Chemotherapy for adult soft tissue sarcoma

Does it work?

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The group of tumours termed adult tissue sarcomas (ASTS) is heterogenous, both with respect to histological types and grade of malignancy. The group is currently divided into approximately 30 distinct tumours, of which several are further subdivided [1]. Futhermore, the group is heterogenous with regard to tissue origin and tumour localisation, with 50–60% in the extremities, 15–20% in the trunk wall, 15–25% in the abdomen and retroperitoneum (15–25%), and 5-10% in the head and neck region [2]. In general terms, the ASTS group is considered only moderately sensitive to cytostatic agents, and chemotherapy has not as yet found of any routine place in adjuvant therapy, and its role in prolonging survival for patients with advanced disease also remains controversial. However, the evaluation of the value of chemotherapy in ASTS is usually based on the entire ASTS goup of tumours considered together, and the question arises whether chemotherapeutic strategies to a larger extent should be designed to match the features of specified subgroups of tumours, the mode of action of individual cytostatic agents, and the particulars of the clinical situation at hand. This paper will briefly review some key points with these challenges in mind.

Activity of individual chemotherapeutic agents

Most investigators agree that doxorubicin and ifosfamide are the most active agents in ASTS, with overall response rates to conventional doses in the 15–30% range. Other agents, including cyclophosphamide, DTIC and dactinomycin, have single agent response rates in the 10–20% range [3]. Ifosfamide is a particularly valuable agent due to its non-cross resistance with doxorubicin and cyclophosphamide [3, 4].

Mode of administration may have a significant impact on the antitumour activity of certain agents. One such example is etoposide, which has previously been considered largely inactive in ASTS [5, 6]. Recent data show that this agent has considerably higher activity when given as a continously infusion over 72 hours, which is most likely a result of its high degree of cell cycle specificity [7]. Also, ASTS tumours have a relatively low S-phase fraction, further advocating prolonged infusions in order to increase the probability of exposing cells in their sensitive phases [8, 9].

There are indications that some cytostatic agents may have higher activity for certain histological types, including ifosfamide and doxorubicin for synovial sarcomas [4, 10], and DTIC-containing combinations for leiomyosarcomas [11, 12].

Activity of combination chemotherapy

Until the late 1980's, the "CYVADIC" combination of doxorubicin, cyclophosphamide, DTIC and vincristine was considered the gold standard in ASTS, with a response rate initially reported in the 50% range [13]. However, subsequent studies were unable to reproduce these results [14], and interest turned towards combinations containing doxorubicin and ifosfamide. Of these, the EORTC doxorubicin/ifosfamide regimen, the Dana Farber "MAID" combination (doxorubicin, ifosfamide and DTIC), and the Scandinavian Sarcoma Group "VIG" regimen (etoposide and ifosfamide) all produced overall response rates of 35-45%, with complete responses in the 10% range [7,15–18]. However, the difficulties in assessing these results are illustrated by the fact that in randomized trials, response rates for the identical regimens are almost invariably lower (25–35%) than in preceding phase II trials (35–50%). This probably reflects both the heterogeneity of the ASTS group and the impact of patient selection in a phase II setting [19].

Prognostic factors for chemotherapy response

Tumours of high malignancy grade or with a high S-phase fraction respond more readily to chemotherapy than low-grade tumours, with response rates in the 40–55% versus 10–20% range, respectively [7, 8, 19, 20]. Tumour site may influence chemosensitivity, and several studies have found that liver metastases have a particularly low sensitivity to systemic chemotherapy, with only very occasional responses [7, 10, 13] (Figure 1). The reason for this is unknown, but may be due to pharmacokinetic and metabolic factors.

High age and poor performance status have been found to be negative factors for tumour response [10, 21], as can be expected from the reduced protocol compliance and dose intensity often associated with these patients. Finally, many investigators are of the opinion that some histological types of ASTS respond poorly to chemotherapy, in particular leiomyosarcomas of gastrointestinal origin. However, convincing evidence for this is difficult to find in the literature [8, 10, 12].

Dose-response relationships

Is there a strong proven dose-response relationship in ASTS, so that the effect of chemotherapy can be increased by simply increasing the dose? This issue remains unclear, as few controlled studies have tested the dose-response relationship for individual agents. A positive relationship is indicated in both phase II and randomized studies with other primary end points, with response rates for doxorubicin increasing with dose to approximately 25% at 75 mg/m^2/course [19]. For ifosfamide, a dose-response relationship is suggested by several phase II studies [19, 22], and with high-dose treatment (14–18 g/m^2) including haematopoietic growth factor support, response rates of 33–100% have been reported in heavily pretreated patients [4, 23, 24]. Also, several preliminary communications have reported objective responses in patients who have previously failed on lower dose levels of ifosfamide, which is supportive of a dose-response relationship [23, 25].

In *combination chemotherapy,* randomized studies have shown increased effect with increased CYVADIC dose intensity, notably an increase in the complete response rate [21]. These findings are supported by two successive SSG studies, where the addition of G-CSF to the VIG regimen led to significantly increased dose levels and an increase in complete resonse rate from 0% to 16% (Figure 1). These results indicate that dose escalation in aggressive combination chemotherapy may convert some partial responders to complete responders, which is supported by the fact that complete responders had significantly higher chemotherapy dose levels than other patients.

Multidrug resistance

Most chemotherapeutic agents used in ASTS are substrates for the P-glycoprotein pump, and thus the expression of the MDR1 gene in these tumours would be expected to lead to chemotherapy resistance. Compared to other malignant tumours, sarcomas frequently express the MDR1 gene, and in a recent review by Stein *et al.* [26], 40–60% sarcomas were MDR1 positive. The significance of this expression remains unclear, as most of the performed studies have been small, with varying methodology and with inadequate correlation of MDR1 expression to histological subtype, malignancy grade, stage and clinical outcome [26]. As regards ASTS, no significant statement regarding a relationship between MDR1 expression and chemotherapy response can be made, however, several longitudinal studies have shown an increase both in the frequency and degree of MDR1 expression following chemotherapy with agents that are substrates for the P-glycoprotein pump [26]. Thus, the available results indicate that MDR1 expression may be an important mechanism for chemotherapy resistance in ASTS. In paediatric bone and soft tissue sarcomas MDR1 expression has been shown to be an important adverse prognostic factor for survival [26, 27]. However, whether this is a result of direct chemotherapy resistance or just a reflection of a more generally unfavourable tumour biology remains to be shown.

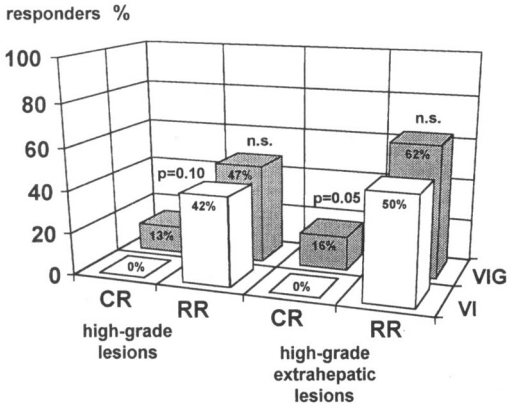

Figure 1. Response rates to etoposide and ifosfamide without (VI) or with (VIG) G-CSF support. Baseline dose etoposide was 600 mg/m^2 (72h continous infusion) and ifosfamide 1500 mg/m^2/day for 3 days. Comparison of two SSG phase II studies. From [19].

Design and results of adjuvant chemotherapy trials

Distant metastases develop in approx. 50% of patients with ASTS, and multiple attempts have been made to use adjuvant chemotherapy to combat micrometastatic disease at an early stage. To date, 15 prospective randomized studies have been performed, of which seven employed single agent doxorubicin and eight employed combination chemotherapy [19, 28–30]. Only two small studies have been able to show significant differences in both metastasis-free and overall survival in favour of the chemotherapy arm. Some other studies were able to demonstrate advantages in relapse-free survival (partially due to reduced local recurrence rate), but no significant benefit in overall

survival [19]. However, problems in a majority of the studies were their small size, patient heterogeneity as regards histological types, tumour localisation and malignancy grade, and inadequacy of the chemotherapy regimens. Recently, a metaanalysis of the studies (1,546 patients) was performed, and although one was able to find a small but significant survival benefit for chemotherapy-treated patients, it was concluded that the approximations that were necessary to merge the hererogenous materials were methodologically unacceptable, and a re-analysis based on individual patient data had to be undertaken [30]. It must be concluded that as of today, adjuvant chemotherapy has no established place in the treatment of adult soft tissue sarcoma, and no subgroup of patients has so far been identified that has a reproducible advantage from such treatment. The inconclusive results must be seen in the light of the heterogeneity of the ASTS group of tumours. Due to the rarity of the tumour, different subgroups of tumours have been pooled together, without considering important prognostic variables such as tumour site, size, malignancy grade, histological subtype, surgical margins and the additional use of radiotherapy. The impact of such factors are twofold; they may be important prognostic variables and in themselves determinants of chemotherapy sensitivity. Future studies should therefore be based on powerful prognostic factors, randomizing only patients at high risk for metastases. One possibility is to randomize on the basis of the Lund prognostication system, where adverse prognostic factors are tumour size >10 cm, the presence of tumour necrosis and the presence of vascular invasion [31]. This system gives a wide separation in survival for the good and poor prognostic groups (80% versus 30%, Figure 2), but as the poor prognosis group contains only 30% of the patient population, a major international cooperative effort would be necessary to conduct a randomized trial with sufficient statistical power.

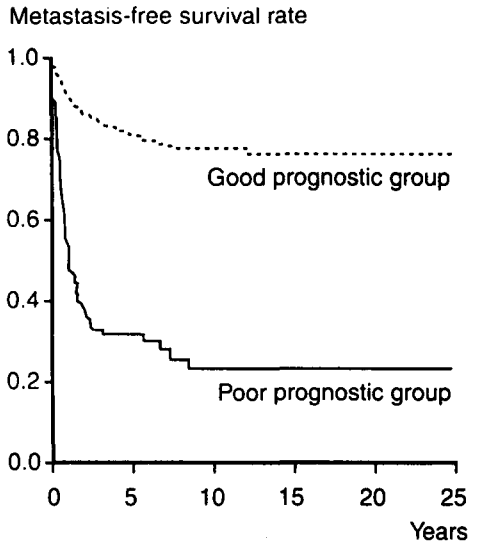

Figure 2. Metastasis-free survival in patients with adult soft tissue sarcoma of the extremity and trunk wall, using tumour size >10 cm, tumour necrosis and vascular invasion as prognostic factors. Upper curve: 245 patient with zero or one of these factors present. Lower curve: 109 patients with two or three factors present. From [31].

Chemotherapy in advanced disease—which are the relevant effect parameters?

In metastatic disease, the most important parameter for the effect of chemotherapy would be prolongation of survival. However, as in other tumour forms, the activity of chemotherapy in advanced ASTS has mainly been judged on the basis of overall clinical response rates, and it has generally not been possible to demonstrate a significant survival benefit for "responders" over "non-responders" [11]. This appears particularly true for partial responders, as several reports describe long term survival for some patients with metastatic disease obtaining a complete clinical remission (CR) with chemotherapy alone. Furthermore, patients who obtain CR following chemotherapy alone have better outcome than patients that are in CR after a partial chemotherapy response followed by metastasectomy [17, 32, 33]. Thus, the clinical complete response rate appears to be a more relevant parameter for the impact of chemotherapy than overall response rate. Although CR rates in ASTS do not generally exceed 15%, it is interesting to note that with increasing chemotherapy dose levels, CR rates appear to increase more than overall response rates [21] (Figure 1).

Further insight into the possible impact of chemotherapy on outcome is provided by studies combining metastasectomy and pre-operative chemotherapy. In this setting, no survival benefit has been demonstrated for radiological responders as compared to non-responders [34]. However, if *histological* rather than *radiological* response is considered, there is a significant advantage in relapse-free survival for good responders (Figure 3) [19, 35]. The failure of partial clinical/radiological responses to predict long term outcome is most likely associated with the persistence of large numbers of chemotherapy-resistant cells even in good partial responders, whereas good histological responders have at most just small foci of remaining cells, which may be removed by immunological mechanisms. The lack of correlation between radiological and histological response is also illustrated in Figure 4. If good histological response (grade III–IV)

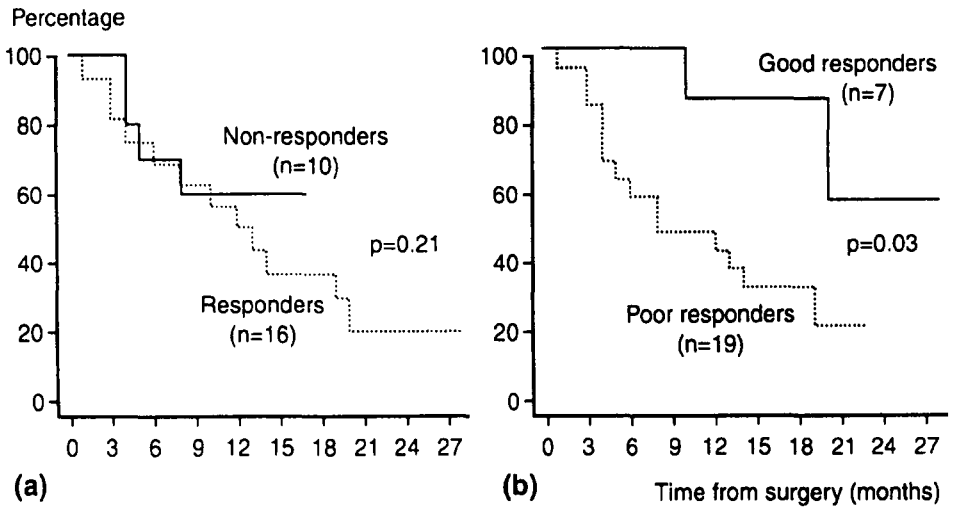

Figure 3. Relapse-free survival following pre-operative chemotherapy and surgery in 26 patients with advanced ASTS, with (a) radiological or (b) histological response to chemotherapy as prognostic indicators. Data from the SSG X study [18, 19, 35].

is defined as total necrosis or only scattered viable foci in the residual tumour, there is a discrepancy in response allocation for approx. 40% of the patients, usually in the sense that the patient is downgraded from responder to non-responder. Figure 4 also indicates that if good histological response was to be used as the criterion for a worthwile chemotherapy effect, the response rate in these 26 patients would fall from 61% to 27%. The results indicate that aggressive chemotherapy may prolong survival in a subset of patients with advanced ASTS, and probably more so when used in combination with surgical treatment.

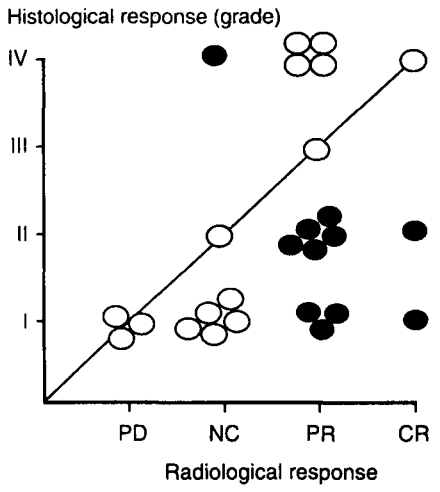

Figure 4. Correlation between radiological and histological response after preoperative chemotherapy in 26 patients with advanced adult STS. Data from the SSG X study [18, 19, 35].

Conclusions

Adult soft tissue sarcomas are a heterogenous group of tumours as regards both tendency towards metastases and chemotherapy sensitivity. Although the available data shows that chemotherapy "works" for a subset of patients, the role of chemotherapy has not been firmly established, neither in the metastatic nor in the adjuvant situation. When considered together, the group can only be termed moderately chemotherapy sensitive, with an overall response rate to the most aggressive regimens in the 40–45% range, and a complete response rate in the 5–15% range. Complete responses appear more relevant for outcome than partial responses, and a good histological response is more relevant than a radiological response. In the future, chemotherapy for patients with advanced disease should to a larger degree be reserved for patients with parameters that indicate increased probability of chemotherapy sensitivity, such as high malignancy grade and extra-hepatic disease. Also, aggressive treatment may be wisely reserved for patients with a curative treatment intent, i.e. where chemotherapy can be combined with surgery. Future studies on adjuvant treatment should also be based on patients with increased risk of metastatic relapse, with relevant prognostic factors being malignancy grade, tumour size, microscopic necrosis and vascular invasion.

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