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## Evidence-Based Series #11-5: Section 1

# Dose-intensive Chemotherapy with Growth Factor or Autologous Bone Marrow/Stem Cell Transplant Support in the First-line Treatment of Advanced or Metastatic Adult Soft Tissue Sarcoma: A Clinical Practice Guideline

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The full Evidence-based Series #11-5 is comprised of 3 sections  
and is available on the CCO website (<http://www.cancercare.on.ca>)

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Section 1: Clinical Practice Guideline

Section 2: Systematic Review

Section 3: Guideline Development and External Review - Methods and Results

### Questions

1. In patients with inoperable locally advanced or metastatic soft tissue sarcoma, does first-line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation improve response rate, time-to-disease progression, or survival, compared with standard-dose chemotherapy?
2. What are the effects of first line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation on toxicity and quality of life?

For the purposes of this practice guideline, “dose-intensive chemotherapy” is defined as regimens administered with the intent to increase standard doses of chemotherapy, supported by the use of hematopoietic growth factors and/or autologous bone marrow/stem cell transplant support. Standard chemotherapy includes regimens that have been previously evaluated in a large phase II trial or a randomized phase III trial without growth-factor support.

### Recommendations

- Dose-intensive chemotherapy with growth factor support is not recommended in the first-line treatment of patients with inoperable locally advanced or metastatic soft tissue sarcoma.

- There is insufficient data to support the use of high-dose chemotherapy with autologous bone marrow/stem cell transplantation as first-line treatment in this group of patients.
- Eligible patients should be encouraged to enter clinical trials assessing novel approaches or compounds.

### Qualifying Statements

- High-dose chemotherapy with growth factor or autologous bone marrow/stem cell transplantation and standard-dose chemotherapy have similar adverse effects. The incidence of grade 3/4 thrombocytopenia is significantly higher; neutropenic fever and febrile neutropenia occur more frequently with high-dose regimens. Compared to standard treatment, the rate of treatment related deaths is also higher with high-dose regimens.

### Key Evidence

- Evidence is available from two phase III randomized trials, one phase II randomized trial, 11 phase II trials, and five phase I dose-escalation trials.
- One randomized trial (N=314) did not detect significant differences in response rate (p=0.65) or survival (log-rank p=0.98) between high-dose doxorubicin (75 mg/m<sup>2</sup>) plus ifosfamide (5 g/m<sup>2</sup>) with granulocyte-macrophage colony stimulating factor (GM-CSF) and doxorubicin (50 mg/m<sup>2</sup>) plus ifosfamide (5 g/m<sup>2</sup>) at standard doses. Progression-free survival, however, was significantly longer in the high-dose arm (log-rank p=0.03). There were higher rates of thrombocytopenia, infection, grade 3/4 asthenia, and grade 3/4 stomatitis with high-dose chemotherapy compared to standard-dose chemotherapy.
- Preliminary results from a second randomized trial (N=162), reported only in abstract form, indicate no benefit with respect to tumour response for an intensified MAID (mesna, Adriamycin [doxorubicin] 75 mg/m<sup>2</sup>, ifosfamide 9 g/m<sup>2</sup>, and dacarbazine 1200 mg/m<sup>2</sup>) regimen with granulocyte-colony stimulating factor (G-CSF) support compared to standard MAID (doxorubicin 60 mg/m<sup>2</sup>, ifosfamide 7.5 g/m<sup>2</sup>, and dacarbazine [DTIC] 900 mg/m<sup>2</sup>). Survival data have not yet been reported for that trial. The rate of grade 4 thrombocytopenia was significantly higher with the high-dose regimen.
- Four phase II trials of high-dose regimens that contained ifosfamide (>7.5 g/m<sup>2</sup>/per cycle) and an anthracycline observed tumour response rates in excess of 50%.
- Dose-limiting toxicity for the dose-intensive chemotherapy regimens evaluated in phase I trials included neutropenia, thrombocytopenia, mucositis, neutropenic fever, vomiting, fatigue, and nephrotoxicity.

### Future Research

Future research in patients with inoperable, locally advanced, or metastatic soft tissue sarcoma should focus on the identification of novel compounds or combinations that improve the response rate or survival of those patients. If high-dose chemotherapy with growth factor support or autologous bone marrow/stem cell transplantation is to be pursued, potentially myeloablative combinations similar to those used in hematological malignancies should be compared to conventional approaches. Outcomes should include survival, response, response duration, symptom control, and quality of life.

### Related Guidelines

- Practice Guideline Report #11-1: *Doxorubicin-based Chemotherapy for the Palliative Treatment of Adult Patients with Locally Advanced or Metastatic Soft Tissue Sarcoma* [completed guideline].
- Draft Practice Guideline Report #11-4: *Ifosfamide-based Combination Chemotherapy in Advanced Soft Tissue Sarcoma* [guideline under development].

## EVIDENCE-BASED SERIES #11-5

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