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Analysis of toxicity profile of EURO.B.O.S.S.: A European chemotherapy protocol for bone-sarcoma in patients older than 40 years

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Background: European Bone Over 40 Sarcoma Study (EURO-B.O.S.S.) is the first prospective multicenter international study for patients 41-65 year old with high-grade bone sarcoma. The first aim of the study was to assess in this age group of patients the feasibility and the toxicity profile of an intensive chemotherapy treatment derived from chemotherapy protocols for younger patients

Methods: Patients with HG Osteosarcoma, HG sarcoma NOS, Fibrosarcoma, MFH, Leiomyosarcoma, Dedifferentiated Chondrosarcoma were included. Chemotherapy: Combinations of cisplatin/doxorubicin (CDP 100mg/m2/ADM 60mg/m2), ifosfamide/CDP(IFO 6g/m2/CDP 100mg/m2) and IFO/ADM (IFO 6g/m2/ADM 60mg/m2) were repeated three times (9 cycles). Surgery was planned after 3 cycles. Methotrexate (8g/m2) was postoperatively added in poor responders. Overall the planned cumulative dose was ADM: 360mg/m2, CDP: 600mg/m2, IFO 36g/m2, MTX:40g/m2. Immediate surgery was allowed and 9 cycles with CDP, ADM, IFO were postoperatively completed.

Results: As of June 2014, 430 patients (median age 52 years) were registered. Patients with wrong diagnosis or with inadequate demographic baseline data (67), who are on treatment or had disease progression during chemotherapy (21), or with missing toxicity data (35) were excluded from the present toxicity analysis that is then restricted to 307 evaluable patients. One surgical-related and one chemotherapy-related death were reported. The median received cumulative dose was lower than the planned (ADM: 300mg/m2, CDP: 480mg/m2, IFO 29g/m2, MTX:16g/m2) and only 28% of the patients completed the treatment without dose reduction. The incidence of Grade 4 WBC and G 3-4 PLT toxicity was 56% and 57% respectively, with 31% of patients who experienced febrile neutropenia. RBC transfusions or PLT transfusion were delivered to 59% and 33% of patients respectively. Renal toxicity was reported in 31% of patients with 3 patients who required dialysis. Nephrotoxicity was reported in 29 (41%) of the 70 patients who received at least 1 MTX cycle. Neurotoxicity (mainly peripheral) was reported in 25% of patients. There was a strong relation between age and chemotherapy compliance, and a higher incidence of febrile neutropenia and transfusion support was observed in female gender.

Conclusions: The EURO.B.O.S.S. protocol is feasible, but the chemotherapy-related toxicity is remarkable. The use of MTX requires a special caution due to the high risk of renal toxicity observed (41%) in this age group. Overall the incidence of renal and peripheral neurotoxity is higher compared to the one observed in younger patients. The chemotherapy compliance decreases over the age and a higher hematological toxicity can be expected in the female gender.