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Perspectives and Commentaries

Amsacrine: a New Drug for Hematological Malignancies

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AMSACRINE, 4′-(9-acridinylamino)methanesulfon-*m*-anisidide (*m*-AMSA), is one of many synthetic amino acridine derivatives described initially by Cain and Atwell in New Zealand [1]. It was selected for phase I and subsequent clinical trials because of its activity in various animal tumor models, including L1210 and the mouse B16 melanoma cell line. The mechanism of action is, at least in part, associated with inhibition with DNA synthesis by intercalation between DNA based peers.

Amsacrine is metabolized into inactive metabolites in the liver. Pharmacokinetic data suggest a biphasic pattern of disappearance: there is a short initial half-life for both the free drug and the protein-bound material, with the secondary half-life being reported to be inexcess of 6 hr [2]. Because of the mechanism of action at the drug plasma levels, there may be irrelevance in assessing probability of clinical activity. A more accurate measurement may be tumor cell uptake and retention, particularly in identifying the amount of drug bound directly to DNA. Techniques for this assay currently are being ionvestigated. Pretreatment evaluation utilizing these techniques can be used to assess prospectively the clinical effects of the drug in patients, particularly with acute myeloblastic leukemia [B. Andersson, personal communication].

Two formulations of *m*-AMSA have been tested clinically, amsacrine lactate and amsacrine gluconate. The majority of phase I and II studies have been performed with amsacrine lactate, which is relatively insoluble, with dimethylacidimide being utilized for solubilizing activity. Because of the question of probable toxicity and biological activity of the dimethylacidimide, the more soluble gluconate was investigated. Preliminary data suggest that there is no difference in clinical activity between these two agents [3]. This formulation has been similarly tested in a subsequent clinical trial in refractory acute leukemia, with results significantly inferior to those seen with the parent compound [M. J. Keating, personal communication].

In the initial phase I studies with the AMSA lactate, doses between 75 mg/m²/day × 5 for solid tumors and up to 120 mg/m²/day × 5 or 7 for acute leukemia were suggested. Phase II studies were initiated with activity being demonstrated primarily in the hematological malignancies [4]. Disappointing, only a small number of solid tumors showed evidence of response, with partial responses being reported in less than 10% and frequently less than 5% in the more common malignancies, including breast, gastric, colorectal and lung [5].

Although initial studies suggested some activity in a relatively heterogeneous group of lymphoid malignancies, including relapsed acute lymphoblastic leukemia and various leukemic transformations of lymphoma [6], these responses were of short duration and expanded clinical trials in the lymphoma area with AMSA both as a single agent and in combinations with various other agents as second-line salvage therapy in relapsing lymphoma have not substantiated these initial results. The current study of amsacrine in refractory lymphoma analyses additional patients with advanced lymphoma as a cooperative phase II study. It is partially complicated by the addition of steroids in a number of patients. Responses again seen in both Hodgkin's disease and lymphoma in a variety of forms were all partial in

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nature and in the main of apparently short duration. Myelosuppressive toxicity was significant in almost all the patients at both 90 and 120 mg/m^2. High doses of the drug with bone marrow rescue in combinations with non-cross-resistant agents are continuing to be investigated; however, the current data suggest that either a single daily dose or continuous infusion therapy with AMSA has little activity in the management of patients that failed conventional regimens [7].

AMSA is now being utilized primarily in combination with other cross-reactive agents, either adriamycin or cytosine arabinoside, with or without thioguanine, vincristine and prednisone in the primary of acute myeloblastic leukemia and in refractory lymphoma which have either failed to achieve complete remission on other therapeutic regimens or have relapsed on maintenance therapy in that group of patients who have had no prior exposure of the drug [8].

In addition, on further analysis of more than 100 patients that we treated with AMSA in phase I and II studies between 1974 and 1980, we were able to demonstrate a number of characteristics identified prior to the start of therapy which would predict for the probability of response [9]. This study was performed to try and identify a subset of patients in whom *m*-AMSA given as secondary therapy would derive substantial benefit. Using initially an univariant analysis, a number of important pretreatment variables were identified. These included a number induction and maintenance regimens and almost 40% of patients with only one prior therapy achieving a complete remission compared to 20% with two and less than 5% with three or greater. A significantly greater number of patients responded if *m*-AMSA was initiated early after the identification of the latest relapse; those with peripheral circulating blast counts of greater than 25,000/mm^3 had a lower response rate and of patients with acute myeloblastic leukemia 20/77 responded compared to 1/17 with acute lymphoblastic leukemia. In addition, when Auer rod status was investigated in the myeloblastic group, those patients that were Auer rod-positive had a 42% (16/38) complete remission rate compared to 4/39 in whom Auer rods could not be identified. When acute lymphoblastic leukemia and undifferentiated leukemia were combined, only 3/25 responded with a complete remission. The final factor that was highly predictive for response in the univariant analysis was the dose of AMSA that the patients received. Those patients receiving total doses of less than 375 mg/m^2 for the first course had a significantly poorer prognosis. When these data were broken down by Auer rod status in the acute myeloblastic leukemias, 15/28 (55%) achieved a complete rate compared to 4/31 (19%) of those with myeloblastic disease that were Auer rod-negative. Multivariant analysis was subsequently performed, and the following factors emerged as independent prognostic variables: (1) Auer rod status; (2) dose of AMSA; (3) differentiation ratio; and (4) absolute circulating blast count.

Subsequent to the phase II studies showing activity, particularly in acute myeloblastic leukemia, *m*-AMSA has been combined in a number pf programs throughout the world with cytosine arabinoside or anthracycline, with or without the addition of thioguanine and/or vincristine and prednisone. In our own institution two studies were performed to identify prognostic factors in *m*-AMSA. A highly predictive model, developed for identification of patients whose prognosis with current standard therapy was less than 60%, was started on therapeutic regimens which included *m*-AMSA, cytosine arabinoside, vincristine and prednisone. Preliminary results from this study have suggested a significant improvement in the patients with the poorer prognosis and data now accumulated in out center and others of a combination of high-dose cytosine arabinoside with *m*-AMSA have again shown a therapeutic advantage to these patients.

In conclusion, *m*-AMSA is the first new drug to be developed since the introduction of the anthracyclines and cytosine arabinoside which has shown significant activity in acute myeloblastic leukemia. Its incorporation into front-line therapy has allowed patients with a poorer prognosis to have an improved chance of response compared to their predictive response on anthracycline ara-C-containing regimens. It has been demonstrated clearly that in the Auer rod-positive acute and promyelocytic disease that *m*-AMSA is at least equally as effective as the anthracycline-containing regimens. It is disappointing that AMSA using current therapeutic programs has been less active in lymphoid malignancies and other solid tumors.

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