

Diagnosis and tumor response in osteosarcoma and Ewing's sarcoma, according to treatment protocols SSG II, SSG VIII, ISG/SSG I, SSG IV and SSG IX

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114 patients with osteosarcoma in the extremities had been reported to the SSG II trial, 132 to the SSG VIII trial and, until October 1998, 99 to the ISG/SSG I trial. The SSG IV trial included 53 patients and the SSG IX trial 104 patients until October 1998.

In the SSG II trial, 19% were good responders (grades III and IV) as compared to 51% in the SSG VIII trial. On reevaluation was the response changed

in one forth of the cases in both the SSG II and SSG VIII trials. In 9 and 10 cases (8%), respectively, the reevaluation resulted in a change from "good responder" to "bad responder". In the ISG/SSG I trial, the preliminary results showed a good response in 22% of the cases. In the SSG IV trial, 44% were good responders (grades III and IV), as compared to 54% in the SSG IX trial.

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The Scandinavian Sarcoma Group has carried out 2 studies on osteosarcoma, the SSG II and SSG VIII and two on Ewing's sarcoma, the SSG IV and SSG IX. The osteosarcoma study ISG/SSG I, in cooperation with the Rizzoli Institute, Bologna, Italy started in spring 1997.

Patients and methods

SSG II

The study was carried out from June 1982 to May 1989 and 114 patients were included. Data in 93 cases (82%) were reevaluated.

SSG VIII

The study started in June 1990 and was ended in February 1997, 132 patients were admitted. Data in 121 cases (92%) were reevaluated.

SSG IV

The study was carried out from June 1984 until January 1990 and comprised 53 patients. Data from 50 cases were reevaluated for diagnosis. Surgery was performed on 35 patients and findings in 32 cases were obtained for reevaluation of the tumor response.

SSG IX

The study started in 1990 and is still going on. Data

on 104 patients has been received. 96 cases (92%) have been reevaluated for diagnosis. Surgery was performed on 58 patients and data in 52 cases were obtained for reevaluation of the tumor response. In these studies, the primary diagnosis was mostly based on open biopsy material and routine microscopic examination, but in the studies on Ewing's sarcoma, fine-needle aspiration biopsy performed used cytogenetic methods were also used in some centers.

The response of the tumors to the chemotherapy was determined from slides using the following criteria originally defined by Huvos for osteosarcoma, and in the SSG IV and SSG IX studies, modified for Ewing's sarcoma:

Grade I: Little if any, identified effect.

Grade II: Areas of acellular osteoid tumor as well as necrotic and/or fibrotic material with other areas of histologically viable tumor.

Grade III: Areas with mainly acellular osteoid tumor as well as necrotic and/or fibrotic material with only scattered foci of histologically viable tumor identified.

Grade IV: No histologic evidence of viable tumor identified in the specimen.

In addition, the SSG IX data were also reevaluated according to the criteria defined by Picci:

Grade I: The response to chemotherapy when the surgical specimen contains at least one "macroscop-

ic" nodule of viable tumor. A "macroscopic" nodule is defined as an individual nodule that is larger than one 10x objective magnification field or scattered nodules that individually are smaller than one 10x field, but the sum of all areas of these nodules exceeds one 10x field.

Grade 2: The response to chemotherapy when the surgical specimen contains viable tumor; the of all areas is less than one 10x field.

Grade 3: The response to chemotherapy when no viable tumor is identified in the surgical specimen.

ISG/SSG I

The osteosarcoma study that started in spring 1997 comprises 99 patients, both the reported diagnoses and tumor responses are preliminary and based on the initial interpretations. The first reevaluation meeting is scheduled for mid-January 1999.

Results

SSG II (92 cases reevaluated)

All reevaluated tumors were again diagnosed as osteosarcoma, but 7 patients had to be excluded because of missing data, the sampling of the surgical specimen being mostly insufficient. Good response to chemotherapy (grades III and IV) was seen in 16 patients (19%), 10 patients had a grade III response and 6 patients a grade IV response.

The poor responders (grades I and II) dominated, with 70 patients (81%) of whom 52 patients had a grade II response and 18 a grade I response.

In the reevaluation the response changed to a better one in 12 patients (11%) and to a worse one in 17 patients (15%). In no patient had the response changed from bad to good, but in 9 patients (8%) it changed from good to poor.

SSG VIII (121 cases reevaluated)

At the reevaluation, 2 patients were found to have a sarcoma other than osteosarcoma and were excluded and an additional 4 patients had to be excluded because of missing data, mostly insufficient sampling of the surgical specimen.

There were 59 (51%) good responders (grades III and IV), of these 43 patients had a grade III and 16 a grade IV response.

There were 56 (49%) poor responders (grades I and II response), of these 49 patients had a grade II and 7 a grade I response.

In the reevaluation the response changed to a better one in 14 patients (11%) and to a worse one in 17 (13%). In 2 patients, the response changed from poor to good and in 10 patients (8%), from good to poor.

SSG IV (50 cases reevaluated)

Almost all tumors reevaluated were Ewing's sarcomas, but in 2 patients the diagnosis was not reliably established so they were excluded and 1 additional patient had to be excluded because of missing data.

The response to chemotherapy was reevaluated in 32 patients, of these, 14 were good responders (grades III and IV) i. e., 6 had a grade III and 8 patients a grade IV response and 18 were poor responders (grades I and II), 9 patients in each group.

SSG IX (96 cases reevaluated)

8 patients were excluded, 2 had alveolar rhabdomyosarcoma, 2 osteosarcoma, 3 small round cell tumors NOS and 1 a metastasis from breast carcinoma.

Reevaluation of the response of chemotherapy was made in 52 patients. Using the Huvo's grading system, we found 28 good responders (grades III and IV) i.e., 11 patients with a grade III response and 17 grade IV.

Of 24 poor responders (grades I and II response), 8 patients had a grade II and 16 a grade I response.

On reevaluation, the response was found to have improved in 2 patients and to have become worse one in 14. In 1 patient, the response changed from poor to good and in 5 patients, from good to poor.

With the Picci grading system there were 24 poor responders (grade 1) and 28 good ones (grades 2 and 3). Of these, 11 were grade 2 patients and 17 grade 3.

Of 8 patients with Huvo's grade II, 7 were classified as Picci grade 1 and 1 as Picci grade 2. Of 11 patients with Huvo's grade III, 1 was classified as Picci grade 1 and 10 as Picci grade 2.

ISG/SSG I

In this study, tumor response is classified as good or poor. Good responders show total necrosis or not more than 10 foci containing not more than 30 cells per focus. Poor responders are all other cases, including those with only one area larger than the focus defined above.

The chemotherapy response has been reported in 62 patients. Of these, 48 were poor and 14 good responders. Total necrosis was reported in 10 patients.

Discussion

In the Ewing's sarcoma groups, an increase in the good responders was found from the SSG IV trial to the SSG IX trial, from 44% to 54%, based on the Huvo's grading system. However, Picci's grading system was easier to use and more informative and it was therefore chosen for the next study, ISG/SSG III.

In the osteosarcoma groups, we found an even greater improvement from the SSG II trial to the SSG

VIII trial, good responders being 19% and 51%, respectively.

In all four trials, poor or insufficient material was a problem and the number of patients who showed a change in response to chemotherapy in terms of grade

after reevaluation was still too high.

In the new osteosarcoma trial ISG/SSG I, the criteria for good response are very strict and for this reason there were many poor responders, 78%.