State-of-the-art approach in selective curable tumours:
soft tissue sarcoma

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introduction

Soft-tissue sarcomas (STS) are rare malignant mesenchymal tumours with an extremely diverse range of clinical behaviours. They are said to comprise no more than 1% of all cancers, with an overall incidence of 30–40 per million per year [1]. They may arise in any part of the body, the majority being found in the limbs or limb girdles. Surgery for localized disease may be curative, but for some aggressive, but chemo-sensitive, tumours with a high incidence of metastatic disease, such as Ewing’s family tumours, this needs to be combined with chemotherapy. However effective the local treatment may be, approximately half of all patients with the commoner types of adult STS will die of their disease, a proportion that has changed little in recent years [2]. The question then is what can be done to enhance the cure rate?

earlier diagnosis

Size is a continuous variable for prognosis of STS, and there is no doubt that better recognition and earlier referral for specialist care have the potential to improve the outlook. The most widely used American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system is weighted towards tumour grade, which has changed little in recent years [3]. The question then is what can be done to enhance the cure rate?

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multidisciplinary teams

Many publications have emphasized the importance of multidisciplinary teams working in specialist centres in improving the care of patients with STS [7–9]; this principle is embedded in various guidelines for sarcoma care [10]. Expert histopathological and radiological diagnostic opinions and the appropriate and judicious use of adjuvant radiotherapy or, on occasion, downstaging chemotherapy, all undoubtedly enhance the value of high-quality surgical expertise. An accurate diagnosis, usually by histological examination of a core biopsy, which has an accuracy of >95%, is vital. Detailed localization of the tumour is clearly necessary for the planning of the surgical excision. Magnetic resonance imaging is preferred for limb sarcomas, but computed tomography (CT) is probably better for abdominal sarcomas, often allowing diagnosis of liposarcoma, the commonest retroperitoneal sarcoma, on the basis of fat content [8]. Staging is important; the commonest site of metastatic disease for most STS is the lungs, usually evaluated pre-operatively by CT.

surgery

The goal of surgery is limb conservation utilizing a wide excision that removes an adequate margin, e.g. 2–3 cm, of normal tissue around the entire tumour. If unavoidable, a planned marginal excision is not associated with an increased risk of relapse, especially if this includes a resectable fascial plane or barrier such as periosteum or perineurium, compared with a true wide excision, provided it is combined with adjuvant radiotherapy. A true wide excision is difficult to achieve in the case of retroperitoneal sarcomas, even if adjacent organs are sacrificed, as is often required. Pre-operative biopsy is best avoided prior to the removal of obviously resectable
condition desmoplastic small round cell tumour, a disease that also employed in the primary management of the rare identical fashion to Ewing’s sarcoma of bone. Chemotherapy is including soft tissue Ewing’s sarcoma and primitive tumours rhabdomyosarcoma and the Ewing’s family tumours substantially improves outcome, namely the small round cell subtype [18].

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radiotherapy

Radiotherapy improves the local control of high-grade or marginally excised limb sarcomas [11] and is usually delivered post-operatively. A randomized trial of pre-operative versus post-operative radiotherapy demonstrated that there was an increased risk of wound complications with pre-operative treatment but that the long-term morbidity was less because the treatment volumes were smaller [12]. Pre-operative treatment has been adopted routinely by some centres. The role of radiotherapy in the treatment of retroperitoneal sarcomas is unclear.

systemic treatment

Conventional chemotherapy has little role to play in the routine primary management of most types of STS. A meta-analysis of adjuvant chemotherapy was published in 1997 which demonstrated a small progression-free survival benefit but no statistically significant survival benefit [13]. A small study performed by the Italian Sarcoma Group in a selected population of patients with large, high-grade limb and limb girdle sarcomas did initially show a statistically significant survival advantage [14], but with longer follow-up the significance was lost [15]. Recently, one of the largest adjuvant studies to be performed in this group of diseases, in which 351 patients were recruited, was reported on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG); this failed to demonstrate a benefit in overall or relapse-free survival [16]. Once metastatic disease has developed very few patients are cured, although long-term survival has been reported in a few cases, either where chemotherapy has resulted in durable complete remission or as a result of successful pulmonary metastasectomy [17]. One of the most promising new approaches to the systemic treatment of STS is inhibition of angiogenesis. A Phase II study by the EORTC STBSG with the receptor tyrosine kinase inhibitor pazopanib, that targets vascular endothelial growth factor receptors (VEGFR), demonstrated a significant level of disease stabilization in all strata apart from liposarcoma, including some partial remissions [18].

However, there are diseases where chemotherapy substantially improves outcome, namely the small round cell tumours rhabdomyosarcoma and the Ewing’s family tumours including soft tissue Ewing’s sarcoma and primitive neuroectodermal tumour (PNET), which are treated in an identical fashion to Ewing’s sarcoma of bone. Chemotherapy is also employed in the primary management of the rare condition desmoplastic small round cell tumour, a disease that usually presents in the abdomen in young men, but the results are somewhat unpredictable.

rhabdomyosarcoma

The small round cell variants of this disease more commonly occur in children, and although rare are actually the commonest sarcomas to occur in this age group. Embryonal rhabdomyosarcoma carries a better prognosis than the alveolar subtype, which is characterized by chromosomal translocations t(2;13)(q35;q14) (PAX3/FKHR) and t(1;13;q36q14) (PAX7/ FKHR). The prognosis varies according to age, site, stage and subtype; patients with localized, stage I embryonal rhabdomyosarcoma enjoy a good prognosis, but the outlook for stage IV disease is still poor, especially for the alveolar subtype. A multidisciplinary approach has resulted in improved outlook, as with other sarcomas [19]. Adults tend to fare much worse, even when presenting with localized embryonal disease; the reasons for this are unclear but may relate to inadequate treatment intensity [20]. It is recommended that adults be treated using paediatric protocols [21]. Combination chemotherapy regimens employ ifosfamide, vincristine, doxorubicin and actinomycin D. Topoisomerase I inhibitors are being investigated as part of first-line therapy and there are pre-clinical data indicating that mammalian target of rapamycin (mTOR) inhibitors may also be of value [22].

Ewing’s family tumours

Induction and maintenance combination chemotherapy with a similar range of agents to those used in the treatment of rhabdomyosarcoma has substantially improved the prognosis of patients with Ewing’s sarcoma and PNET. In patients with localized disease at diagnosis the cure rate is the region of 65% in the best series. In the series of trials performed by the CESS group in Germany and Austria it was demonstrated that ifosfamide appeared to be of particular value, and moderately high-dose ifosfamide has been incorporated into subsequent studies [23]. The current European trial, EURO-EWING 99, utilizes a four-drug induction regimen of vincristine, ifosfamide, doxorubicin and etoposide. It also addresses the question of whether high-dose chemotherapy is of additional value in patients with a sub-optimal histological response to induction chemotherapy or pulmonary metastases at presentation, a proportion of whom are still cured. Additional agents of interest are topoisomerase inhibitors, a synthetic retinoid called fenretinide [24], angiogenesis inhibitors, such as bevacizumab [25] and, most recently, inhibitors of insulin-like growth factor one receptor (IGF-1R), known for some years to be a potential target in Ewing’s sarcoma [26]. In a Phase I clinical trial of a monoclonal antibody inhibitor of IGF-1R, R1507, a number of patients with refractory Ewing’s family tumours responded extremely well [27]. Although the role of IGF signalling was known, until recently there were no agents capable of selectively inhibiting the target without simultaneously inhibiting the insulin receptor. A number of clinical trials are now under way to investigate IGF-1R inhibitors in Ewing’s sarcoma and, if successful, such an agent is likely to be incorporated into first-line therapy trials.
gastrointestinal stromal tumour

In addition to mTOR and IGF-1R inhibitors, mentioned above in relation to rhabdomyosarcoma and Ewing’s sarcoma, one of the most important developments in sarcoma therapy has been the introduction of imatinib for the treatment of GIST [28]. Unresectable or metastatic GIST was essentially untreatable prior to the advent of imatinib, and there is no doubt that it has had a major impact on the prognosis of this disease [29]. However, it is less clear whether or not imatinib has a role in enhancing the curability of GIST. There are clearly patients with bulky tumours that are unresectable or of only borderline resectability at presentation who may be rendered operable by prior therapy with imatinib [30, 31]. This will undoubtedly improve their outlook. However, such patients, with large tumours >10 cm in diameter, have a very high risk of recurrent or metastatic disease. Will imatinib treatment lead to cure in a proportion of these patients? Currently we do not know the answer to this question. However, adjuvant trials are already demonstrating that imatinib can enhance relapse-free survival. One such study, the Phase III US Intergroup Study ACOSOG Z9001, randomized patients with completely resected GIST >3 cm in diameter to 12 months of imatinib 400 mg daily or placebo. The study demonstrated a statistically significant improvement in 1-year relapse-free survival from 83% to 97%, with particular benefit being seen in the high-risk group (large tumours, mitotic rate >5/50 high-power fields) [32]; This study was not powered to demonstrate a survival benefit, but a study currently being conducted by the EORTC STBSG, trial 62024, has survival as the primary endpoint. This trial randomizes patients with intermediate and high-risk tumours to 2 years of treatment with imatinib or observation alone, has so far recruited 750 patients and is due to recruit another 150 patients before it closes. Another study, currently being conducted by the Scandinavian Sarcoma Group, aims to answer a slightly different question and is randomizing patients with exclusively high-risk disease to 1 or 3 years of imatinib therapy. This does not have a no-treatment arm. Clearly as more is learnt about the molecular determinants of prognosis in this fascinating disease it may be possible to target such therapy more precisely to those patients who are likely to benefit.

conclusions

A proportion of patients with soft tissue sarcomas with localized disease are cured by surgery. A small minority of patients with metastatic spindle cell sarcomas with a complete remission following chemotherapy have prolonged survival [17]. This is also seen in a proportion of patients who have pulmonary metastasectomy [33]. The true incidence of prolonged disease-free survival in this highly selected group of patients is probably in the region of 20%. The ‘paediatric’ small round cell sarcomas rhabdomyosarcoma and Ewing’s family tumours are generally responsive to cytotoxic chemotherapy, which together with improved local therapy has resulted in steadily improving outcomes, especially in Ewing’s. The inhibitor of KIT and PDGFRA, imatinib, is a proven therapy for GIST and is being studied in the adjuvant setting, where it could lead to a further improvement in the outlook of patients with high-risk disease. New molecularly targeted therapies are currently being tested, including inhibitors of IGF-1R (Ewing’s family tumours and other sarcomas including rhabdomyosarcoma and synovial sarcoma) and angiogenesis inhibitors. Currently their potential to influence long-term prognosis or curability is unknown, but if a significant benefit in the treatment of advanced disease is proven they also clearly have the potential to exert a significant effect in the adjuvant setting which may improve our ability to cure these rare and fascinating tumours.

In the short term what is important is to try and ensure that patients are diagnosed earlier and that they are then referred to appropriately skilled and experienced multidisciplinary teams. Evidence points to significant improvements in outcome for patients treated in specialist centres, hence the establishment and implementation of guidelines for diagnosis and referral, and ensuring that the skills required for management of these patients are in place, have the potential to generate significant benefits for sarcoma patients [9, 34, 35]. Regular audits are then required to determine the level of compliance, since in spite of evidence that care is enhanced by the application of management guidelines, conformity to these is only likely to happen in specialist centres, another reason for the centralization of care [34]. The success of imatinib in treating one small subset of patients has raised the profile of sarcomas in general, but it is improvements in diagnosis and multidisciplinary care that are likely to lead to the greatest improvements in outcome for the foreseeable future.

disclosures

The author has received honoraria from Novartis, Pfizer, PharmaMar, GSK and Ariad for attendance at advisory boards and company sponsored symposia in relation to sarcoma.

references


