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Closing remarks

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A total of 14 presentations were given at the conference, and two more appear in the ECCO proceedings. Ifosfamide (IFO) is clearly an active drug that is essential to our chemotherapeutic arsenal. Some points need to be emphasised concerning (1) doses of IFO and the frequency of its administration; (2) plasma levels and the excretion of this agent; (3) its combination with other cytostatic drugs; (4) its toxicity to the bone marrow, neurological system, kidney and bladder; and (5) phase II and III studies of IFO.

Most of these studies use the regimen involving 3,000 mg/m^2 given on days 1 and 2, which was developed by de Kraker in 1982 and consistently yields the highest response rates. Other combinations include 1,600 mg/m^2 given for 5 days; 2,000 mg/m^2 given for 5 days; and 5,000–8,000 mg/m^2 given for 1 day. Some conclusions concerning the dose schedule can be drawn from the study presented by Ninane et al. These authors show that the half-life of the alkylating substance on the 1st day is 1–7 h, but it is significantly shorter on the 2nd day. These observations point out the disadvantage in giving IFO for more than 2 days; thus, its administration for 5 days does not seem to be advisable. Ninane et al. also report that 19% of the drug is excreted very rapidly and that after 24 h its excretion is complete. A study is needed to investigate the excretion rate obtained after the infusion of 5,000–8,000 mg/m^2. Moreover, the observations of Ninane et al. seem to favour a 2-h infusion over a 24-h infusion when a given level of alkylating agent in the CSF is desired. To achieve an active level in the CSF, a high peak serum level must be attained; this can only be done by the brief infusion of a high dose.

From these studies it can be concluded that treatment with IFO alone enables its administration every 2 weeks. However, in combination regimens one course every 3 weeks is advisable. A great variety of tumours respond to IFO monotherapy: neuroblastomas, nephroblastomas, and malignant mesenchymal tumours including the rhabdomyosarcomas, Ewing's sarcoma, osteosarcoma and non-Hodgkin's lymphoma. Many different IFO multidrug combinations have been used, mostly that including vincristine, Adriamycin and actinomycin D. The combination with cisplatin seems to be very active but involves increased nephrotoxicity.

Toxicity is most pronounced in the bone marrow, but it seems to be lower than that seen with cyclophosphamide. The neurotoxicity reported by Pratt et al. remains an open question; its cause is not clarified, although the studies reported by de Kraker and Voûte suggest that such neurotoxicity is connected with proximal tubular disturbances. A typical, massive aminoaciduria of the Debré-de Toni-Fanconi type occurs, worsening with subsequent courses. This induces a considerable disturbance of the protein metabolism of the body, which can easily cause cerebral shifts that result in neurological problems. As de Kraker and Voûte point out, this disturbance of protein metabolism can also produce an anti-tumour growth-inhibition effect. In the long run, repair of the tubules takes place. Bladder toxicity does not occur when mesna is used as a uroprotector and a sufficient fluid intake is ensured.

A sufficient number of phase II studies have been carried out to prove the activity of IFO. However, studies comparing high-dose IFO with high-dose cyclophosphamide are still needed. The phase III studies currently under way are the very comparable SIOP and German studies on rhabdomyosarcoma, which indicate an advantage for the use of IFO over that of cyclophosphamide. The comparable French and German studies on Ewing's sarcoma promise a similar result. In an EORTC/MRC SIOP study, IFO is currently being used as the primary treatment for metastatic osteosarcoma at diagnosis in a combination regimen with platinum and Adriamycin (PIA); it is too early for a report on the results thus far obtained.