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PII: S0959-8049(98)00016-1

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THE RESPONSE rate for treatment of soft tissue sarcoma is approximately 25%, complete and partial responses combined. Active drugs are doxorubicin, ifosfamide and its predecessor cyclophosphamide. No survival benefit for the treatment option has been demonstrated so far. This summarises in three sentences the points made by Rouëssé and Bourgeois [1].

We should realise that a surgeon with a success rate of 25% and no survival benefit would be dismissed immediately. The results of treatment of locally advanced and/or metastatic soft tissue sarcoma are very disappointing indeed! The lack of any better possibility takes for granted the current status, and the next EORTC protocol for advanced or metastatic soft tissue sarcoma focuses on two investigational schedules of ifosfamide compared with standard dose doxorubicin. This phase III study looks at progression-free survival and overall survival and considers a difference of 10% in 1-year progression-free survival at the 15–25% level as clinically significant.

It is probably also clinically significant in the view of Benjamin, who argues for chemotherapy based on anecdotal clinical experiences [2]. Taking the results of the University of Texas M.D. Anderson Cancer Center together, the outcome is similar to figures given by Rouëssé and Bourgeois: 55 complete responses plus 26 partial or minor responses out of 331 patients, a response rate of 24%. This level of activity means that approximately 75% of treated patients will accept therapy without benefit. Despite statistical outcomes, the results of treatment can be worthwhile for the individual patient, as Benjamin demonstrates with the help of 3 cases.

As a playwright, Shakespeare needs some theatrical exaggeration to gain the dramatic impact needed. He goes for the extreme and Benjamin follows. The mere impossibility of discerning the patient who will benefit from chemotherapy is, for Benjamin, reason to apply chemotherapy in order not to withhold from the patient a chance, however small. In addition, the sequelae of disease justify in this perception the toxicity of treatment, no matter how serious.

Although the points of view seem to be extremely opposed—the cautious approach versus the tough approach —they come to almost the same conclusion. Benjamin proposes disease-specific phase II studies for the histological subtypes leiomyosarcoma of gastrointestinal origin, alveolar soft part sarcoma and chondrosarcoma, because of the lack of activity of standard drugs. Rouëssé and Bourgeois extend this recommendation to the whole range of subtypes among soft tissue sarcomas. A similar disease-oriented phase II approach was discussed several years ago concerning melanoma and colorectal cancer. The low response rate and the

lack of survival benefit have made a case for the use of investigational drugs upfront for systemic therapy naive tumours. It is conceivable that the cultural background of patients may modulate this approach. A patient in Houston probably demands treatment with known activity. In that case, a 25% response rate sounds better than 0%, which is the starting point for a disease-oriented phase II trial. The European patient might be apt to accept investigational drugs without known activity in view of a second opportunity for treatment with standard drugs.

When to treat? In the absence of a survival benefit induced by chemotherapy, there is no gain in starting treatment without the presence of clinical symptoms. Unresectable locally advanced disease which can be turned into resectable disease by application of cytostatic drugs is a clear-cut indication for chemotherapy. Benjamin calculates a chance for cure in this situation to be around 5–6%. However, even when the combined modalities of chemotherapy followed by resection do not result in cure, the palliative result might be clinically highly beneficial. The approach of clinically silent liver or lung metastases, which are beyond the surgical option, elicits a different debate. The mere apprehension of metastatic, life-threatening disease is for many patients unbearable and even vexing. The threshold to start treatment is low due to emotional reasons. Technically, there are no reasons to endorse early therapy. Again social backgrounds play a role. Patients spending private money buy whatever they want, even health-care products regardless of their activity. Patients invoking their health insurance encounter the mutuality, which not only cares for the individual patient but also looks after cost-effectiveness items. Economic parameters can be subjects of study within controlled clinical trials, but they do not play a decisive role.

What else can be done to ameliorate the prospects of patients with soft tissue sarcoma? Education of the public can avoid people presenting for medical attention after the tumour has already gained weight of 1 kg or more. In addition, primary care healthcare workers should be aware of the possible malignant character of soft tissue masses. Surgeons would preferably plan diagnostic procedures with a view to subsequent definitive surgery. A biopsy or excision of a lesion assumed to be benign should never preclude curative resection of a soft tissue sarcoma. The histological diagnosis of soft tissue sarcoma should never be a surprise!

Current developments are exciting. Isolated limb perfusion with high dose tumour necrosis factor-α combined with interferon-γ and melphalan has resulted in a clinical response rate of 82%. The median tumour size in patients with one tumour was 18 cm and 24% of the patients had multifocal primary sarcomas or multiple recurrent tumours. However, at a median follow-up of 2.25 years, 15 of 46 patients who underwent limb perfusion in the absence of systemic disease developed systemic metastases [3]. The adverse prognostic factors for distant metastasis are intermediate (5–10 cm) and large (> 10 cm) tumour size, high histological grade and locally recurrent disease. In the Memorial Sloan Kettering series, 41% of soft tissue sarcoma of the extremities were smaller than 5 cm [4]. Although the microscopy of surgical margins does not predict distant metastasis, positive surgical margins are a risk factor for local recurrence and disease-specific survival. Local recurrence is adversely associated with distant metastasis. We would be eager to know whether expanding the indication for limb perfusion to extremity-located soft tissue sarcomas smaller than 5 cm, is capable of facilitating surgery, and able to reduce the incidence of distant metastasis.

For an increasing number of subtypes in soft tissue sarcoma, a specific chromosomal translocation is described and characterised [5]. The translocation is of help in defining criteria for diagnosis where morphological criteria fail. Translocations in different types of sarcoma show remarkable similarities: a gene with an RNA binding domain fuses with a transcription factor gene. The relationship between genetic configuration and phenotype is far from clear. Insights into the function of oncogenes have their origin in finding the homology between Rous Sarcoma Virus and proto-oncogenes. In acute promyelocytic leukaemia, the chromosomal translocation results in expression of retinoic acid receptor, which has therapeutic implications [6]. It might be expected that knowledge and understanding of the molecular basis of disease eventually results in better therapy.

The indication for chemotherapy is seldom a matter of right or wrong. Where moderate efficacy and moderate to considerable toxicity prevail, a prudent approach is justified. As soon as therapy results in control over disease at the cost of acceptable toxicity, the threshold comes down. The future is promising, provided preclinical and clinical research continues.

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