THE MANY FACES OF OSTEOSARCOMA

Some dilemmas and challenges in its current management

Øyvind S. Bruland[1] and Alexander Pihl
Department of Oncology[1]The Norwegian Radium Hospital
N-0310 Oslo, NORWAY

The evolution of osteosarcoma treatment has been a long and difficult journey. It has been an exciting adventure, ample with challenges and disappointments, but - indeed - also with some spectacular rewards. The path to the present stage has been a "navigation between Scylla and Charybdis", a true Odyssey.

In a previous paper we have critically reviewed the current management of osteosarcoma (OS), and put forward for discussion a modified treatment strategy, which takes into account the dilemmas and challenges that currently confront the clinicians treating patients with this disease (1).

This is the time to ask: What have we learned, where do we stand, and where do we go from here?

Biology and Clinical Features. OS is a disease with many faces, each having unique features. To set the stage for the forthcoming lectures and discussions, and for the benefit of the non-clinicians in the audience, we shall briefly review the salient characteristics of OS and focus on some aspects of its current management.

Osteosarcoma is a rare disorder which primarily strikes children and adolescents (2,3). The disease displays considerable heterogeneity and appears in clinical entities showing a great span in tumour biology and prognosis (1-5). In its most common form, "the classical type", OS strikes people below the age of 30 years with primary tumours of "high grade histological malignancy", localised to the long bones of the extremities, predominantly in the metaphyseal regions. By definition, patients with "classical OS" have no demonstrable metastases at presentation. OS emerging in the bones of the axial skeleton is more often seen in elderly patients and carries a much poorer prognosis (4-6). Many of these do not die from metastases, but from local treatment failure (6). Such cases confront us with gruesome clinical pictures; true disasters for the patient, for the family, and for the hospital staff. In our institution we see several such patients.

An important feature of OS is its propensity for early hematogenic dissemination. Thus, after surgical removal of the primary tumour as the sole treatment, about 80 % of the patients with "classical OS" eventually die from metastatic disease developing from micrometastases that must have been present already at presentation.

The Management of Osteosarcoma. Like in many other forms of cancer, the choice of treatment and its outcome depend on the: 1. Anatomical localisation of the disease, 2. Histological grade of malignancy, 3. Clinical stage at primary diagnosis, 4. Age and performance status of the patient.

Corner-stones in the current therapy of OS are radical surgery in conjunction with heavy adjuvant chemotherapy (2,3,7). Surgery is still the best procedure to attain local control, and remains an essential step in curative treatment. In recent years surgery has attained a new role in OS, as in selected patients surgical extirpation of isolated lung metastases has curative

potential (8-12).

Before the advent of modern chemotherapy, the principal treatment of OS was radical surgery only, in most cases involving amputation of the affected limb. It was observed that, in "classical OS", surgery alone could cure as many as 20% of patients with OS in the extremities. This implies that some of these tumours have not yet disseminated at the time of primary treatment. In low grade OS it is warranted to refrain from drastic procedures and make do with local therapy alone.

The progress in survival during the past two decades has been impressive, at least for young, non-metastatic patients where the survival has been raised by about 40 % to at least 60% (2,3,13-18), primarily by the use of adjuvant chemotherapy to eradicate micrometastases.

However, the prognosis is still grave in other subgroups (6,19,20), such as: 1. In patients with overt metastases at presentation, 2. Among elderly patients, 3. When the OS-tumour is located in the bones of the axial skeleton. Altogether more than half of the patients in an non-selected OS population eventually succumb to the disease (1). Are we presenting a too optimistic picture of the treatment efficacy to these patients and their relatives?

Conventional external radiotherapy is currently used only to a limited extent. However, local radiotherapy may be effective and useful under special circumstances (see below and in subsequent papers in the proceedings from this symposium). Thus, some of the early non-metastatic patients who refused amputations, turned out to be cured by the radiation treatment alone (7,21-23). That local control of OS can be achieved by radiotherapy, at least in some cases, has been confirmed also in some recent studies (24). Evidence exists that a radiation-dose/effect relationship obtains also in OS (25). Even large OS tumours can indeed be sterilised by external radiation at doses above 80-90 Gy. However, this too often incurs unacceptable damage to surrounding normal tissues among long term survivors. Fortunately it now seems possible to deliver the remaining dose required for sterilisation of OS-tumours, i.e. that above the normal tissue tolerance to external radiotherapy, by giving concomitant boost irradiation, employing brachytherapy or targeted radioisotope treatment (26,27, and see below).

Because progressive lung metastases are a frequent cause of death, the effects of prophylactic external lung irradiation have been explored in several studies (28,29). As OS lung metastases are usually distributed throughout the lungs, both lungs must be irradiated. To avoid disabling lung fibrosis the externally given radiation dose must be limited to 20 Gy (1.5 Gy x 13). Theoretically, this may prevent further growth of metastases containing less than 10^6 tumour cells (see Olsen & Bruland in this synopsis). However, the doses required to reliably sterilise the whole spectrum of lung metastases are higher than those that can be safely given by external radiotherapy alone.

Critical Questions Awaiting Answers. The evaluation of drug regimens and treatment results is problematic, partly due to the operation of confounding factors that have not been not sufficiently appreciated (1). Hence, the literature contains several apparent contradictions and inconsistencies. An important goal of this symposium is to discuss critically the influence, in previously reported studies, of confounding factors such as: 1. Selection bias, 2. Stage migration, 3. Protocol compliance, 4. Dose intensities of individual drugs.

In attempts to further raise the survival, several centres have recently introduced increasingly toxic poly-drug combination-chemotherapy. However, the cost and consequent side effects are serious and the net gain is questionable (1). A possible marginal early survival

benefit may well be offset by late toxicity. It is noteworthy that this aggressive strategy has been implemented to the entire "classical OS"-population without having first been demonstrated to improve its efficacy in patients with dismal prognosis. Obviously, a thorough and iconoclastic discussion of this important and difficult question is long overdue.

How much of the currently established gain in survival, credited the use of adjuvant chemotherapy, can be attributed to stage migration by the systematic staging of patients with CT-examinations of the lungs?

Does the tacit assumption that the chemotherapy effect on the primary tumour adequately reflects that on the micrometastases hold true for all drugs and drug combinations?

Is the degree of primary tumour necrosis less predictive of clinical outcome when the number of drugs used pre-operatively is increased and the time to primary surgery is prolonged?

In patients with "classical OS" a survival plateau of approximately 60% may be obtained by several different drug combinations and regimens (1). The inclusion of additional drugs has not convincingly improved the survival (30,31), probably because the drugs may have overlapping rather than additive effects. When complex poly-drug combinations are employed, the full potential of each individual drug can often not be realised due to combined toxicity, necessitating an overall reduction in dose intensity. Patient compliance with scheduled chemotherapy has been a problem (31). Longer overall treatment time is probably favouring the induction of drug resistance.

Novel Therapeutic Approaches. Clearly, there is a strong need to explore new avenues. Several possibilities are now under clinical investigation and deserve our consideration: 1. Immunotherapy, 2. Targeted radiotherapy, 3. Cytostatics based on new principles.

As pointed out above, the additional radiation dose needed in addition to that which can be safely given by conventional external radiotherapy may be supplied by targeted radionuclide treatment. For this purpose either radiolabelled monoclonal antibodies, which bind to specific epitopes on cell surface antigens, or bone-seeking radiopharmaceuticals which bind to osteoid and bony elements produced by the osteosarcoma cells can be employed (for review see 32,33).

In a clinical pilot study we have shown that in several patients where all conventional treatment modalities had failed, serious pain was significantly relieved by ^{153}Sm-EDTMP-treatment (27). In one patient, bedridden with paraparesis and impaired bladder function due to a vertebral lesion, the pareses gradually subsided after two radionuclide administrations (26). In five other patients significant growth delays were observed, lasting for more than two years (27,34).

It could be calculated that tumour doses as high as 60 Gy may be obtained after a single injection of ^{153}Sm-EDTMP (35). Dosimetric and radiobiological considerations indicate, however, that the dose-schedule used in our preliminary study was far from optimal. An attractive treatment strategy, which now is being explored, is to use ^{153}Sm-EDTMP already in the primary treatment of osteoblastic OS as a boost to conventional external radiotherapy.

In our view the available evidence indicates that targeted radiotherapy may be useful:

A) as a concomitant boost to external irradiation in patients:

- with primary tumours in the axial skeleton not amenable to complete removal by surgery without unacceptable mutilation
- where histological examination of the tumour specimen shows inadequate surgical margins
- as adjunct to postoperative lung irradiation following incomplete metastasectomy

B) together with total lung external irradiation in high-risk patients such as

- those presenting with overt metastases
- those relapsing and not responding to second-line chemotherapy and who can not be salvaged by surgical metastasectomy

Immunotherapy has for many years been considered a promising approach, also in OS. One interesting clinical observation, left at the wayside, and in our opinion underestimated, is the finding by Strander and co-workers that the adjuvant use of interferon-alpha alone affords a DFS above 50% at 5 year follow up (36,37). This observation deserves to be adequately challenged. Is this reproducible? And, if so, could the effect of alpha-interferon be additive, or even synergistic, to that of chemotherapy?

The current status of other promising approaches, such as systemic therapy employing liposomal encapsulated MTP-PE (see Kleinermann et al.), and inhalation therapy with IL-2 liposomes (see Skubitz et al.), will be reviewed by other speakers at this symposium.

Risk-adapted Chemotherapy. Are we ready to apply this principle, well established in some other forms of cancer, also in OS? Does recent knowledge concerning strong prognostic factors such as the expression of MDR, volume of the primary tumour, and possibly serum alkaline phosphatase pre-treatment, justify the use of simplified adjuvant chemotherapy in those patients deemed to have good prognosis?

We believe that time has come for such a strategy, and have proposed a two drug regimen consisting of HDMTX and doxorubicin in low and medium risk patients (1). One aim is to retain the present gain in survival at a lower price in terms of late morbidity.

New technologies are rapidly appearing, enabling us to ascertain the presence of tumour cells, either trapped in bone marrow or circulating in peripheral blood, by the use of super-paramagnetic immunobeads (see Bruland et al. in this synopsis). An important task is to establish the clinical significance of such cells. A multi-institutional effort to settle this question is now under way (clinical & research protocols ISG/SSG I and II).

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