Dose-intensive chemotherapy in advanced adult soft tissue sarcoma
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Authors' objectives
To assess the effectiveness of high-dose chemotherapy for managing adult soft tissue sarcomas (STS).

Searching
MEDLINE, Cancerlit, the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register were searched. The authors stated that the emphasis was on studies published between 1995 and 2001. They did not report the search terms used or eligible languages of publication. The reference lists of retrieved studies were also checked.

Study selection
Study designs of evaluations included in the review
The authors prioritised randomised controlled trials (RCTs), but phase I and II studies were also included. Phase I studies were included if they documented all toxicities and commented on either dose-limiting toxicity or mean tolerable dose. Phase II studies were required to have at least 20 participants. Pilot studies and those providing 'preliminary' findings were excluded.

The review included randomised trials, and phase I and II studies. The authors did not further define phase I and II studies.

Specific interventions included in the review
Studies were eligible for inclusion in the review if they assessed dose-intensive or high-dose chemotherapy regimens, supported by growth factors or autologous bone marrow or stem-cell therapy. The focus was on comparing a high-dose regimen with a lower or standard-dose regimen, but single-regimen dose-finding studies were also included. The exact regimens varied, although the main chemotherapy agents were ifosfamide, doxorubicin and epirubicin. The specific regimens were tabulated in the review.

Participants included in the review
Studies of people with adult histology metastatic STS were included, whereas studies of adults with STS contracted in childhood were excluded. The authors did not describe the demographic characteristics of the participants.

Outcomes assessed in the review
Studies were eligible for inclusion if they reported overall survival, time to progression, response rate, toxicity, quality of life, or cost.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the sample size, treatment, maximum tolerated dose and outcomes.

Methods of synthesis
How were the studies combined?
The authors provided a narrative synthesis and tabulated key findings from each study.

**How were differences between studies investigated?**
The authors narratively described differences between the studies. They divided their reporting into different sections for each type of study (phase I, II, or RCTs).

**Results of the review**
Twenty-one studies with more than 1,477 participants were included. There were 4 RCTs (more than 756 evaluable participants; 1 trial did not report the number of participants), 10 phase II studies (473 evaluable participants) and 7 phase I studies (248 evaluable participants).

In the 4 RCTs there were no consistent data about the effect of high-dose chemotherapy on progression-free and overall survival.

**Single-agent high-dose chemotherapy.**
In a randomised phase II trial that compared 5 g/m² ifosfamide with 3 g/m² daily for 3 days, the response rate was higher in the patients given a total dose of 9 g/m² (25% versus 10%). Toxicity was manageable in both arms, although grade 3-4 leukopenia was higher in the high-dose arm (57% versus 19%).

An RCT comparing epirubicin (150 mg/m²) given by two different schedules with doxorubicin (75 mg/m²) found that the response rates and toxicities were similar in both groups. Overall myelosuppression was greater in the epirubicin arms.

In 5 phase II studies of high-dose ifosfamide, the response rates ranged from 0 to 39%. In four of these studies the median overall survival ranged from 13 to 20 months. Adverse events were common: up to 100% patients suffered grade 3-4 leukopenia; 16 to 80% of patients suffered neutropenia; 10 to 89% of patients suffered febrile neutropenia; 18 to 23% of patients suffered grade 3-4 thrombocytopenia; and 32% of patients in one study suffered grade 3 neurotoxicity. Treatment-related toxic deaths were rare.

**Combination chemotherapy.**
An RCT compared a standard dose of doxorubicin and ifosfamide with a high-dose of doxorubicin combined with a standard dose of ifosfamide and growth factor GM-CSF. The response rates and survival were similar between the two groups (21% versus 23%, respectively, and 56 versus 55 weeks). Progression-free survival was statistically significantly longer in the high-dose group (29 versus 19 weeks; P=0.03). A statistically significantly higher number of patients in the high-dose group experienced infections (16.6% versus 4.6%; P=0.0004), grade 3-4 asthenia (16% versus 4.5%; P=0.0005) and grade 3-4 stomatitis (13% versus 3.9%; P=0.008). Grade 3-4 thrombocytopenia was also higher in the high-dose group (50% versus 8%; P-value not reported).

Preliminary results from an RCT that compared standard-dose MAID (mesna, doxorubicin, ifosfamide and dacarbazine) with ‘MAID+25%’ plus growth factor G-CSF showed no significant difference in response. However, grade 4 thrombocytopenia was significantly higher in the high-dose arm (64% versus 21%; P=0.0001). Toxicity-related deaths were also higher in the high-dose arm (5 out of 72 versus 0 out of 76), as was febrile neutropenia (non significant difference).

Four phase II studies that combined ifosfamide with an anthracycline (one or both given at a high dose) found response rates ranging from 50 to 65%. The median overall survival also appeared to be higher, ranging from 19 to 50 months in 3 studies. In a phase II study that combined high-dose ifosfamide with cisplatin and doxorubicin, the response rate was 52%, the complete response rate was 17%, and the median overall survival was 12 months in responders and 8 months in nonresponders. Adverse events were similar to those observed in phase II studies of high-dose single-agent ifosfamide.

In 7 phase I studies the response rates ranged from 28 to 58% for various combination chemotherapy regimens.
Authors' conclusions
Combining chemotherapeutic agents in high doses with growth factor or autologous cell support was associated with higher response rates for adult STS in comparison with standard-dose chemotherapy. High-dose chemotherapy appeared to have acceptable toxicity, but there was no improvement in the outcomes observed.

CRD commentary
This systematic review was incorporated into a broader literature summary. While the population of interest was clearly defined, other inclusion criteria were unclear or may not have been predefined. In many instances the authors stated their priority but then went on to include other things in the review. The search strategy generally appeared appropriate, but it was uncertain whether the authors excluded unpublished studies or those in languages other than English. Restrictions such as these may be associated with language and publication bias. The exact publication dates of the studies included in the review were also unclear. The authors stated that they placed ‘an emphasis on’ studies published between 1995 and 2001, but it was unclear whether studies outside this period were also eligible. The authors provided no details of the process they used to assess the relevance and quality of the identified studies. This lack of methodological details made it difficult to evaluate the overall quality of the review process and the individual studies on which it was based. However, most of the studies in the review were relatively low-quality phase I and II studies.

The narrative synthesis appeared appropriate, as it would have been difficult to pool the data given the varying treatment regimens used. However, the authors might usefully have focused on comparing and contrasting the studies, and on synthesising more explicitly the results of those studies that did use similar regimens. The authors stated that their focus was on phase III randomised trials, yet they allocated more space to describing phase I and II studies.

Overall, the conclusion that there was inadequate information on the outcomes of high-dose chemotherapy appear to be supported by the data presented. However, the lack of methodological detail, as well as the lack of explicit predefined inclusion and exclusion criteria, may limit confidence in the review.

Implications of the review for practice and research
Practice: The authors stated that RCTs had not yet found improved outcomes from high-dose chemotherapy with growth factor or autologous cell support. Further research in the adjuvant and metastatic setting is needed before this treatment can be incorporated into routine practice.

Research: The authors stated that more RCTs targeting specific histologies or sites would be desirable. They suggested that international collaboration was needed to conduct highly targeted histology-specific trials.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.