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Evidence-based Series # 11-4: Section 1

Ifosfamide-based Combination Chemotherapy in Advanced Soft Tissue Sarcoma: A Clinical Practice Guideline

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The full Evidence-based Series #11-4 is comprised of 3 sections
and is available on the CCO website (<http://www.cancercare.on.ca>)

PEBC Sarcoma DSG page at:

<http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/sarcoma-eps/>

Section 1: Clinical Practice Guideline

Section 2: Systematic Review

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

Questions

1. In adult patients with inoperable locally advanced or metastatic soft tissue sarcoma, do combination chemotherapy regimens containing ifosfamide have an advantage in terms of response rate, time to progression, or survival, compared with similar regimens without ifosfamide, when used as first-line therapy?
2. What are the adverse effects and effects on quality of life of ifosfamide-containing combination chemotherapy, compared with similar regimens without ifosfamide?

Recommendation

- In patients with metastatic soft tissue sarcoma, the addition of ifosfamide to standard first-line doxorubicin containing regimens is not recommended over single-agent doxorubicin. However, in patients with symptomatic, locally-advanced, or inoperable soft tissue sarcoma, in whom tumour response might potentially result in reduced symptomatology or render a tumour resectable, it is reasonable to use ifosfamide in combination with doxorubicin.

Qualifying Statements

- In combination with doxorubicin-containing regimen, the dose of ifosfamide should not exceed 7.5 g/m² given as either a split bolus or continuous infusion.

Key Evidence

- Evidence was available from three randomized phase III trials and 22 single-arm phase II trials. Three randomized controlled trials of ifosfamide-containing versus non-ifosfamide-containing chemotherapy in patients with metastatic or inoperable locally advanced soft tissue sarcoma have been reported to date.
- Two meta-analysis of published data from three randomized trials were conducted (N=1039). In two of the trials, patients were randomized to one of three chemotherapy regimens; however, only two of the three arms in both trials were included in the meta-analysis.
 - A small, statistically significant improvement in tumour response rate was observed with ifosfamide-containing chemotherapy compared to non-ifosfamide-containing chemotherapy (relative risk, 1.52; 95% confidence interval, 1.11 to 2.08; p=0.009).
 - Meta-analysis of published one-year mortality rates from those randomized trials did not detect a significant difference between ifosfamide and non-ifosfamide-containing chemotherapy (relative risk, 0.98; 95% confidence interval, 0.85 to 1.13; p = 0.28).
- Higher rates of adverse events, particularly grade 3-4 myelosuppression were observed in patients who received regimens that contained ifosfamide. A higher rate of toxic deaths was reported in two of the three randomized trials, for the ifosfamide-containing regimen.

Future Research

- Future research should investigate the use of ifosfamide as part of a neo-adjuvant chemotherapy regimen for patients with inoperable locally advanced STS in order to determine if it can render the tumours in these patients resectable.
- Future trials should include measures of 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]. This guideline recommends that "single-agent doxorubicin is an appropriate first-line chemotherapy option for advanced or metastatic soft tissue sarcoma."
- Practice Guideline Report #11-5: *Dose-Intensive Chemotherapy With Growth Factor or Autologous Bone Marrow/Stem Cell Transplant Support in Advanced or Metastatic Adult Soft Tissue Sarcoma* [completed guideline].

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