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## Mitoxantrone and Ifosfamide as Second-line Therapy of Epithelial Ovarian Cancer. A Pilot Study by the I.T.M.O. Group

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MITOXANTRONE (DHAD) and ifosfamide (IFO) have both been tested as single-agent regimens in ovarian cancer patients with platinum-derivates [1-5] and promising results have been reported [1, 3]. Furthermore, it has been suggested that both DHAD and IFO have a dose-response effect [6, 7]. Therefore, between July 1991 and December 1992, the I.T.M.O. group decided to evaluate an intensive regimen of DHAD plus IFO in patients with persistent or relapsed (within 1 year) disease after first-line chemotherapy with platinum derivates. DHAD 12 mg/m<sup>2</sup> intravenous (i.v.) day 1, IFO 4000 mg/m<sup>2</sup> i.v. days 1, 2, mesna 800 mg/m<sup>2</sup> i.v. three times daily days 1-2 and granulocyte colony-stimulating factor (G-CSF) 5 mcg/kg/day intramuscularly (i.m.) days 6-19 were repeated every 21 days. Local ethical committee approval and the informed consent of the patients were obtained. 19 patients entered this single-centre pilot trial. 5 of the 19 patients did not show clinically or radiologically measurable disease, and so tumour response was not evaluable. Median age was 48 years (range 26-62) and performance status (PS) 0-1 for all patients. 10 out of 19 patients (53%) were resistant to platinum-derivates because they showed unchanged or progressive disease after first-line treatment. Patients with unchanged disease were classified as resistant only if they had received at least 450 mg/m<sup>2</sup> of cisplatin or 1800 mg/m<sup>2</sup> of carboplatin. Among 14 evaluable patients, 8 were classified as resistant to platinum-derivates. IFO was given at 93% and DHAD at 95% of the planned dose. All the patients received at least two cycles of therapy. 6 patients (32%) completed the entire treatment programme without any delay. 7 of the 14 evaluable patients showed objective tumour regression with three CRs (response rate 50%; 95% confidence interval 24-76%); of the remaining patients, 3 stabilised and 4 progressed. The median response duration was 5 months. Median TTF and median survival for all 19 patients were, respectively, 8 and 13 months. In the 14 patients with measurable disease, median TTF and median survival were, respectively, 5 and 12 months. Grade 3-4

(NCI classification) side-effects in the 19 entered patients were anaemia (47%), vomiting (11%) and mucositis (5%). Sixty-three percent of patients had alopecia, and in 6 of 19 cases (32%) a worsening of pre-existing neuropathy due to platinum-derivates, was observed. Anaemia was the most relevant side-effect observed because all the treated patients suffered from this, and red blood cell transfusions were given during 12 of the 72 cycles (17%). Five episodes of infection were reported in 5 different patients (pharyngitis in 2 patients and 1 case each of pneumonia, cystitis and pyodermitis). All 5 patients recovered completely. Febrile neutropenia was diagnosed during 10 cycles. Antibiotics were given for a mean time of 1.4 days per cycle. No episodes of bleeding were observed, and median platelets nadir was 70 000/mm<sup>3</sup> after 11 days of treatment. In relation to patient compliance, 1 patient refused to recycle every 3 weeks for three consecutive cycles (due to grade 2 asthenia), and 2 patients refused to continue chemotherapy because of grade 2 asthenia and vomiting. The results of the present trial raise some questions concerning the evaluation of the efficacy of second-line therapies in ovarian cancer. Although we obtained seven responses (including three CRs) in 14 evaluable patients, and responses were observed even in patients who had failed to respond to first-line therapy with platinum derivates, the median values of response duration (5 months), time to treatment failure (8 months) and overall survival (13 months) of our patients were unsatisfactory. Furthermore, there were frequent reports of side-effects and anaemia, in particular, which proved to be a significant problem in completing all of the five planned treatment cycles without delays. We, therefore, believe that response rates should be considered only approximate indicators of chemotherapy activity in second-line treatments of ovarian cancer, and that further clinical data concerning response duration, TTF and survival also need to be obtained before the clinical utility of a proposed regimen can be fully assessed. The evaluation of side-effects should also be mandatory, given that the second-line treatment of ovarian cancer has a palliative objective. On the basis of these considerations, we have decided not to pursue our original aim of setting up a large Phase II trial in order to evaluate the combination of DHAD and IFO given at full doses.

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