Melanoma and sarcoma

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Does increasing dose intensity in patients with operable osteosarcoma of the extremity improve outcome? A randomised controlled trial of the European Osteosarcoma Intergroup (EOI)

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Background: The European Osteosarcoma Intergroup consists of the UK Medical Research Council, the European Organisation for Research and Treatment of Cancer, the UK Children's Cancer Study Group and the International Society of Paediatric Oncology and has been conducting trials in osteosarcoma since 1980. Previous EOI randomised trials have shown that a two-drug chemotherapy regimen of cisplatin (CDDP) and doxorubicin (DOX) is an effective and tolerable treatment for patients with operable osteosarcoma. The aim of this trial was to investigate whether increasing the dose intensity of this regimen would improve survival.

Materials and Methods: Previously untreated patients aged 40 or under with biopsy-proven, non-metastatic osteosarcoma of an extremity were eligible for this trial. Patients were randomised between the standard two-drug regimen and the same regimen intensified by the addition of granulocyte colony-stimulating factor (G-CSF). In the standard arm (S), chemotherapy consisted of six three-weekly cycles of CDDP (100mg/m2 24-hour infusion) and DOX (25mg/m2/day by 4-hour infusion for three days). The doses of CDDP and DOX were identical in the intensified arm (I), but cycles were given every two weeks intensified by G-CSF (5mcg/kg/day on days 4-13 of the cycle). Surgery was scheduled for week 6, after 2 cycles in the S arm and 3 cycles in the I arm.

Results: Between May 1993 and September 2002, 504 patients (250 S arm, 254 I) were randomised; 64% were aged 16 or under and 60% were male. Sites of tumour were 61% femur, 28% tibia/fibula, 10% humerus, 1% radius/ulna. Six cycles of chemotherapy were received by 78% of patients in the S arm and 82% in the I arm. Grade 3 or 4 haemotological toxicities were observed in each arm as follows: leucopenia 81% S, 69% I; neutropenia 93% S, 79% I; thrombocytopenia 58% S, 77% I. Overall dose intensity was increased in the I arm compared to the S arm by 25% for both CDDP and DOX.

Good histological response, defined as > 90% necrosis, was observed in 36% of patients in the S arm and 51% in the I arm (p = 0.002, chi-square test). No difference was observed in survival (hazard ratio [HR]=1.07, 95% confidence interval [CI] 0.73-1.57, p=0.65) or progression-free survival (HR=1.13, 95% CI 0.82-1.54, p=0.32). Survival at 3 years was 65% (S) and 66% (I), PFS at 3 years was 41% (S) and 46% (I).

Conclusions: Although it achieves a moderate increase in dose intensity and good histological response rate, the intensification of CDDP/DOX chemotherapy with G-CSF does not improve long-term outcome in resectable osteosarcoma.

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EORTC 62011: phase II trial of brostallicin for soft tissue sarcoma

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Background: Brostallicin is a distamycin A analogue that binds to DNA in the minor groove resulting in disruption of cell cycle progression and tumour cell death. Pre-clinical studies suggest that brostallicin may have an increased activity in tumours expressing high levels of glutathione (GSH) and glutathione-S-transferase-pi, known to be associated with high grade sarcoma and with drug resistance. A single patient with a gastrointestinal stromal tumour (GIST) was noted to have a durable tumour response during the phase I trials. This drug was therefore selected for further phase II screening in patients with soft tissue sarcomas (STS).

Materials and Methods: Patients were recruited in two groups. One group had soft tissue sarcoma other than GIST (non-GIST) and had previously been treated with either doxorubicin or alkylating agents or both. The other group had GIST and had been treated with Imatinib. All patients had inoperable locally advanced or metastatic disease and had progressive disease prior to study entry. All patients' histological diagnosis was reviewed centrally. In the non-GIST group, planned sample size was 40 in a standard Fleming one step design (p0 = 10%, p1 = 25%, alpha = beta = 0.1). In the GIST group, a Simon two step design was followed: first step 18 patients, total 32 patients (p1 = 20% p0 = 5% alpha = beta = 0.1). Patients received Brostallicin 10mg/m2 IV every three weeks with tumour assessment every two cycles. RECIST criteria were followed and all responses were confirmed by independent investigators.

Results: We are reporting the results in the non-GIST group that has accrued 43 patients (42 treated) between 11/06/02 and 09/12/02. Preliminary analysis of results show that in general the drug was well tolerated. WHO grade 3 or 4 toxicity was as follows: granulocytopenia: 70%; fatigue: 15%; febrile neutropenia: 12%. There was one confirmed toxic death due to neutropenic septicaemia from a staphylococcal skin infection. Anti-tumour activity has been observed with 2 confirmed partial responses to date. A further 17 patients had progression arrest by cycle two (45%).

Conclusions: The confirmed objective response rate is currently low. However, the incidence of progression arrest is in the range of other agents considered active in STS, and this may predict for substantial first line activity as reported by van Glabbeke et al EJC 38(4):543-9, 2002. Further investigation in STS appears warranted.

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An EORTC phase I study to determine the safety of combined caelyx and ifosfamide in previously untreated adult patients with advanced or metastatic soft tissues sarcomas.

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Background: Caelyx seems to have the same efficacy in adult soft tissue sarcomas as doxorubicin with an improved toxicity profile. It could thus be an alternative to doxorubicin and may well be easier to combine with agents such as ifosfamide. The present phase 1 study has evaluated the toxicity of combined caelyx and ifosfamide given as 1st line to patients (pts) with advanced and/or metastatic soft tissue sarcomas.

Material and methods: Eligibility included soft tissue sarcomas progressing within 6 weeks, no previous chemotherapy for advanced disease, WHO PFS < 2, age >18< 70 years and adequate cardiac, liver, renal and haematological function. The treatment was caelyx 30 mg/m^2/1-h d 1 q 3 w + ifosfamide (with mesna) at Xg/m^2/4-h d 1-3 q 3 w at 4 doses: Level 1: X=1.7 g; level 2: X = 2 g; level 3: X=2.5 g; level 4: X=3 g. Cohorts of 3 pts were entered at each dose level with escalated ifosfamide doses unless a DLT occurred, defined as ANC < 0.5 x 10^9 lasting for 7 days or for 3 days + fever at least 38.5 °C, grade4 thrombocytopenia, any grade 3-4 toxicity except nausea, vomiting and alopecia, and any toxicity requiring a 2 w delay. In case of DLT in 1/3 pts a new cohort were added. Toxicity was evaluated by CTC. Non-evaluable pts were replaced.

Results: 15 pts have been included. Median age was 59 years (29-69). Four pts were included at dose level 1, 8 pts at level 2 and 3 pts at level 3. No DLT was observed at these dose levels. Toxicity has generally been acceptable. 3 patients had grade 4 granulocytopenia and 3 patients had grade 3 and 4 patients grade 4 leucopenia. Other haematological toxicities > grade 2 were few. PPE > grade 1 was not seen. We will soon increase the dose to level 4. If no DLT is observed at this level we plan to add 2 further dose levels: Level 4 with caelyx at 40 mg/m^2 and caelyx 40 mg/m^2/1-h d 1 + ifosfamide 3g/m^2/4-h d 1-4 q 3 w.

Conclusions: Combined caelyx and ifosfamide seems to be feasible in pts with advanced soft tissue sarcomas and this combination may allow administration of ifosfamide at a dosage similar to that used when given alone.