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Concluding remarks

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As long ago as 1967, during the 5th International Congress on Chemotherapy in Vienna, Brock presented a report on ifosfamide [1]. Many clinical investigators, initially especially in Germany, later also in the United States of America, have reported on this drug though the severe nephrotoxicity it caused prevented its wider use for a long time. The development of an adequate antidote has led to its revival and a new series of investigations.

Before the pertinent data on the activity of the drug are reviewed it must be mentioned that the most pressing question about the drug that has not yet been solved is that of the optimal administration regimen.

In this Symposium several methods have been described, but none can be definitively said to be the optimum. The reported dosage range was from 5 g/m^2 given over 30 minutes on 1 day with oral mesna rescue to 6 g/m^2 given as a continuous infusion over 5 days with i.v. rescue. Where retreatment with ifosfamide is generally scheduled if possible at day 22 from the first infusion, the shortest infusion period with oral rescue should be preferred if it does not lead to too much loss in activity. The improved quality of life made possible by this shorter stay in hospital favours this choice, and is especially important in palliative treatment.

Ifosfamide is the second drug active in soft tissue sarcoma as has been reported from Germany [3], the United Kingdom [5] and now from the USA and by the EORTC after a large study. Two further important aspects of these studies in this disease have emerged: ifosfamide in a less myelotoxic dose than cyclophosphamide has shown substantially more activity, and the reported responses observed in cyclophosphamide-resistant patients in both studies strongly suggest only partial cross-resistance. The proper role of ifosfamide in the treatment of soft tissue sarcomas is the objective of several ongoing cooperative group studies in Europe and the USA. Within the next 5 years its definite place will no doubt emerge.

Further investigations are also needed in osteosarcoma, Ewing's sarcoma, embryonal rhabdomyosarcoma and in several solid childhood malignancies, to substantiate the proper place of ifosfamide in the treatment of patients with these diseases. The data from all phase II studies strongly support these investigations on the basis of the considerable activity reported.

The reported first-line activity in small cell lung cancer must lead to its administration in combination with the other most active drugs adriamycin, etoposide and carboplatin. The cure rate in this disease, which has slowly been increasing over the last 5 years, encourages addition of new active drugs to the existing combinations. The outcome of these studies has to be awaited.

Two studies reported on a possible role for ifosfamide in the treatment of advanced non-small cell lung cancer. Several large randomized studies [6] in this disease have hitherto failed to demonstrate substantial prolongation of survival, the justification for routine administration of drugs in this disease. Therefore, large controlled studies should be performed before the general application of ifosfamide can be advised, but as stated, this holds for the use of any chemotherapy in this disease.

The data from Indiana confirm the published German data [4] on the activity of ifosfamide in testicular cancer. Despite the major progress in the curability of this disease, the discovery of an other active drug might be essential for the treatment of patients with bulky disease, whose cure rate is still only 40%. Studies on this issue are in progress.

The activity of ifosfamide in pancreatic cancer reported during this symposium and previously by other investigators [2] invite its use in combination with other drugs that are active in this disease, in which results have hitherto been so dismal.

The superior activity of ifosfamide compared with cyclophosphamide, observed in the EORTC study of soft tissue sarcomas, suggests the initiation of studies in other diseases, in which cyclophosphamide has shown substantial activity, e.g., esophageal, bladder, cervical and ovarian cancer. In these diseases, however, some caution must be exercised in the case of patients with decreased renal function. During the discussions the possibility of encephalopathy developing in patients with a disturbed clearance of the drug was mentioned.

To summarize, in this encouraging meeting pertinent data have led us to the conclusion, that ifosfamide has a role in the treatment of several types of cancer. Further investigations, will be needed, however: in the treatment of diseases in which activity has been shown, an optimal administration regimen still needs to be found, and its proper place has yet to be defined; in other diseases phase II studies must be initiated.

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