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Letter to the Editor

Assessment of the Role of Chemotherapy and Radiotherapy as Adjuvant in the Treatment of Osteosarcomas of the Limbs

A Trial of the E.O.R.T.C. (Clinical Cooperative Group Radiotherapy/Chemotherapy) and of the S.I.O.P.

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THE PROGNOSIS of patients with an osteosarcoma of the limbs is determined by the development of distant metastases, usually in the lungs, which occurs in about 80% of the patients [1–3]. It has proven extremely difficult to eradicate with either radiotherapy or chemotherapy lung metastases once they have become clinically detectable. Therefore it has been tried in recent years to treat these metastases when they are still in a microscopic stage. Radiotherapy as well as chemotherapy have been used as adjuvant therapy immediately after treatment of the primary.

In a randomized clinical trial by the cooperative group on radiotherapy of the E.O.R.T.C., a substantial benefit was achieved by a whole-lung irradiation of 2000 rad [4]. About 20% of all patients who would have developed metastases were cured by the lung irradiation. A similar fraction of disease-free patients was also found after lung irradiation by Newton and Barrett [5]. However, this was a non-randomized study concerning a small number of patients. A second remarkable feature of the randomized E.O.R.T.C. trial was the fairly high proportion of patients without adjuvant therapy which did not develop lung metastases. While in the historical groups of patients metastases-free survivals were as low as 15%, this was 28% in this study. This improvement in the natural prognosis of this disease has also been shown by the group from the Mayo Clinic [6] and re-emphasizes the absolute necessity of carrying out randomized trials for the evaluation of the value of any form of adjuvant therapy. Whether this improvement in prognosis is due to change in the biology of the tumour or to a more careful screening of these patients is impossible to define and not relevant from the clinical point of view. Since the discovery of some cytostatic drugs which seemed effective against osteosarcomas, adjuvant chemotherapy for this disease has been strongly advocated by many people. Three different approaches were used: monochemotherapy with methotrexate [7] or adriamycin [8] or polychemotherapy [9]. Although initially extremely good results were published, it has to be stressed that none of these studies were carried out on a randomized basis, thus always referring to the dismal results of the older control series, and that usually follow-up times were very short. Reassessing the data now [10, 11] it appears that only one chemotherapy series [12] has a disease-free fraction of over 50% while most of the other ones are closer to 40% or even lower [13–15].

The conclusion thus seems to be that, although adjuvant chemotherapy has resulted in

a higher survival of patients with osteosarcoma, in comparison with historical controls, this form of treatment has not proven to be superior to the lung irradiation previously tested. A prospective, randomized trial was therefore initiated as a joint venture between the E.O.R.T.C. and the S.I.O.P. (International Society for Pediatric Oncology), comparing chemotherapy to lung irradiation (Fig. 1).

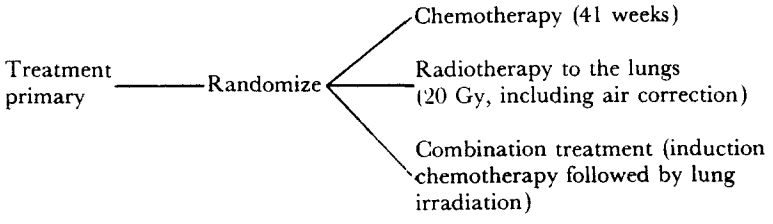

Fig. 1.

The chemotherapy will be a combination of methotrexate (MTX) (6 g/m^2 with citrovorum rescue) and vincristin (1.5 mg/m^2), adriamycin (70 mg/m^2) and cyclophosphamide (1200 mg/m^2) and will take 42 weeks. After a heavy induction therapy with only MTX and adriamycin during 8 weeks (MAMAM) this will be followed by a lighter maintenance therapy with cytoxan alternating with the MTX and adriamycin (CACM, 4 times) (Table 1). The lung irradiation covers the whole thoracic cavity and is 2000 rad, after correction for the lesser absorption in the lungs. With the hope of adding some of the beneficial effect of both agents, a third arm has been introduced into the trial which will test a combined treatment. Here the heavy induction chemotherapy (MAMAM) will be followed by a lung irradiation.

As it has been claimed before that adjuvant therapy would not only increase the number of patients remaining disease-free, but also could reduce the number of lung metastases in patients who do develop disseminated disease, an annex study on the feasibility of metastatectomies has been connected to this trial. This trial will try to answer very fundamental questions on adjuvant therapy in osteosarcoma and the results will undoubtedly be of great value in the further evolution of the treatment of this disease. As this is a fairly rare disease and a 3-arm trial has been set up, the active participation of as many centres as possible is necessary. All further information can be obtained from the secretariat for the trial: E. van der Schueren, Radiotherapy Department, Wilhelmina Gasthuis, Eerste Helmersstraat 104, Amsterdam, The Netherlands.

Table 1

	Induction					Consolidation			
Weeks	1	3	5	7	9	11	13	15	17
CFA						|		|	
ADRIA		|		|			|		
VCR/MTX/CF	|		|		|				|

Cycles of consolidation chemotherapy to be given for a total of 4 times, up to week 41.

Methotrexate	6000 mg/m^2/6 hour infusion	MTX
Citrovorum factor	15 mg/6 hour/x 12	CF
Vincristin	1.5 mg/m^2/i.v. (max. 2 mg)	VCR
Adriamycin	70 mg/m^2/i.v.	ADRIA
Cyclophophamide	1200 mg/m^2/i.v.	CFA

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