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Arbiter

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SOFT TISSUE sarcoma of adults is not highly responsive to chemotherapy. Doxorubicin is the best single agent, but a dose of 60–75 mg i.v. every 3 weeks produces a response rate only of the order of 20% (15–35%) and change in the schedule of administration has not resulted in improvement [1]. The analogue epirubicin has been evaluated in a large randomised trial by the EORTC but no advantage over doxorubicin has been demonstrated [2]. Other analogues have also been shown to have limited activity. Ifosfamide is also of value in treating patients with advanced sarcoma and is capable of producing tumour responses in patients previously treated with doxorubicin. Its use as a single agent produces responses of a similar magnitude to doxorubicin [3, 4]. Other alkylating agents have limited or no activity in adult patients with sarcoma. The case for dacarbazine (DTIC) having useful activity is less convincing, but the agent when used singly has been reported in the early literature to be accompanied by a response rate of 17% [5]. A large number of other single agents have been evaluated in phase II trials but no useful response rates have been observed, although these drugs have usually only been tested in previously treated and refractory patients. The agents we have available provide only modest benefit and new more effective agents are urgently required.

The evidence for combination chemotherapy being more effective than full-dose single-agent doxorubicin therapy is rather weak and, although some randomised trials have shown a beneficial effect associated with the addition of ifosfamide or DTIC to doxorubicin in terms of response rate, survival has not been improved [1, 6, 7]. Other randomised studies have shown no such benefit [8–10], although the results may have been compromised by the addition of relatively ineffective drugs (cyclophosphamide and vincristine) in the first two studies and the use of a lower dose of doxorubicin in the group of patients receiving combination chemotherapy in the EORTC study [10].

Some evidence that the dose and dose intensity of doxorubicin is important in improving the response rate is available [11], but no studies have been carried out with an appropriate randomised design to confirm this. However, two randomised studies comparing different dose intensities of the CYVADIC combination have shown an advantage for the higher dose intensity [12, 13], although the higher dose intensity was the standard approach and the alternative schedule was of lower intensity. It is difficult to increase the dose intensity of doxorubicin to levels providing a realistic chance of improving the complete response rate and survival for adults with sarcoma. A 5-fold increment in dose intensity has been obtained using G-CSF but the doses of 100–150 mg every 2 weeks × 3 were accompanied by unacceptable toxicity [14].

Relatively modest increases in the dose intensity of single-agent ifosfamide (up to 3-fold) have produced responses in patients shown to be refractory to standard-dose therapy [15, 16]. The response rate associated with the higher doses, 28–55%, seems promising but this apparent advantage requires confirmation using a randomised study.

Single-agent studies suggest that a dose-intensive combi-

nation of doxorubicin and ifosfamide would provide the best prospect for improving the complete response rate and survival in patients with advanced disease. A pilot study by the EORTC using this combination with a modest increase in dose intensity in association with GM–CSF resulted in a 45% overall response rate (10% complete response rate) in 111 patients, a better result than in any other previous trial conducted by the EORTC. However, a subsequent randomised trial failed to confirm any advantage for the higher dose intensity [17]. A more dose-intensive regimen using 12.5 g/m^2 ifosfamide and 90 mg/m^2 epirubicin has been attended by an overall response rate of 52% (21% complete response rate) in a phase II study, but again this apparent improvement needs confirmation in a randomised study [18].

It must be concluded that at the present time the evidence that combination chemotherapy delivered with a modest increase in dose intensity is of little practical advantage over the use of standard-dose chemotherapy in the management of patients with advanced sarcoma.

Although no randomised trials have been carried out, the use of myeloablative chemotherapy has been evaluated using phase II trials. Apparently high response rates have been reported with some long-term survivors using a variety of myeloablative therapies but the majority of patients treated have been children or adolescents with rhabdomyosarcomas, Ewing's sarcoma or other undifferentiated sarcomas with a reported high response rate to standard chemotherapy. It is in these groups of patients where a benefit of high-dose chemotherapy is most likely to lie. Patients shown to be responsive to initial chemotherapy are those most likely to benefit from high-dose chemotherapy for their residual disease. Randomised trials to demonstrate any benefit will be difficult since the tumours are uncommon and their biology is diverse. In addition, centres where patients with sarcomas are treated are often not those where facilities for high-dose chemotherapy are readily available. Nevertheless, if answers to these important questions are to be found, randomised trials involving the most likely patients to benefit must be carried out. This is the role of an intergroup combining the resources of those involved in the management of both paediatric and adult sarcoma.

New approaches are required if long-term survival is to be increased substantially in adults with sarcoma. One approach might be to use isolated limb perfusion to allow dose-intensive therapy for locally advanced tumours which are not curable using initial surgery. Promising results have been obtained by Eggermont and colleagues using isolated limb perfusion with TNF–alpha interferon-gamma and melphalan at 39–40°C [19]. Major tumour responses were seen in 87% with success in limb salvage following subsequent surgery of 86% for the lower and 71% for the upper limb. This seems a remarkably effective way of reducing the tumour burden allowing a subsequent potentially curable approach.

The management of patients with sarcoma involves a multidisciplinary approach with surgery, radiotherapy and chemotherapy all playing their part. Most patients who die do so with metastatic disease and this plays a leading part in the cause of death. Substantial improvement in the long-term survival of patients with sarcoma requires methods for dealing with this and a dose-intensive approach in a setting of minimal residual disease is a technique well worth further investigation. Phase II methods are important as a preliminary, but the patient diversity between centres carrying out these studies indicates that meaningful comparisons between studies is impossible without an appropriate phase III study. Until this is done the case for dose-intensive chemotherapy will remain unproven.

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