Reviewer’s report

Title: Ten-year follow-up results of perioperative chemotherapy with doxorubicin and ifosfamide for high-grade soft-tissue sarcoma of the extremities: Japan Clinical Oncology Group study JCOG0304

Version: 0 Date: 09 Aug 2019

Reviewer: Scott Michael Schuetze

Reviewer's report:

The authors Kazuhiro Tanaka et al. submit a manuscript describing results of 10 years of follow-up of patients with high-grade, high-risk, soft tissue sarcoma of proximal limb girdle or extremity treated peri-operatively with doxorubicin and ifosfamide. A more detailed description of the phase 2, single-arm clinical trial results including radiologic and histologic tumor responses, adverse effects and 5-year PFS and overall survival rates have been published previously (PMID 25838293). The current study finds that the 10-year PFS is the same as the 5-year PFS rate; there were no late relapses of sarcoma after 5 years. The authors provide update on long term toxicity/adverse events which were experienced by a small minority. The authors also mention 6 patients developed secondary malignancy which were felt to be unrelated to clinical trial protocol therapy. Overall, the manuscript is well written and provides some new information as well as long-term survival results from a phase 2 clinical trial which are often lacking in published medical literature.

Specific comments:

The authors mention that 6 cases of secondary malignancy developed. It may be more accurate that 6 cases of second malignancy or cancer developed. Secondary malignancy usually implies that the cancer was related to the original disease or treatment of the disease. It would be helpful to include the type of cancer that developed in the 6 patients so that the reader may consider whether or not the second cancer may be unrelated to treatment.

Under histologic subtype on page 17 (line 235) and page 20 (line 289), the authors write "undifferentiated, pleomorphic sarcoma". the common in this location is confusing and it would be better to write "undifferentiated pleomorphic sarcoma".

It is of interest that the majority of patients did not receive adjuvant or neoadjuvant radiation. Radiation is a currently accepted standard of care. In this trial, radiation was used at discretion of treating physicians after protocol therapy was completed. Only 17% of patients received radiation and local relapse was noted in only 7% of patients. The manuscript would be more
interesting, and perhaps more important, if the authors provided more detail on decision to administer radiation (e.g. R1 resection which occurred in 5 patients), and potential impact of no adjuvant radiation on local recurrence. For example, were all cases of local recurrence in patients who did not have radiation (or in patients with R1 resection)? And what was impact of local recurrence on patient survival? I would be interested in the authors thoughts on whether adjuvant radiation may be omitted in patients who receive pre-operative chemotherapy? or in which cases of high-grade, high-risk STS that it would be appropriate to not give adjuvant radiation?

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
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Yes

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I am able to assess the statistics

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