



Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study

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Summary

Background

The optimum treatment for high-risk soft-tissue sarcoma (STS) in adults is unclear. Regional hyperthermia concentrates the action of chemotherapy within the heated tumour region. Phase 2 studies have shown that chemotherapy with regional hyperthermia improves local control compared with chemotherapy alone. We designed a parallel-group randomised controlled trial to assess the safety and efficacy of regional hyperthermia with chemotherapy.

Methods

Patients were recruited to the trial between July 21, 1997, and November 30, 2006, at nine centres in Europe and North America. Patients with localised high-risk STS (≥ 5 cm, Fédération Nationale des Centres de Lutte Contre le Cancer [FNCLCC] grade 2 or 3, deep to the fascia) were randomly assigned to receive either neo-adjuvant chemotherapy consisting of etoposide, ifosfamide, and doxorubicin (EIA) alone, or combined with regional hyperthermia (EIA plus regional hyperthermia) in addition to local therapy. Local progression-free survival (LPFS) was the primary endpoint. Efficacy analyses were done by intention to treat. This trial is registered with [ClinicalTrials.gov](#), number [NCT 00003052](#).

Findings

341 patients were enrolled, with 169 randomly assigned to EIA plus regional hyperthermia and 172 to EIA alone. All patients were included in the analysis of the primary endpoint, and 332 patients who received at least one cycle of chemotherapy were included in the safety analysis. After a median follow-up of 34 months (IQR 20–67), 132 patients had local progression (56 EIA plus regional hyperthermia vs 76 EIA).

Patients were more likely to experience local progression or death in the EIA-alone group compared with the EIA plus regional hyperthermia group (relative hazard [RH] 0.58, 95% CI 0.41–0.83; $p=0.003$), with an absolute difference in LPFS at 2 years of 15% (95% CI 6–26; 76% EIA plus regional hyperthermia vs 61% EIA). For disease-free survival the relative hazard was 0.70 (95% CI 0.54–0.92, $p=0.011$) for EIA plus regional hyperthermia compared with EIA alone. The treatment response rate in the group that received regional hyperthermia was 28.8%, compared with 12.7% in the group who received chemotherapy alone ($p=0.002$). In a pre-specified per-protocol analysis of patients who completed EIA plus regional hyperthermia induction therapy compared with those who completed EIA alone, overall survival was better in the combined therapy group (HR 0.66, 95% CI 0.45–0.98, $p=0.038$). Leucopenia (grade 3 or 4) was more frequent in the EIA plus regional hyperthermia group compared with the EIA-alone group (128 of 165 vs 106 of 167, $p=0.005$). Hyperthermia-related adverse events were pain, bolus pressure, and skin burn, which were mild to moderate in 66 (40.5%), 43 (26.4%), and 29 patients (17.8%), and severe in seven (4.3%), eight (4.9%), and one patient (0.6%), respectively. Two deaths were attributable to treatment in the combined treatment group, and one death was attributable to treatment in the EIA-alone group.

Interpretation

To our knowledge, this is the first randomised phase 3 trial to show that regional hyperthermia increases the benefit of chemotherapy. Adding regional hyperthermia to chemotherapy is a new effective treatment strategy for patients with high-risk STS, including STS with an abdominal or retroperitoneal location.

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