately 10–20% are alive after 5 years [17–19].

In the pre-chemotherapy era, up to 20% of all patients with classical OS were cured by surgery alone [20–23], indicating that approximately a fifth of the patients were free of micrometastases at presentation (Figure 2). The remaining 80% died, usually within 2 years, of metastases present as micrometastases at the time of the initial diagnosis. The improved outcome of OS over the past two decades has primarily been achieved by the use of adjuvant chemotherapy to control the micrometastases. Surgical removal of the primary tumour is still an obligatory step in curative treatment as it remains the only reliable way of assuring local control. In patients with tumours localised to the limbs, removal of the primary tumour with wide margins is nearly always feasible, either by amputation or today most often by a limb-sparing procedure [24–26]. The contribution of radiotherapy to cure has been limited. Radiation treatment is now mainly used in cases with inoperable tumours and when adequate margins cannot be secured by surgery.

When the lungs are the only site of solitary or a few metastases, surgical removal of these is a treatment with curative potential [27–31]. In some centres the proportion of relapsing patients where metastasectomy with curative aim is attempted has risen to more than 50%. Several groups have reported long-term survival in 20–50% of selected cases after complete removal of all macroscopically evident metastatic tissue. In many patients re-thoracotomies are necessary to remove subsequently appearing metastases [15]. In contrast, when radical surgical removal of lung metastases was not possible, all patients succumbed to their disease within 2 years.

The chemotherapy of OS has evolved in a stepwise manner from single-agent to multidrug therapy, and from low-dose to high-dose treatment. OS is relatively resistant to single chemotherapeutic agents, and in the initial search for active agents, few drugs induced objective responses at rates above 15%. Notable exceptions were doxorubicin, high-dose methotrexate (HD-MTX), cisplatin, and more recently, ifosfamide [32–36].

In the late 1970s and early 1980s, different combinations of these agents given as adjuvant chemotherapy after surgery soon resulted in an improvement in the relapse-free survival by approximately 40% compared with that previously obtained by surgery alone [37–41], with a survival plateau approaching 60% (Figure 2). In the light of current knowledge, the dose intensities of the various drugs used in these studies were suboptimal. A scrutiny of the literature indicates that in classical OS patients a survival of approximately 60% may be obtained by several different drug combinations. These data suggest that inclusion of additional drugs, known to be active in OS when given as single agents, did not improve the survival significantly above that of a two-drug combination [41]. Even today the current multidrug combinations have not convincingly raised survival above the 60% level. One obvious reason may be that many of the drugs used may not have additive, but more or less overlapping effects. Moreover, when many drugs are given in complex combinations, the full potential of each individual drug can often not be realised due to their combined toxicity. Frequently, the toxicity renders it necessary to introduce reductions in the doses of the individual drugs, as well as longer intervals

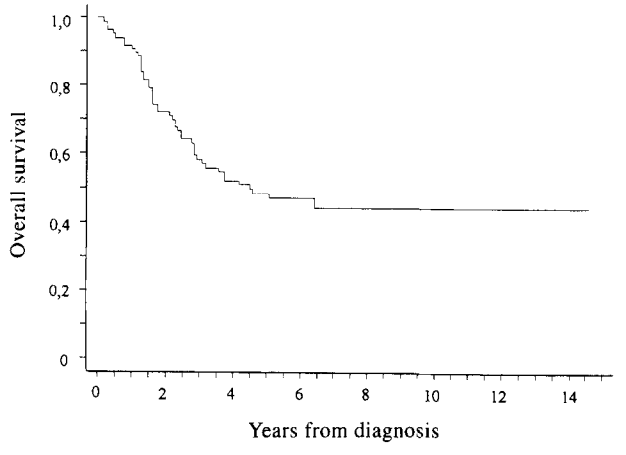

Figure 1. Outcome in an unselected group of 86 osteosarcoma patients with high-grade tumours treated at The Norwegian Radium Hospital (1981–1993). Overall survival 47% (+/– 10%) at 5 years. Minimum follow-up 3 years for living patients. 19% of patients with detectable metastases at primary diagnosis; 14% were above 40 years of age; 27% non-extremity localisation of the primary tumour.

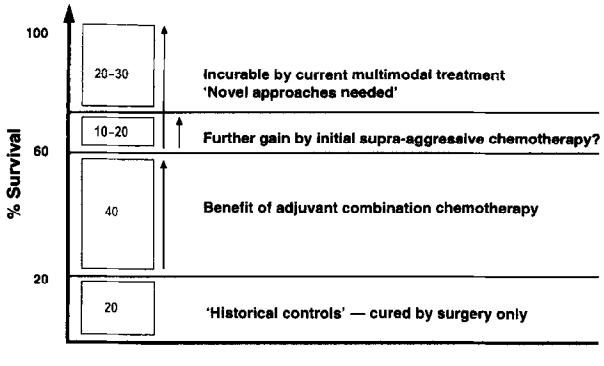

Figure 2. Treatment results in classical osteosarcoma. Schematic illustration of the treatment evolution in patients with classical osteosarcoma.

between courses, resulting in an overall reduction in the dose intensities and an increased incidence of drug resistance.

Since malignant cells are more efficiently eliminated when the tumour load is minimal, most treatment regimens today involve both pre- and postoperative chemotherapy. Such neoadjuvant chemotherapy, an approach pioneered by Rosen and associates [42–46], permits histological evaluation of the primary tumour's response to the drug(s). The patients are classified as good or poor responders on the basis of the degree of drug-induced necrosis [43, 47–49]. Currently, this is the most trusted prognostic parameter [50]. Also, effective pre-operative chemotherapy enhances the possibility for successful limb-sparing procedures by reducing the risk of local relapse. Moreover, neoadjuvant chemotherapy enables poor responders to be switched postoperatively to other cytostatic agents (salvage therapy). A drawback of pre-operative chemotherapy is that in poorly responding patients, tumour growth may continue and dissemination may occur while surgery is being postponed. This is of particular concern today when the pre-operative period is significantly prolonged due to the inclusion of an increasing number of drugs.

Despite the initial encouraging results reported by Rosen and associates, the more recent 'salvage regimens' have largely failed to raise the survival of poor responders to that of good responders. The reason may be that in several of these reports, in contrast to the situation in the study of Rosen and associates, most of the active drugs in salvage therapy have already been given initially and hence the tumour cells may have developed resistance. Significantly, the Bologna group [10] has reported that salvage treatment of poor responders with combinations of drugs to which the patients had not been previously exposed resulted in a 5 year relapse-free survival rate similar to that of good responders.

Today patients presenting with overt metastases are usually given the same first-line chemotherapy as those without metastases. However, they respond much more poorly to this treatment than do non-metastatic and relapsing patients and their prognosis is dismal, even if surgical elimination of all macroscopic tumour tissue is accomplished [17–19]. The poor results show that these OS patients require a different primary treatment than those presenting without metastases (see below).

Patients eventually relapsing with metastases after adjuvant chemotherapy have fewer lung metastases today than in the pre-chemotherapy era and the metastases appear later. This has significantly facilitated surgical metastasectomy. The relative incidence of extrapulmonary metastases seems to be increased after adjuvant chemotherapy, but in the majority of cases most metastatic episodes still involve lung deposits only [51–55].

The role of second-line chemotherapy prior to thoracotomy is still controversial. Recently it has been reported that second line chemotherapy combining cisplatin, etoposide, ifosfamide and dose-escalated methotrexate resulted in improved survival after the first occurrence of metastases [55]. Also a recent study from our institution indicates benefit if 'adequate chemotherapy' is instituted before and after surgical metastasectomy [15].

An interesting corollary of the above results is that a significant fraction of the cures obtained by the combination of surgery and chemotherapy may be attributed to the surgery component of the treatment. Thus, the surviving group obviously includes the 20% who previously were saved by surgery alone. This implies that of the 60% of classical OS patients rescued today, as many as a third may in fact have been cured by the surgery (Figure 2).

IS A REVISED TREATMENT POLICY CALLED FOR?

OS is a heterogeneous disease. The patients must therefore be carefully and consistently stratified with regard to anatomical, tumour biological and demographical variables, to permit an adequate evaluation of the benefit of various therapeutic procedures. Otherwise, misleading conclusions may be reached when different studies are compared. A case in point is the confusion that arose when results from early studies conducted at the Mayo Clinic [56] were compared with those of a later study from the same institution [57]. In contrast to virtually all previously published results, a 44% relapse-free survival after surgery alone was found, and the conclusion was drawn that adjuvant chemotherapy afforded no significant increase in the survival. The discrepancy was resolved and the beneficial effect of adjuvant chemotherapy in OS was established in two subsequent randomised studies [58, 59]. In hindsight the results from the Mayo Clinic were most probably due, not to a 'change in natural course of the disease' [60], but primarily to selection bias, resulting in a skewed patient population. Although the reported results are not valid for an unselected population of classical OS, they demonstrated what may be achieved by surgery alone in a selected OS population.

When improved diagnostic procedures are introduced concurrently with new therapeutic methods, the role of stage migration is easily overlooked. Thus, part of the reported improvement in the treatment of classical OS, usually attributed to adjuvant chemotherapy, may be accounted for by the advent of more sensitive methods to detect metastases. Small lung metastases, which previously would have escaped unnoticed, are now detected by the high-resolution CT examination currently used. Today as many as 20% of OS patients present with detectable lung metastases ([17, 18] and Figure 1), compared with only 10% previously [61]. This signifies that, among the patients previously staged as classical OS, several actually had small metastases. A significant number of these are now detected, and, accordingly, the patients are now not included in the classical OS group. Such an upward stage migration of a subgroup of patients from seemingly non-metastatic to metastatic disease will in fact improve the prognosis in both groups [62].

Another confounding factor is the uncertainty in the validity of the histological distinction between good and poor responders following pre-operative chemotherapy, and in the methodological difficulties involved. This prognostication is based on the tacit assumption that the chemosensitivity of the primary tumour adequately reflects that of the micrometastases. As recently pointed out by Rosen, this may not always be the case for all drugs (data not shown, 1996). To give consistent and comparable results among different laboratories this *in vivo* prognostication must be carried out under strictly standardised conditions. This requirement is difficult to fulfil due to the large variations in the pre-operative treatment schemes used, some of which even involve intra-arterial infusion of cisplatin. When the number of drugs is increased and the time to primary surgery is prolonged, the degree of necrosis may be less predictive of outcome. The histological assessment of drug-induced necrosis in a specimen from a

large primary tumour containing abundant areas with spontaneous necrosis is difficult and subjective. The evaluation is time-consuming and the interpretation depends on the number of slices examined, as well as the skill and experience of the pathologist. It is therefore hardly surprising that the observed differences in survival between 'good' and 'poor' responders have not been pronounced in all studies. Today a similar evaluation can be made following surgical removal of lung metastases in relapsing patients where the distinction should be easier and more valid when small lung metastases are studied after pre-operative chemotherapy.

Treatment progress in OS now seems to have reached an impasse [63]. In our view, the available data do not justify the trend to expose the entire OS population to increasingly toxic chemotherapy. The current attempts to demonstrate a further gain in survival in a population which includes a 60% 'noise', namely 20% cured by surgery alone and 40% rescued by previous standard chemotherapy (Figure 2), is obviously difficult. So far a clear survival benefit of the ultra-aggressive chemotherapy has not been demonstrated. What is needed is a convincing demonstration that such multidrug treatment is indeed capable of rescuing a significant percentage of patients in the poor prognostic groups and then to reserve this treatment for such patients only.

As pointed out above, ultra-aggressive chemotherapy is associated with enhanced acute toxicity and a disquieting long-term morbidity. Toxic deaths occur and the long-term effects of kidney damage are unknown. The frequent incidence of subclinical cardiac failures in young survivors, as well as increased risk of secondary malignancies, are especially worrisome. Overtreatment with undue toxicity is of particular concern in the 60% of patients with classical OS who previously were cured by less toxic regimens. Moreover, the economic aspects of multidrug high-dose chemotherapy with the need for growth factor support cannot be disregarded.

For the above reasons, we believe that the time has come to explore an individualised, better-stratified therapy in OS based on risk evaluation. Such an approach is essential in the current treatment of adult patients with testicular cancer, Hodgkins' and other types of lymphoma, as well as in children with Wilms' tumour, acute lymphoblastic leukaemia and neuroblastoma.

A MODIFIED TREATMENT STRATEGY

An alternative treatment philosophy, proposed for consideration, is outlined below. The aim is to retain the current treatment results at a lower price in terms of toxicity and morbidity. We suggest that in classical OS patients, initially only HD-MTX and doxorubicin should be used. This approach should reduce the current overtreatment in the 60% of classical OS patients cured. The most aggressive drug combinations are restricted to poor prognostics groups.

HD-MTX is particularly valuable due to its low acute haematological toxicity and its lack of serious late effects. HD-MTX permits high-dose treatment at 1–2 week intervals between courses or between HD-MTX and a myelosuppressive combination. Doxorubicin is probably the most effective single drug in OS [64], and despite its cardiotoxicity linked to the total accumulated dose and bolus infusions, this drug cannot with impunity be omitted from treatment schemes. A high dose intensity of the doxorubicin component is important both for primary tumour response and for relapse-free survival [65, 66].

Some authors may argue that a two-drug combination is a less efficient treatment than utilising three to four drugs in combination. We do not believe that this is the case. An essential point in our proposal is that the two most active drugs should be given at optimal dose intensities (mg/m^2/week). Based on recent evidence, this may well lead to improved outcome with a survival plateau above 60%.

The value of adding HD-MTX to other active agents has been questioned. In our opinion this is unwarranted as the lack of clear MTX effect in some studies may be ascribed to factors such as the use of modest doses of MTX, inadequate dose intensity, short treatment duration, extensive overhydration and/or premature institution of leucovorin rescue. Presently as much as 12 g/m^2 MTX, infused over the course of 4–6 h with leucovorin not instituted until after 24 h, is considered necessary. A significant positive relationship between MTX serum levels and tumour response as well as survival has recently been demonstrated by several groups [9, 67, 68]. It now seems advisable to individually adjust the MTX dose according to the patients' pharmacokinetic profile, as the optimal effect of MTX will only occur at a serum concentration of at least 1000 μM at the end of a 6 h infusion [69].

On this basis we suggest that patients with classical OS receive a two-drug pre-operative schedule involving four courses of HD-MTX at 1 week intervals with an individualised dose escalation of 2 g/m^2 if adequate levels of MTX are not achieved at 4 h. After having completed the first course of MTX, one 24 h infusion of doxorubicin (90 mg/m^2) should be interposed.

Table 1. Outline of the suggested treatment strategy

1. All patients receive neo-adjuvant systemic treatment. Classical osteosarcoma patients are given optimal doses of doxorubicin and high-dose methotrexate, aiming at effective eradication of micrometastases. This step should insure:
   (a) a survival in the 60% range, including cure of the majority of the cases with chemoresponsive micrometastatic disease;
   (b) an acceptable acute and long-term toxicity among those patients cured, including those that could be cured by surgery only;
   (c) retention, in those eventually relapsing, of the established shift in metastatic profile induced by combination chemotherapy, i.e. a reduced number of lung metastases appearing at a later time point.
2. In patients responding pooly to the above pre-operative treatment and in relapsing patients, several active drugs to which the patient has previously not been exposed can now be used for salvage therapy. In patients presenting with overt metastases initial highly aggressive treatment, combining all available drugs, is warranted and justified.
3. Those hopefully few patients who respond poorly to this chemotherapy, as well as patients where complete metastasectomy cannot be performed, should be considered candidates for experimental strategies such as:
   (a) bone-marrow ablative chemotherapy with peripheral blood stem-cell support
   (b) immunotherapy
   (c) targeted internal therapy using ^{153}Sm-EDTMP as a concomitant boost to external radiotherapy.

Good responders should continue postoperatively with the same two-drug combination. In poor responders, treatment should be intensified by the addition of cisplatin and high-dose ifosfamide. Early relapsing patients, and those with detectable metastases at primary diagnosis, should be treated according to the aggressive guidelines recently suggested by SSG/IOR, utilising all available active drugs 'up front' [16].

The more individualised treatment suggested here requires a close and systematic follow-up to detect relapses early which can then be treated aggressively with active drugs not previously used in these patients. In addition to reducing undue long-term toxicity, this strategy may possibly limit the early development of multidrug resistance. In refractory and relapsing patients, it is necessary and warranted to resort, as an ultimate recourse, to the remaining drugs presently known to be active in OS as single agents. These drugs, to which the patients have not been previously exposed, should now be used in combination and at dose intensities exploiting their full potential. This procedure might secure adequate salvage chemotherapy and hopefully translate into improved survival (Table 1).

NEW THERAPEUTIC POSSIBILITIES

Novel treatment options are sorely needed in the management of OS. While we are awaiting the appearance of new improved drugs and approaches, efforts to utilise more efficiently the therapeutic armamentarium currently available should be continued. The above proposal represents one such attempt.

Today data are available on morphological, biological and biochemical properties of OS tumours that seem to have prognostic value [50, 70–72]. However, prognostic factors are currently taken into consideration only to a limited extent, as there is as yet no consensus with regard to their relative roles. If agreement can be obtained between leading groups in the field, risk-adapted therapy should be implemented and explored efficiently. In that event our proposal may become even more relevant than today.

If it were possible to identify those patients who most likely might be cured by surgery only, this would strongly affect the choice of therapy. Efforts in this direction are made by attempts to ascertain the presence or absence of micrometastases in bone marrow aspirates by the use of paramagnetic beads tagged with OS-selective monoclonal antibodies [73], and by strategies to improve the diagnosis of lung metastases [74].

Recent studies have demonstrated that the expression of Pgp in tumour cells is an important indicator of their aggressiveness. The lack of Pgp production encoded by the *MDR1* gene in the OS tumour cells has recently been shown to signify a favourable prognosis [75]. A majority of relapsing patients had Pgp-positive primary tumours, as was the case with the patients presenting with metastatic disease. These findings open the possibility to identify, at presentation, OS patients who will not respond to conventional chemotherapy. In such patients it would be logical to test the use of agents capable of downregulating expression of the MDR gene product [76].

An urgent task is to design more effective multimodal therapy for primary treatment of the subgroups of OS patients where current chemotherapy has only modestly improved the survival. New and promising approaches in this direction involving immunotherapy [77, 78] and targeted radionuclide treatment as a boost to external radiotherapy [79–81] are now being explored.

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