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Current Controversies in Cancer

Should Patients with Advanced Sarcomas be Treated with Chemotherapy?

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PATIENTS WITH advanced sarcomas present either with metastatic disease or with primary tumours that are too large or too closely involve vital structures for definitive surgical resection. Is there a role for chemotherapy in the management of such patients? Is chemotherapy indicated routinely in the management of such patients? Does chemotherapy add to surgery in patients suitable for surgical resection? What other options exist? Possible indications for chemotherapy in the management of patients with sarcomas include treatment of micrometastases, improvement of local control following resection, conversion of unresectable tumours into resectable tumours and the treatment of metastatic disease. Only these last two indications will be considered in this paper.

The objectives of chemotherapy treatment of metastatic sarcomas include cure, prolongation of survival and relief of symptoms. While it seems unusual on the one hand to be debating whether chemotherapy has a role in the routine management of patients with advanced sarcomas and on the other hand to be discussing cure, it is clear that a small number of patients with advanced sarcomas can be cured with chemotherapy, despite the relative resistance of these tumours to most chemotherapeutic agents [1, 2]. In a review by Yap of patients treated at the University of Texas M.D. Anderson Cancer Center on a series of chemotherapy protocols between 1971 and 1977, a cohort of patients was identified with continuous disease-free survival in excess of 5 years. 55 of 331 patients achieved a complete remission with chemotherapy. An additional 26 patients who had achieved either a minor response or a partial response to initial chemotherapy were rendered free of disease with subsequent surgical resection. The most important prognostic factor for long-term disease-free survival among patients with complete response was the character of the advanced disease: locally advanced disease versus metastatic disease. Patients with locally advanced disease, that is, localised tumours not initially suitable for surgical resection, had a 35–45% long-term continuous disease-free survival if they achieved complete remission either with chemotherapy or surgery (Figure 1a). Patients with metastatic disease had less favourable results. None the less, 12–25% of those patients achieving complete remission either with chemotherapy alone or with chemotherapy plus surgery were long-term disease-free survivors (Figure 1b). Since the overall complete remission rate was only 25% (counting both chemotherapy and surgery) and since only approximately 25% of those patients are cured, the overall cure rate is around 5–6%. However, without chemotherapy, the cure rate would be 0!

The second objective of chemotherapy for patients with advanced sarcomas is prolongation of survival. While statisticians tell us that it is improper to compare the survival of chemotherapy responders with that of non-responders, the following case will illustrate the clear-cut causal relationship between chemotherapy effect and prolongation of survival, even in patients who are not cured. A 19 year old man presented in November 1987 with a synovial sarcoma of the right proximal thigh and a barely visible pulmonary metastasis. The primary tumour was treated with radiation therapy without surgery. The patient was advised that chemotherapy was not effective in the treatment of synovial sarcoma and he remained untreated for 5 months and presented to us with the X-ray shown in Figure 2(a). Clearly, considering the rate of progression of his disease from the time of his diagnosis until his presentation at M.D. Anderson, no one would estimate his life expectancy to have been more than 2 or 3 months. He was started on chemotherapy on our protocol for cyclophosphamide, doxorubicin and dacarbazine (*CyADIC*) plus granulocyte-macrophage colony stimulating factor [3], and when he was admitted for fever and neutropenia 2.5

weeks later, he was already in partial remission (Figure 2b). Response stabilised in late September (Figure 2c), and his chemotherapy was changed from CyADIC to ifosfamide. He had another partial response (Figure 2d) followed by attempted surgical resection of residual disease. However, the residual tumour could not all be resected. Eventually the tumour progressed, and he died of a cerebral haemorrhage secondary to brain metastases in October 1989. Thus, from his presentation in April 1988, when his life expectancy was only a month or so, he survived 18 months as a result of his partial response to chemotherapy.

The third objective of chemotherapy is relief of symptoms. When the patient just described presented to our institution, he was dyspnoeic on minimal exertion and required oxygen. After his initial response to chemotherapy, the patient's symptoms disappeared and he resumed normal function. While there is no way to predict the degree of response in any patient a priori, it is obvious that if one had known the responsiveness of this young man's disease to chemotherapy, it would have been given at the time of his presentation with minimal disease 5 months earlier. The opportunity for cure may have been lost in this patient because of the extent of metastatic disease present by the time chemotherapy was finally initiated.

While it is clear that younger patients tolerate aggressive chemotherapy much better than older patients, this fact should not restrict the use of chemotherapy in older patients. Figure 3(a) shows the X-ray of a 63 year old woman with metastatic angiosarcoma of the scalp. Figure 3(b) shows her response after one course of ifosfamide chemotherapy at a dose of 2 g/m^2 as a 2-h infusion given daily for 5 consecutive days.

Another indication for the use of chemotherapy is an attempt at making otherwise unresectable tumours resectable. That is, the involved site may be too large or in the wrong location for adequate surgical resection. Figure 4(a) shows the chest X-ray of a 53 year old woman with a metastatic unclassified sarcoma. She presented in 1988 with a large unclassified sarcoma of the left thigh that was resected and treated with six courses of adjuvant single-agent doxorubicin therapy. In 1990, she had a local recurrence, which was resected followed by ifosfamide chemotherapy. In 1993, she again had a local recurrence treated with hip disarticulation and doxorubicin/dacarbazine (DTIC) chemotherapy. In June 1994, she developed a left pulmonary metastasis which was treated with resection and paclitaxel chemotherapy. She presented to us in November 1995 with rapidly growing pulmonary metastatic disease as shown in Figure 4(a). She was presented at our Multidisciplinary Thoracic Sarcoma Planning Clinic and the thoracic surgeons declined resection of the pulmonary mass because of its size, location and rapid growth. We therefore recommended high-dose ifosfamide chemotherapy: 2 g/m^2 every 12 h for seven doses [4]. Chemotherapy was started in December. After four courses of chemotherapy she had an apparent good partial response as indicated in Figure 4(b), and underwent resection of the residual tumour. The resected mass contained necrotic debris but no viable tumour cells. Thus, she had a pathological complete remission, despite multiple courses of prior chemotherapy, including lower doses of the same drug to which she subsequently had complete response.

Figure 5(a) shows a computed tomography (CT) scan of a 47 year old woman with a metastatic pleomorphic sarcoma rising in the chest wall and metastatic to the mediastinum. She was treated with doxorubicin/ifosfamide chemotherapy at a dose of 75 mg/m^2 doxorubicin as a 72-h infusion and 10 g/m^2 of ifosfamide in divided doses of 2 g/m^2 over 2 h daily for 5 days [5]. After three courses of chemotherapy, there was no reduction in the size of the tumour and even, perhaps, a slight increase. However, the mass showed considerable central necrosis (Figure 5b). The tumour was resected, together with a portion of the aorta, which was replaced with a graft. The mass consisted predominantly of haemorrhagic and necrotic

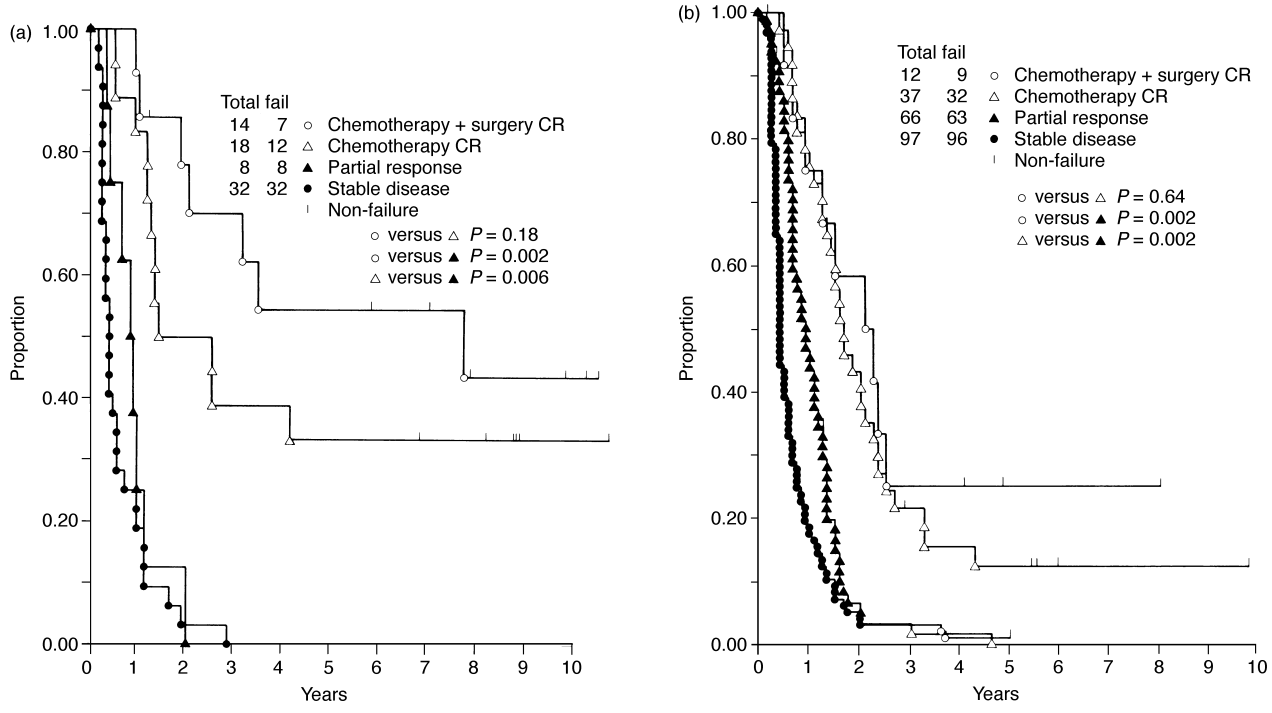

Figure 1. Soft tissue sarcomas. Time to progression (a) locally advanced disease; (b) distant metastases.

tissue. Less than 1% of the mass showed viable neoplastic cells, and these demonstrated a marked effect of therapy. Thus, what might have appeared to be stable or even progressive disease, was actually nearly a complete response. These last two cases indicate that traditional criteria of response do not always apply when evaluating patients with metastatic sarcomas. The elements of response may include a decrease in tumour size, but an increase in necrosis or even a change in the pattern of growth may indicate a response to therapy. Whenever possible, surgical resection and pathological evaluation of the tumour specimen should be utilised to determine the efficacy of therapy. The corollary to these statements is that patients with sarcomas treated with chemotherapy should continue therapy until clear-cut progressive disease. Otherwise, one might stop treatment in a responding patient and allow a treatable tumour to progress and ultimately kill the patient.

So, back to the original questions: is chemotherapy indicated routinely in the management of patients with advanced or metastatic soft tissue sarcomas? Does chemotherapy add to surgery in the management of patients with advanced or metastatic sarcomas? I hope that the previous examples have indicated that the answer to these questions is yes. I would also suggest that they are the wrong questions. The real questions we should ask are the following: are current results adequate for routine use? Which regimen should be used? Which strategy should be used? While the answer to these questions are beyond the scope of the current article, focusing on developing the answers may lead us to improved methods of treatment.

There are a few special cases that should be noted as exceptions to the rule. While patients with advanced disease all deserve a trial of chemotherapy, in my opinion, patients with leiomyosarcoma of gastrointestinal origin, alveolar soft part sarcoma and most patients with chondrosarcomas rarely respond to the standard drugs used in the treatment of other soft tissue sarcomas, that is, doxorubicin and ifosfamide [6–10]. It makes little sense, in my opinion, to treat

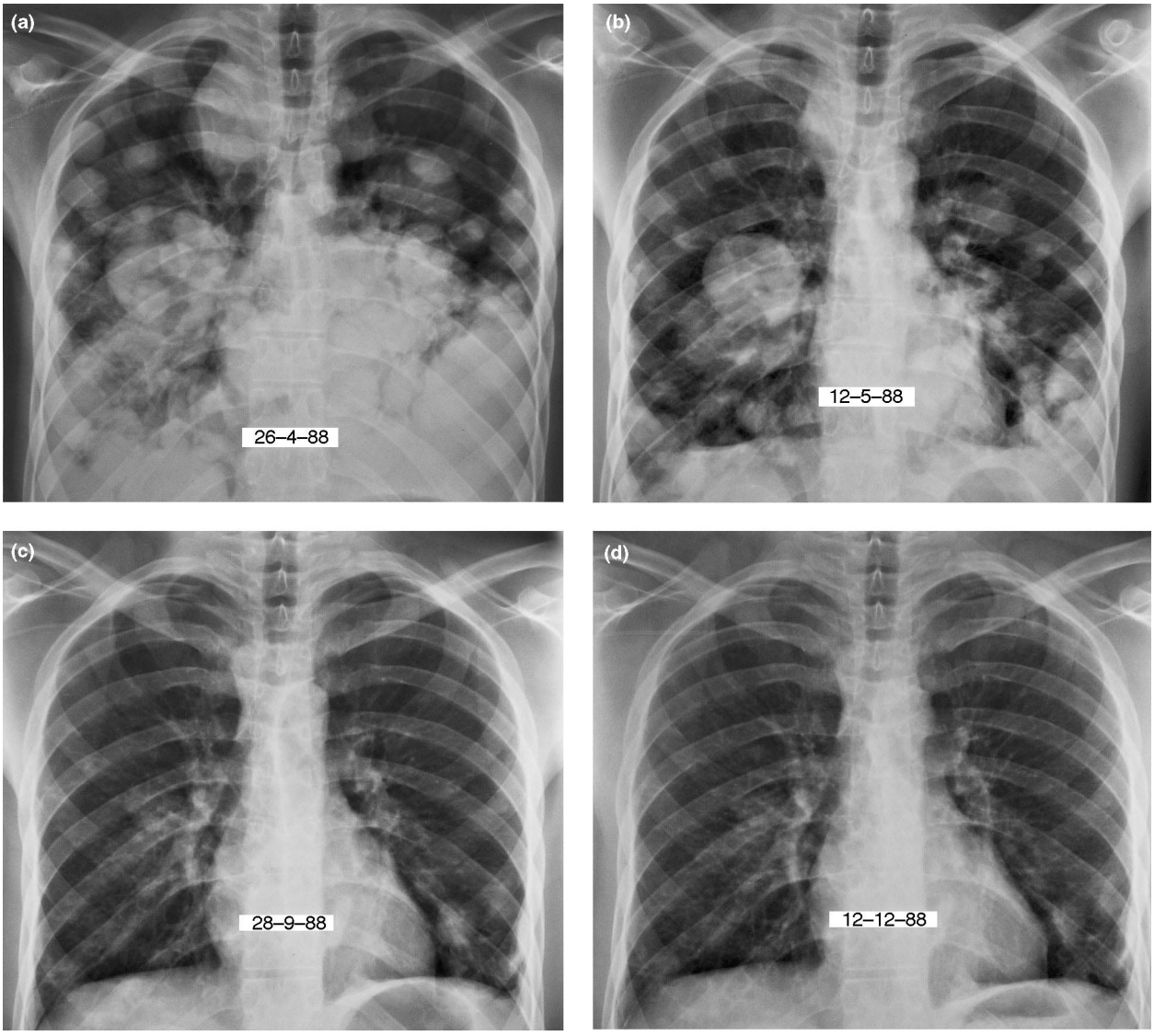

Figure 2. Metastatic synovial sarcoma. (a) Baseline chest X-ray. (b) Partial remission with CyADIC. (c) Maximum response with CyADIC. (d) Further partial response with ifosfamide.

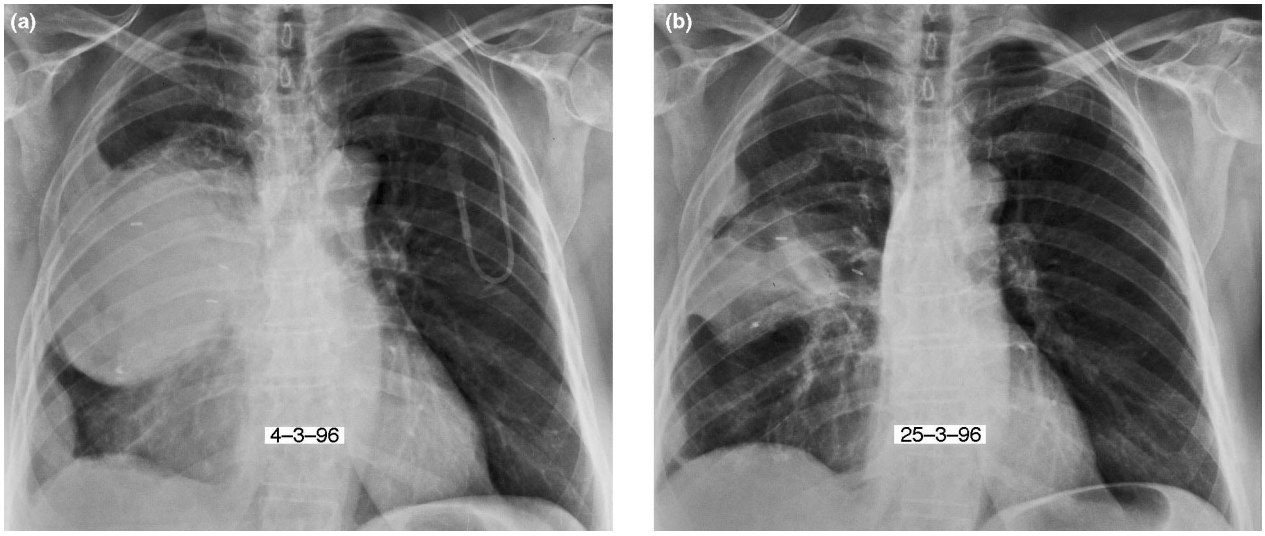

Figure 3. Metastatic angiosarcoma in a 63 year old woman (a) before; and (b) after one course of ifosfamide.

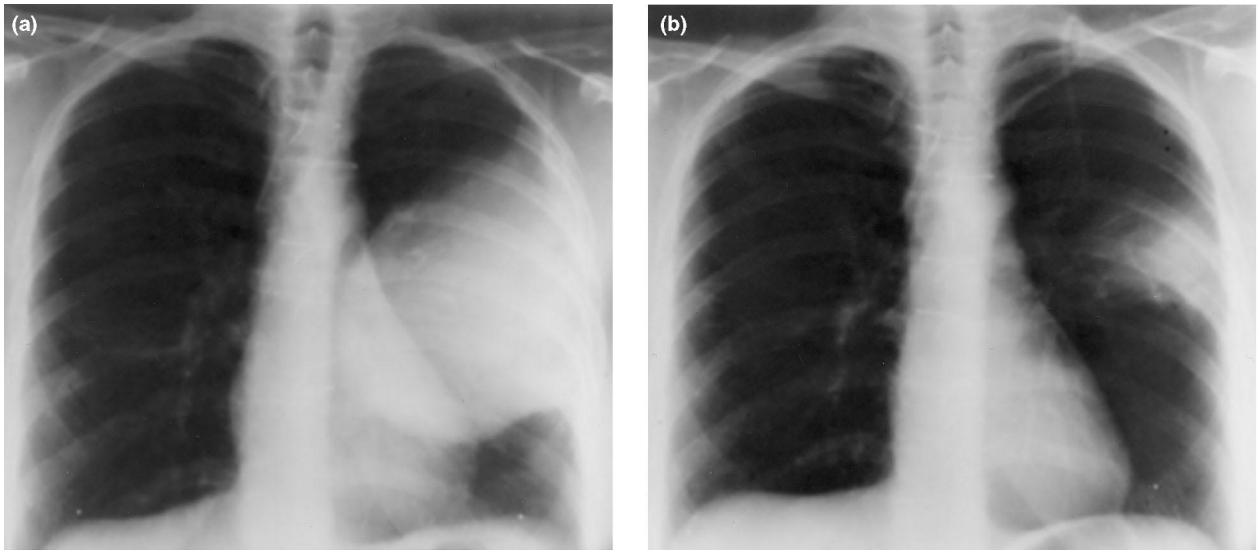

Figure 4. Metastatic unclassified sarcoma. (a) Unresectable tumour prior to chemotherapy. (b) Resectable residual with no viable tumour at surgery.

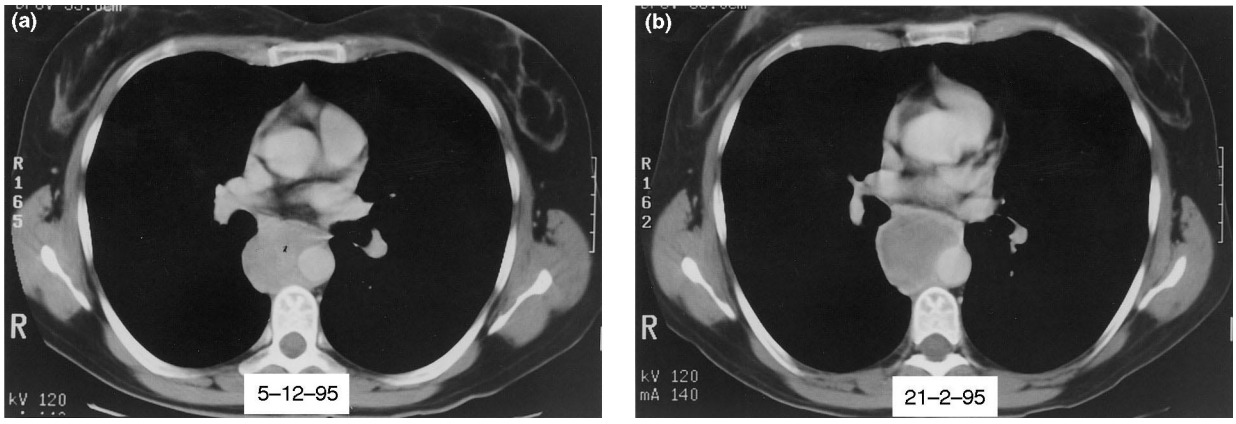

Figure 5. Malignant fibrous histiocytoma (a) before; and (b) after doxorubicin/ifosfamide chemotherapy. Less than 1% of the mass in (b) was viable tumour.

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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11. Hippocrates. see I, 6. *Aphorisms*.
12. Shakespeare W. *Hamlet* IV, iii, 9.

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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