such patients with those agents, and I would suggest that disease-specific phase II studies for these tumours be undertaken and that they be excluded from phase III trials.

At present, for patients with advanced soft tissue sarcomas, we are limited to solutions that will ultimately seem barbaric, once we learn the specific molecular therapy with total selectivity for each specific cancer being treated. Our only weapons against these tumours today are intensive, toxic, chemotherapeutic programmes, but we must be reminded of the teachings of Hippocrites [11].

> Diseases desperate grown
> By desperate appliance are reliev'd
> Or not at all.

Shakespeare's elegant translation [12] of the aphorism.

> For extreme illnesses extreme treatments are most fitting.

Translated to medical oncology, I would suggest the following rendition:

> The worst toxicity is progressive cancer.

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Contra:

J. Rouëssé and H. Bourgeois

Centre René-Huguenin de Lutte Contre le Cancer, 35 rue Dailly, 92210 Saint-Cloud, France

Is it ethical to offer patients with disseminated soft tissue sarcoma (locally advanced and/or metastatic) first-line chemotherapy in a phase II trial, i.e. anything other than 'routine' chemotherapy? An advanced soft tissue sarcoma, unless it can be adequately excised, is almost always fatal, with a median survival time of approximately 1 year. The few drugs that, alone or in combination, have appeared to be effective in this setting have only given very low response rates. The question, thus, arises as to whether these patients should be treated systemically, especially when they are asymptomatic, given the lack of satisfactory treatment, and whether patients with symptomatic manifestations should start with a known, but poorly effective, treatment or a new therapy with unknown efficacy.

RESULTS OF PUBLISHED PHASE II AND PHASE III TRIALS

It should be noted that the great majority of drugs selected for their efficacy in the treatment of soft tissue sarcomas were chosen on the basis of phase II trials involving patients in whom first-line chemotherapy had failed, either immediately or secondarily. Of the 20 or so products tested by the EORTC Soft Tissue and Bone Sarcoma Group, four appeared to be effective, with response rates ranging from 5 to 15%; they comprise doxorubicin [1], ifosfamide [2–6], high-dose DTIC ($> 1\ g/m^2$) [7] and docetaxel [8]. To this list can be added a nitrosourea, nimustine, which appears to have been abandoned because of its toxicity [9].

The three main products used in first-line therapy (doxorubicin, ifosfamide and DTIC) have given response rates of around 20% when used alone [1, 9–17]. These three products have been combined with each other and also with actinomycin D and vincristine, the latter showing no significant efficacy during phase II trials. The reported objective response rate to these combinations varies between 20 and 50%, with 3–12% of complete responses [9–14].

Several randomised trials have demonstrated that multidrug regimens have no advantage in terms of objective responses. The EORTC randomised trial [15] involving more than 700 patients, gave an objective response rate of 28% with the doxorubicin–ifosfamide combination and the classic Cyvadic regimen (cyclophosphamide, vincristine, doxorubicin, DTIC), compared with 23% with doxorubicin monotherapy ($75\ mg/m^2$), a difference that was not statistically significant. It must be noted that the dose of doxorubicin monotherapy is higher than that used in combinations

(50 mg/m^2). Indeed, some trials have shown a dose–effect relationship. To improve the activity of the doxorubicin–ifosfamide combination, the EORTC conducted a randomised trial comparing this combination with and without granulocyte-macrophage colony stimulating factor (GM-CSF), a haematopoietic growth factor; patients receiving GM-CSF were given 75 mg/m^2 doxorubicin, compared with only 50 mg/m^2 in the arm without GM-CSF; the ifosfamide dose was the same in both arms. The response rates were similar: 23.2% and 20.9% with and without GM-CSF, respectively [16].

INCIDENCE OF THE RESPONSE RATE ON SURVIVAL

Another question is whether the response rate to chemotherapy has an influence on survival. Some trials have effectively revealed statistically significant differences between objective response rates. This was the case in one of the first EORTC trials, which compared Cyvadic every 28 days with a modified Cyvadic in which the cyclophosphamide–doxorubicin combination was only given every 8 weeks; although the response rate was 35% with conventional Cyvadic and 14% with modified Cyvadic (a statistically significant difference) there was no difference in the survival rate [17]. Similarly, there was no difference in survival in the SWOG–CALGB trial comparing the MAID protocol (doxorubicin, ifosfamide, DTIC) and the ADIC combination (doxorubicin, DTIC, cyclophosphamide), despite a statistically significant difference in response rate (32% with MAID, 17% with ADIC) [18]. Only an old study by the EORTC comparing doxorubicin (objective response rate 20%) with carminomycin (objective response rate 3%) showed a small but significant difference in terms of survival, which disappeared when only patients with evaluable targets were considered [19]. The objective response rate is of limited value as it bears little relation to survival [13, 17]. This is why treatment with doxorubicin alone at a dose of 60–75 mg/m^2 every 3 weeks can be considered as the reference first-line treatment.

In light of these results it seems acceptable to switch directly to phase II trials with drugs that have no documented efficacy in this setting. It may even be best not to treat at all when the patient is asymptomatic, but this approach has not apparently been studied specifically.

PROGNOSTIC FACTORS IN DISSEMINATED FORMS

It is important to ensure that there are no subgroups of patients with good prognostic forms who might benefit substantially from conventional therapy. The EORTC trial involving 1742 patients with metastatic soft tissue sarcomas who were enrolled in phase II and phase III protocols between 1976 and 1990 identified predictive criteria for objective responses and overall survival [20]. Patients over 60 years of age, those with poor general status (performance status 3–4) and those with liver metastases had a poorer outcome than other patients. Finally, certain histological subtypes, such as leiomyosarcoma, appear to respond less well to chemotherapy, while a lipomatous or synovial component is generally favourable.

Some surgical series have shown a 5-year survival rate of around 20% in patients with pulmonary metastases able to undergo metastasectomy, which is far from negligible in this disease. Certain conditions must be met, such as a total number of metastases below five, a doubling time exceeding 21 days, and a free period of more than 1 year [21].

Similarly, in locally advanced forms, first-line chemotherapy with or without external radiation therapy can lead to tumour regression (even less than 50%) that permits surgical excision, possibly followed by radiation therapy, which would otherwise have been impossible or only feasible at a cost of major mutilation. Multidisciplinary approaches give a 2-year survival rate of more than 50% in many published series [22–25].

It is, therefore, important to isolate patients with locally advanced lesions and/or a small number of pulmonary metastases, which are slowly progressive and suitable for surgery. These patients should receive an approach comprising conventional neoadjuvant chemotherapy (e.g. a combination of doxorubicin–ifosfamide or doxorubicin–DTIC) in order to obtain tumour regression before surgery. In such conditions of neoadjuvant chemotherapy, a certain degree of therapeutic intensification may be warranted, with haematopoietic growth factor support to obtain an optimal response and to facilitate surgical excision. The response to induction chemotherapy seems to be a favourable predictive factor for overall survival and relapse-free survival.

For all other patients, the potential benefit of conventional chemotherapy appears to be nil in terms of survival, and treatment intensification combining reference products (doxorubicin and ifosfamide) has not improved median survival rates. It therefore seems perfectly ethical and even advisable to test new potentially active drugs in prospective and intensive clinical research, both to improve the poor results otherwise obtained and to give these patients the chance of benefiting from drugs that have shown promise in other settings.

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Arbiter:

Q.G.C.M. van Hoesel

University Hospital Nijmegen, Department of Internal Medicine, Division of Medical Oncology, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

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