IFOSFAMIDE IN SOFT TISSUE SARCOMA

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Ifosfamide, a congener of Cyclophosphamide[1], was originally introduced into clinical practice in 1971, but has not been widely used because of severe dose limiting urotoxicity, particularly when used as a single agent in large doses. A resurgence of interest in Ifosfamide followed the demonstration that urotoxicity could be lessened or abrogated by fractionated administration[2] or, more effectively, by the concurrent administration of sulphahydryl compound mesna (2- mercaptoethanesulphonate), a highly uroprotective agent[3]. It is now clear that Ifosfamide has a broad spectrum of activity in human cancer[1-4]. This study reports our experience with Ifosfamide in patients with soft tissue sarcomas.

PATIENTS AND METHODS

All 14 patients (13 males 1 female) entered into the study had histologically diagnosed ‘soft tissue sarcoma Nine of them were previously treated with chemotherapy and radiotherapy. Ages of the patients ranged from 2 to 65 years. Seven cases had rhabdomyosarcoma, 2 soft tissue sarcoma (NOS), 2- neurofibrosarcoma, and one each had fibrosarcoma, epithelimoid sarcoma and myxosarcoma. Nine patients had extensive metastatic disease at the time of treatment. Lung metastases and inguinal lym¬phadenopathy were the most common manifestations. Ifosfamide was given initially as a 5-day continuous infusion at a dose of 1.5gm/sqm daily. Mesna was given as 5-doses, each dose was 20% of the daily Ifosfamide dose. Adriamycin was given on day 1 as I.V. push in 40mg/sqm dose. As haematuria was being noticed the dose of Mesna was later increased to 60% of the dose of Ifosfamide (Table).

TABLE. Drug Combinations.

Drugs	Doses	Duration (in days)	No. of Patients
Ifosfamide	1.5gm/M^2	1-5	
Mesna	20% of Ifosfamide	1-5	11
Adriamycin	40mg/M^2	1 only	
Ifosfamide	1.5gm/M^2	1-5	
Mesna	20% of Ifosfamide	1-4	2
Actinomycin-D	0.5mg	1-3	
Ifosfamide	1.5gm/M^2	1-5	
Mesna	20% of Ifosfamide	1-5	1
Etoposide	100mg	3	

Cycle was repeated in three to four weeks. All patients were treated with at least two courses of the regimen unless progression of the disease or clinical events prevented the further treatment with this regimen. Three patients had6 courses, 3 had4, 2had3, 4had 2 courses, and 2 had one course only. Eleven patients had Ifosfamide + Adriamycin. Two had already received adriamycin to total tolerance dose, therefore, in one case Actinomycin-D (at a dose of 0.5mg as intravenous push daily for 3 days) and in the other Etoposide (100mg/sqm intravenous infusion for 3 days) was given. Complete physical examination, tumour size measurement, X-ray chest, complete blood picture, liver and renal function studies were performed in all patients during the administration of the drug and prior to the next cycle of the therapy.

RESULTS AND DISCUSSION

Fourteen patients entered into the study. Three were excluded, having failed to complete 2 cycles of therapy. Two with non- measurable disease were also not included. Three showed complete response, three had partial remission, whereas three had no response. Out of the three good responders, one had a recurrence at 11 months for which 2 more cycles of therapy were given and he responded to treatment. All three complete responders were young patients, two of them had rhabdomyosarcoma, and one had soft tissue sarcoma of non- specified nature. Two of these had pulmonary secondaries, and one had retroperitoneal mass. After completion of 4 courses of therapy, pulmonary secondaries disappeared completely. Two patients showed relapse of pulmonary disease at 10-11 months and were given 2 additional courses of chemotherapy with good response. The retroperitoneal mass showed complete

regression on ultrasound examinations. The responders attained a Karnofsky status of 100%. Three partial responders had very advanced disease; one patient had neurofibrosarcoma with a big intra-abdominal mass. This patient after 2 courses of therapy had a mass size rcduction of 40 to 45%. Another patient with a sarcoma of the thigh had retroperitoneal mass which was excised but recurred, after 2 courses of chemotherapy, there was about 50% reduction in the size of the mass. He did not report for the third course of therapy and died due to deep vein thrombosis and pulmonary embolism. All non-responders showed progressive disease. The side effects included nausea and vomiting in all (mild two, moderate 7 and severe 5) which was controlled with anti emetic drugs. Mild to moderate alopecia was also observed in all cases. Other side effects were diarrhoea (6), anaemia (8),leucopenia (2), fever (5), haematuria (3), skin pigmentation (3). Ifosfamide is an active agent in variety of &oft tissue sarcomas. The best response was seen among the patients who did not have prior chemotherapy. In thig subset of tumours, there is published data demonstrating activity of Ifosfamide. Stuart-Harris et al, [7] trcated 67 patients with sarcomas (previously treated and untreated) with high dose of Ifosfamide with urothelial protection Mesna. Sixteen responses (24%) were seen, including 6 complete responses. Klein used high dose continuous Ifosfamide infusions (between 60-85 mg/kg B.W/day for 5 days), with Mesna and observed responses in S of 12 patients with differentiated soft tissue sarcoma[8]. Ifosfamide in a dose of 5gm/sqm was compared with cyclophosphamide at expected equitoxic dose[9,10]. The toxicity with Ifosfamide especially in terms of myelosuppression was, however, less and therefore Ifosfamide was combined with adriamycin. In 16 months over 200 patients were treated of whom 178 proved eligible and valuable. The response rate was 36% with 9% complete responders[10]. Responses have also been reported in other sarcomas and childhood solid tumours[11]. Although we cannot comment on the relative activities of Ifosfamide versus Cyclophosphamide from our result, it is clear that Ifosfamide can produce response in patients previously treated with cyclophosphamide containing regimen. Moreover, all of our patients bad progressive tumour at the time of entry into protocol and were receiving or had received cyclophosphamide containing regimens. Though CNS toxicity as a side effect has not been mentioned, one patient manifested reversible confusional state. CNS toxicity has racently been dealt with in more detail by Pratt et al, who have recommended dose modification depending upon the degree of toxicity encountered[12]. The cause of this side effect is not known, although the 4-hydroxymetabolite of Ifosfamide does enter the cerebrospinal fluid.

REFERENCES

1. Brade, W.P., Herdrich, K. and Varini, M. Ifosfamide-pharmacology, safety and therapeutic potential. Cancer Tret. Rev., 1985; 12:1.
2. Rodriguez, V., Bodey, G.P., Freireich, E.J., McCredie, KB., Mckelvey, E.M. and Tashima, C.K. Reduction of ifosfamide toxicity using dose fractionation. Cancer Res., 1976; 36: 2945.
3. Brock, N., Habs, M., Phol, J., Schmahl, D. and Stekar, J. Mesna (natrium-2-mercaptoethaesulphonate). Therapiewoche, 1982; 32:4977.
4. Scheulen, M.E., Niederle, N., Bremer, IC, Schiitte,J. and Seeber, S. Efficacy of ifosfamide in refractory malignant disease and uroprotection by mesna; results of a clinical Phase II - study with 151 patients. Cancer Treat. Rev., 1983; 10 (Suppl. A) : 93.
5. Hunter, H.L. and Harrison, E.F. The anticancer spectrum of ifosfamide. Semin. Oncol., 1982; 9 (4 Suppl) : 96.
6. Brade, W., Seeber, S. and Herdrich, K Comparative activity of ifosfamide and cyclophosphamide. Cancer Chemother. Pharmacol., 1986; 18 (Suppl. 2): 51.
7. Stuart-Harris, RC., Harper, P.O., Parsons, C.A., Kaye, S.B., Mooney, C.A., Cowing, N.F. and Wittshaw, B. High-dose alkylation therapy using ifosfamidè infusion with mesna in the treatment of

adult advanced soft-tissue sarcoma. Cancer Chemother. Pharmacol., 1983; 11: 69.
8. Klein, H.O., Wickramanayake, P.D., Coerper, C., Christain, B., Pohl, J. and Brock, N. High-dose ifosfamide and mesna as continuous infusion over five days - a phase I/il trial. Cancer Treat. Rev., 1983; 10 (Suppl. A): 167.
9. Bramwell, V.H., Brugarolas, A., Mouridsen, H.T., Cheix, F., De Jager, F.van Oosterom, A.T., Vindrik, C.P., Pinedo, H.M., Syl vester, Rand De Panco, M. EORTC. phase II studyofcisplatinum in cyradic resistant soft tissue sarcoma. Bur. J. Cancer, 1979; 15:1511.
10. Bramwell, V., Mouridsen, H.T., Santoro, A., Blackledge, 0., Somers, R, Werweij, J. et al. Cyclophosphamide versus ifosfamide, final report of randomized phase II trial in adult soft tissue sarcomq. Eur. J. Cancer Gin. Oncol., 1987; 23:311.
11. Shutte, J., Dombernowsky, P., Santoro, A., Skward, W., Mouridsen, H.T., Somers, It et al. Adriamycin (A) and ifosfamide (I), a new effective combination in advanced soft tissue sarcoma; preliminaiy report of a phase II study of the EORTC soft tissue and bone sarcoma group. Proceedings European Conference on Clinical On cology, 1987; 4: 232.
12. Pinkerton, C.R., Rogers, H. et al. A phase-II study of ifosfamide in children with recurrent solid tumors. Cancer Chemother. Pharmacol., 1985; 15 : 258.
13. Prab, C.B., Green, AS., Horowitz, M.E. et al. Central nervous system toxicity following the treatment of pediatric patients with ifosfamide/mesna. J. Clin. Oncol., 1986; 4: 1253.