Significant survival gains from neoadjuvant chemotherapy for high-risk soft tissue sarcoma

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Neoadjuvant chemotherapy with an anthracycline plus ifosfamide was associated with significant survival gains in patients with soft tissue sarcoma of the trunk or extremities who are at high-risk of recurrence, in an interim analysis that led to the early discontinuation of a trial presented today at the ESMO 2016 Congress in Copenhagen.

The study compared this chemotherapy with tailoring chemotherapy regimens to histology sub-types.

"The benefit of adjuvant chemotherapy in soft tissue sarcoma has been debated a lot over recent years because of contradictory study outcomes," said principal investigator Dr Alessandro Gronchi, Chair of the Sarcoma Surgery at the National Cancer Institute, Milan, Italy.

In this multi-center study, researchers recruited 287 patients with high-risk soft tissue sarcoma of the trunk or extremities, from five histological subtypes which represent around 80% of all soft tissue sarcomas arising in an extremity or trunk wall.

Patients were randomized 1:1 either to three cycles of epirubicin (120 mg/sqm) plus ifosfamide (9 g/sqm), or three cycles of one of five histologically-tailored regimens: gemcitabine+docetaxel in undifferentiated pleomorphic sarcoma; trabectedin in high-grade myxoid liposarcoma; high-dose prolonged-infusion ifosfamide in synovial

sarcoma; etoposide+ifosfamide in malignant peripheral nerve sheath tumors; or gemcitabine+dacarbazine in leiomyosarcoma. All regimens were given pre-operatively.

After a median follow-up of 12.3 months, patients randomized to epirubicin plus ifosfamide showed significantly higher probability of relapse-free survival at 46 months compared to patients randomized to a histology-driven regiment (0.62 vs. 0.38, p=0.004), and of overall survival (0.89 vs. 0.64, p=0.033).

"In this 80% of patients who have a high-risk soft tissue sarcoma of the trunk or extremeties, it is worthwhile considering chemotherapy with epirubicin plus ifosfamide because their prognosis is improved by 20%," Gronchi said. "We look forward to further follow-up of this trial to provide confirmation of this interim analysis as this is the first time that convincing evidence favoring the use of neoadjuvant chemotherapy is provided."

While the study failed to show any benefit from histologically-tailored regimens, sub-group analysis did suggest that patients with high-grade myxoid liposarcoma who were treated with trabectedin had similar progression-free and overall survival to those treated with epirubicin plus ifosfamide.

"Trabectedin is far less toxic than conventional chemotherapy, so we will now expand this subgroup to assess if there is no difference between the two in terms of outcomes," Gronchi said, pointing out that histology-driven therapy was not associated with any detrimental effects.

Commenting on the study, Professor Thomas Brodowicz, Program Director of the Bone and Soft Tissue-Sarcoma Unit at the Medical University Vienna, Austria, said, "Investigators wanted to show a one-third reduction in the relapse risk in favour of histology-driven therapy,

so that means the trial did not meet the primary objective."

"What we can conclude out of this is that the neoadjuvant anthracycline plus ifosfamide is better than the histology-driven regimens, but the question still is, is it better in comparison to no treatment?" Dr Brodowicz asked. "Furthermore, are three cycles of histology-driven therapy enough and is the neoadjuvant approach the right approach for all high risk patients?"

Brodowicz commented that there had been a lot of interest in histology-driven regimens for metastatic disease, and that while the results of this study in localised disease were negative, the conclusions could not be extended to metastatic disease.

"As it was not apparent that the histology-driven therapy could have been associated with any detrimental effect per se, the main interest of these findings (if confirmed by a longer follow-up) is proof that using a neo-adjuvant therapy in patients affected by high risk soft tissue sarcoma of the extremities or trunk wall, is associated with a clear-cut overall and relapse-free survival advantage, as compared with any other available strategy, including no treatment," Gronchi concluded.

More information: Full-dose neoadjuvant anthracycline+ifosfamide chemotherapy is associated with a relapse-free survival and overall surviva benefit in localized high-risk adult soft tissue sarcom of the extremities and trunk wall: interim analysis of a prospective randomized trial, 'will be presented by Dr. Alessandro Gronchi during Presidential Symposium 3 on Monday 10.10.2016 at 16:30(CEST).

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