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Perspectives and Commentaries

m-AMSA: a Review of Clinical Data

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THE PAPER of Miller and Bleumink relates to toxicity on immune system of *m*-AMSA and possible immunomodulation induced by this agent [1].

Amsacrine (AMSA, 4′-(9-acridinylamino) methanesulfon-*m*-AMSA/anisidide) is an acridine derivative which was recently shown to be of interest in the treatment of acute leukemia and malignant lymphomas. This drug was selected for clinical trial from a large number of related compounds because of its activity in preclinical cultures and animal tumor systems, including L1210 leukemia, B16 melanoma and P388 leukemia. This paper will focus on the results of most clinical trials published on *m*-AMSA, since its biological properties, mechanism of action and pharmacology are considered separately.

For clinical use, the drug is provided as a 75-mg solution in 1.5 ml of *N,N*-dimethylacetamide (DMA). This solution is then diluted in 0.0353 M L-lactic acid to a total of 15 ml, yielding a concentration of 5 mg/ml. The appropriate dose is further diluted in 5% dextrose in water to a volume of 250–500 ml and infused over 1 hr through a running peripheral or central i.v. line. Contact with chloride solutions must be avoided. A gluconate formulation without DMA has been also utilized.

PHASE I STUDIES, AND PHASE II TRIALS IN SOLID TUMORS

Phase I studies have shown that, when administered at a dose of 90–120 mg/m^2 in 1- or 3-day courses every 21–28 days, *m*-AMSA produces consistent but acceptable myelosuppression, with mild non-hematologic, especially gastrointestinal, toxicity [2, 3]. Antitumor activity has been noted in acute leukemia [4], melanoma [4], Hodgkin's disease [5], chronic lymphocytic leukemia [5], and carcinomas of ovary [2], breast, lung [4], esophagus [5] and unknown origin [2].

Several phase II studies have been performed in solid tumors, in untreated as well as heavily pretreated or relapsed patients, with disappointing results, with an overall response rate lower than 10% [3]. No antitumor responses occurred in 22 evaluable patients with non-small cell lung cancer [7], 15 small cell carcinomas of the lung and 16 renal cell carcinomas [8], and only one partial response among 23 advanced large bowel carcinomas [9]. Moderate antitumor activity was also observed in metastatic breast cancer [10] and melanoma [11].

The poor activity in human solid tumors was confirmed by studies on the xenograft system in nude mice [12]. Some reasons for these poor results have been advanced on the basis of the effects of environmental variables on experimental cell kill [13]. Besides drug transport limitation, the acid environment could limit the activity of the agent, as well as the non-cycling or slowly cycling character of the majority of cells; on the other hand, hypoxemia *per se* is unlikely to influence sensitivity of cells in solid tumors [13]. New analogs of AMSA could hopefully overcome these obstacles.

m-AMSA IN ACUTE LEUKEMIA

Contrary to its small effect in solid tumors, *m*-AMSA appears at the present time as a major drug for the treatment of acute leukemia. The results of various monochemotherapies and drug combinations including *m*-AMSA in acute leukemia have recently been reviewed [14].

The phase I–II studies in acute leukemia have utilized dose-schedules quite different from those defined for solid tumors: the drug was administered daily during 3- to 7-day courses, at

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escalating doses from 50 to 200 mg/m² q d and from 200 to 1000 mg/m² total per course [15, 16]. Myelosuppression is not the major limiting factor in acute leukemia, but extrahematologic toxicity, especially at the oral and gastrointestinal levels (*vide infra*). The best therapeutic regimen was defined by Legha *et al.* in 37 patients receiving a total dose of 450 mg/m² or higher during 5–7 days, with 27 (30%) achieving a complete remission (CR) and three (8%) a partial remission (PR) [16]. Longer courses resulted in undue hematological toxicity.

Further studies have confirmed the value of *m*-AMSA in the treatment of acute leukemia, and attempted to define the response rate in patients refractory to previous therapies, as well as in various cytological types of acute leukemia [15, 17–23]. The results are shown in Table 1. The response rate was 27%, not significantly different between AML and ALL. It was apparently lower in blast crisis of chronic myelocytic leukemia (BC-CML), but the number of such patients was relatively low [17, 19, 23]. Analysis of the results has shown that the expected CR rate is around 23% in patients receiving a sufficient total dose (>450 mg/m²) of the drug. The duration of remission was relatively short, illustrated in the most important series by a median duration of 12 weeks, with a range of 3–59 weeks [18]. It must be emphasized that all these patients were heavily pretreated, generally with anthracyclines, and that most of them were refractory to these treatments.

Table 1.

Reference	Type	Patients (*n*)	CR (%)	PR (%)
[25]	AML	17	3 (17)	0 (0)
	ALL	11	3 (27)	0 (0)
[27]	AML	23	2 (9)	5 (22)
	ALL	8	2 (25)	1 (12)
	BC-CML	9	2 (22)	0 (0)
[28]	AML	82	23 (28)	1 (1)
	ALL	17	1 (6)	0 (0)
[29]	AML	27	3 (11)	6 (22)
	ALL	11	2 (18)	4 (36)
	BC-CML	6	0 (0)	2 (33)
[30]	AML	8	0 (0)	0 (0)
	ALL	18	3 (16)	1 (5)
[31]	AML	17	4 (24)	0 (0)
	ALL	5	0 (0)	1 (20)
	BC-CML	5	0 (0)	0 (0)
[32]	ALL	12	5 (41)	
[33]	AML	41	8 (20)	
	ALL	12	3 (25)	6 (10)
	BC-CML	6	0 (0)	
Total	AML	215	43 (20)	
	ALL	94	19 (20)	
	BC-CML	26	2 (8)	
	all types	335	64 (19)	27 (8)

In further studies *m*-AMSA has been associated with other antileukemic drugs in various combination chemotherapy programs [14]. The drug was frequently associated with cytosine arabinoside, either alone or in complex combinations. Arline *et al.* have replaced the daunorubicin by *m*-AMSA in their DAT protocol (L14) for AML, the drug being administered at the daily dose of 225 mg/m² during the first 3 days of a 5-day course, along with cytosine arabinoside (ara-C) and 6-thioguanine [24]. The result of this AAT protocol was eight (32%) CR and three PR in 25 AML patients treated during their first relapse. The results of the AAT protocol were then compared to DAT by randomization in 72 untreated patients, yielding comparable results (48% vs 44% CR of apparently the same duration during the early follow up) [25]. They therefore advocated the replacement of anthracyclines by *m*-AMSA in the induction treatments of AML, to avoid excessive cardiac toxicity. Of interest is the fact that, among the patients entered in the trial, 16 patients had acute promyelocytic leukemia: seven were treated by AAT and all achieved a CR after one [6] or two [3] courses, whereas nine received a DAT protocol with only three CR; moreover, two patients with persisting leukemia after one course of DAT achieved CR after one course of AAT [26].

Weil *et al.* treated 49 patients, mainly children, with *m*-AMSA + ara-C, 200 mg/m² of each q d for 5 days [22]. They observed 17 CR (45%) out of 37 ALL treated, and three (25%) out of 12 AML, most of them heavily pretreated. McCredie *et al.* also replaced daunorubicin by *m*-AMSA in their induction regimen for both AML and ALL, *m*-AMSA being administered at low doses (30 mg/m²/day) for 7 days along with ara-C, prednisone and one injection of vincristine. The result of this AMSA-OAP treatment is three CR and three PR in 27 previously treated patients, and five CR (45%) in 11 untreated patients with poor-risk AML [27].

Other associations have been tested in previously treated and refractory AML. Interesting results have been reported when *m*-AMSA was associated with VP16 [28], 5-azacytidine [29] and cyclocytidine [30], and VP16, ara-C and thioguanine [31]. The most impressive ones were observed with *m*-AMSA and high-dose ara-C (³ g/m² q 12 hr): Hines *et al.* treating 40 relapsed or refractory AML with high-dose ara-C for 6 days, followed by 3 days of *m*-AMSA 75–100 mg/m² q d, obtained 28 CR (70%) [32]. With different dose schedules, 90–120 mg/m² *m*-AMSA for 5 days with four injections of high-dose ara-C

during the first 2 days, we observed 12 CR (46%) in 26 relapsed or refractory AML, with a high rate (44%) of CR in refractory leukemias.

It can be concluded from these studies that *m*-AMSA is a potent antileukemic intercalating agent, and a candidate for the treatment of this disease either as a replacement of anthracyclines—especially in cases of prior cardiac history—or for introduction as an alternate treatment during consolidation. The present AML6 protocol of the EORTC randomizes, in patients achieving a CR after daunorubicin plus ara-C, between continuous treatment, or an alternate regimen with *m*-AMSA, high-dose ara-C and 5-azacytidine. Patients refractory to induction treatment with anthracyclines should also be treated with *m*-AMSA, in view of the apparent lack of cross-resistance in the clinic, contrary to the experimental observations in P388 leukemia [33].

m-AMSA IN MALIGNANT LYMPHOMAS

Several studies are currently ongoing to assess the activity of *m*-AMSA in advanced malignant lymphomas. Few results have been reported [20, 34]. Cabanillas *et al.* treated patients refractory to previous treatments, including adriamycin, with *m*-AMSA 40 mg/m^2 daily × 3 every 21 days (30 mg/m^2 in the case of compromised marrow reserve). They observed ten objective responses in 30 such patients, with three CR and three PR in 21 high-grade malignant lymphomas [34].

Further studies should define the value of *m*-AMSA in combination treatments in various histological types of malignant lymphomas.

TOXICITY IN CLINICAL STUDIES

The toxicity of *m*-AMSA has been precisely defined in a number of studies. The main toxicities are hematological and digestive.

In phase I trials with 1- to 3-day courses every 21–28 days [3, 4], leukopenia was the major dose-related toxic effect, with 120 mg/m^2 as the recommended total dose. Mild thrombocytopenia was also observed, without evidence of cumulative myelosuppression. The time to recover more than 1×10^9/l polymorphonuclears and 100×10^9/l platelets was best defined in remitter patients and was generally between 3 and 5 weeks. Legha *et al.* observed a duration of hypoplasia of 3–4 weeks after total doses of 450–630 mg/m^2, and frequently longer than 6 weeks after doses >750 mg/m^2, with increased mortality [18]. Deaths after treatment by *m*-AMSA are generally related to severe and prolonged myelosuppression and infectious complications.

Immunosuppression also occurs to some extent in most patients. The immunosuppressive activity has been assessed mainly in experimental models [1, 35]. Cell-mediated capacity, i.e. T lymphocyte mitogenic responsiveness, delayed-type hypersensitivity reaction and host vs graft reaction, is depressed during the leucopenic phase, as are the inflammatory responses, but restoration parallels the recovery of leucocytes, and thymus-dependent antibody response appeared unexpectedly increased [1].

Severe stomatitis is also frequent after total doses >600 mg/m^2 [17, 18] and is universal at doses of 1000 mg/m^2, leading to severe dysphagia and malnutrition. Nausea and vomiting are common, depending on the dose schedule, but they are less severe with intermittent treatments. Diarrhea has been reported after combination treatments [27] and necrotizing colitis after association with ara-C [28]. Increased bilirubin—predominantly conjugated—and alkaline phosphatase are frequently observed after treatment of acute leukemia, but liver enzymes are generally normal or slightly elevated [18, 20, 23], except when other toxic or infectious factors are associated.

When evaluable, alopecia is universal [15, 23]. Cutaneous toxicity is unfrequent, or related to associated drugs such as high-dose ara-C [29]. Local pain during infusion and phlebitis is sometimes observed [8, 17, 18, 21], but may be avoided by careful dilution of the drug, especially when infused in a peripheral vein [17]. Mild hearing loss is infrequently noted [17].

A few patients developed grand mal seizures, probably related to associated metabolic disorders [36].

One of the major problems raised by the clinical trials of *m*-AMSA is its potential cardiac toxicity, since this drug is advocated to replace the anthracyclines in patients with acute leukemia, especially in cases of past history of cardiac disease or large cumulative doses of anthracyclines already administered. In animal studies the cardiotoxic effects of lethal doses *m*-AMSA were less severe than with adriamycin. In a review of the clinical literature involving more than 3000 patients there was a 1–9% incidence of arrythmia and 0.4% of cardiomyopathy [37]. Fatalities occurred in 12% of the arrythmic episodes (0.2% of the total population). Virtually all of these patients had been heavily pretreated with anthracyclines, and many were hypokalemic at that time. Careful monitoring and correction of electrolyte abnormalities is therefore essential during *m*-AMSA treatment [18, 37]. The possible role of DMA has been also advanced, but three cases of cardiomyopathy have been observed after treatment by DMA-free *m*-AMSA gluconate in patients heavily pretreated with anthracyclines.

REFERENCES

1. Miller T, Bleumink N. Quantitative and qualitative effects of *m*-AMSA (amsacrine) on cellular immune components. *Eur J Cancer Clin Oncol* 1984, **20,** 1307–1316.
2. Van Echo DA, Chiuten DF, Gurmley PE *et al.* Phase I clinical and pharmacological study of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide using an intermittent biweekly schedule. *Cancer Res* 1979, **39,** 3881–3884.
3. Von Hoff DD, Howser D, Gormley P *et al.* Phase I study of methanesulfonamide, *N*-(4-(9-acridinylamino)-3-methoxyphenyl) (*m*-AMSA) using a single-dose schedule. *Cancer Treat Rep* 1978, **62,** 1421–1426.
4. Legha SS, Gutterman Ju, Hall SW *et al.* Phase I clinical investigation of 4′-(9-acridinylamino)methanesulfon-*m*-anisidide (NSC 249992), a new acridine derivative. *Cancer Res* 1978, **38,** 3712–3722.
5. Goldsmith MA, Bhardwaj S, Ohnuma T, Greenspan EM, Holland JF. Phase I study of *m*-AMSA in patients with solid tumors and leukemia. *Cancer Clin Trials* 1980, **3,** 197–202.
6. Grillo-Lopez A, Hess F. Amsacrine: an effective new antileukemia agent. 13th Int. Congr. Chemother Vienna, 1983, SE 12.1.1-7, part 237, 56–62.
7. Casper ES, Gralla RJ, Kelsen DP *et al.* Phase II evaluation of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA) in patients with non-small cell lung cancer. *Cancer Treat Rep* 1980, **64,** 345–437.
8. Fuks JZ, Van Echo DA, Aisner J, Kravitz S, Wiernik R. A phase II trial of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA) in patients with renal cell carcinoma (RCC) and refractory small cell carcinoma of the lung (SCCL). *Proc ASCO* 1980, **21,** 477.
9. Ferraro J, Hillinger S, McNamee R, Rudkdeschel JC. Treatment of advanced large bowel cancer with *m*-AMSA. A GITSG pilot study. *Proc* 1980, **21,** 420.
10. Legha SS, Blumenschein GR, Buzdar AU *et al.* Phase II study of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA) in metastatic breast cancer. *Cancer Treat Rep* 1979, **63,** 1961–1964.
11. Hall SW, Benjamin RS, Legha SS *et al.* AMSA: a new acridine derivative with activity against melanoma. *Proc AACR ASCO* 1979, **20,** 336.
12. Sordillo PP, Helson L, Lesser M. Evaluation of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (*m*-AMSA, NSC 249992) on human tumor in nude mice. *Cancer Clin Trials* 1981, **3,** 385–889.
13. Wilson WR, Giesbrecht JL, Hill RP, Whitmore GF. Toxicity of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide in exponential-and plateau-phase Chinese Hamster cell cultures. *Cancer Res* 1981, **41,** 2809–2816.
14. Arlin ZA. Current status of amsacrine (AMSA) combination chemotherapy programs in acute leukemia. *Cancer Treat Rep* 1983, **67,** 967–970.
15. Arlin ZA, Sklaroff RB, Gee TS *et al.* Phase I and II trial of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide in patients with acute leukemia. *Cancer Res* 1980, **40,** 3304–3306.
16. Legha SS, Keating MJ, Zander AR *et al.* 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA): a new drug effective in the treatment of adult acute leukemia. *Ann Intern Med* 1980, **92,** 17–21.
17. Lawrence HJ, Ries CA, Reynolds RD *et al.* AMSA—a promising new agent in refractory acute leukemia. *Cancer Treat Rep* 1982, **66,** 1475–1478.
18. Legha SS, Keating MJ, McCredie KB, Bodey GP, Freireich EJ. Evaluation of AMSA in previously treated patients with acute leukemia: results of therapy in 109 adults. *Blood* 1982, **60,** 484–490.
19. Slevin ML, Shannon MS, Prentice HG, Goldman AJ, Lister TA. A phase I and II study of *m*-AMSA in acute leukemia. *Cancer Chemother Pharmacol* 1981, **6,** 137–140.
20. Tan CTC, Hancock C, Steinherz PG *et al.* Phase II study of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (NSC 249992) in children with acute leukemia and lymphoma. *Cancer Res* 1982, **42,** 1579–1581.
21. Van Echo DA, Markus SD, Schimpff SC, Wiernik PH. A phase II trial of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA) in adult relapsed acute leukemia. *Proc AACR* 1981, **22,** 230.
22. Weil M, Auclerc MF, Schaison G *et al.* Activité clinique de la *m*-AMSA et de l'association de *m*-AMSA et de cytosine arabinoside. *Nouv Presse Med* 1982, **11,** 2911–2914.
23. Winton EF, Hearn EB, Vogler WR *et al.* Amsacrine in refractory adult acute leukemia: a pilot study of the Southeastern Cancer Study Group. *Cancer Treat Rep* 1983, **67,** 977–980.

24. Arlin ZA, Flomenberg N, Gee TS *et al.* Treatment of acute leukemia in relapse with 4′-(9-acridinylamino) methanesulfon-*m*-anisidide in combination with cytosine arabinoside and thioguanine. *Cancer Clin Trials* 1981, **4,** 317-321.
25. Arlin ZA, Gee TS, Mertelsmann R *et al.* Randomized trial of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA) in combination with cytosine arabinoside (ara-C) and thioguanine (TG) vs. daunorubicin with ara-C and TG in adults with acute non lymphoblastic leukemia (ANLL). In: *Amsacrine: Current Perspectives and Clinical Results with a New Anticancer Agent.* Princeton, NJ, Communication Media for Education, 1983, 77-84.
26. Arlin ZA, Kempin S, Mertelsmann R *et al.* Primary therapy of acute promyelocytic leukemia: results of amsacrine-and daunorubicin-based therapy. *Blood* 1984, **63,** 211-212.
27. McCredie KB, Keating MJ, Estey EH *et al.* Use of a 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA), cytosine-arabinoside (Ara-C), vincristine, prednisone combination (AMSA-OAP) in poor risk patients in acute leukemia. *Proc ASCO* 1981, **22,** 479.
28. Letendre L, Hineman V, Hoagland CH, Kiely J, Kovach JS. Phase I trial of VP-16 and AMSA in combination in patients with refractory acute non-lymphocytic leukemia (ANLL). *Proc ASCO* 1984, **3,** 189.
29. Kahn SB, Sklaroff R, Lebedda J *et al.* 4′-(9-Acridinylamino) methanesulfon-*m*-anisidide (*m*-AMSA) and 5-azacytidine (AZA) in the treatment of relapsed adult acute leukemia. *Am J Clin Oncol* 1983, **6,** 493-502.
30. Miller L, Miller D, Meyers P, Wollner N, Tan C. 4′-(9-Acridinylamino) methanesulfon-*m*-anisidide (AMSA)-cyclocytidine(cyclo) in children with acute leukemia. *Proc AACR* 1982, **23,** 119.
31. Hurd DD, Peterson BA, Bloomfield CD. 4′-(9-Acridinylamino) methanesulfon-*m*-anisidide (AMSA), VP-16-213 (VP), cytosine arabinoside (ara-cO) and 6-thioguanine (6TG) in the treatment of relapsed and refractory acute nonlymphocytic leukemia (ANLL). *Blood* 1981, **58,** Suppl. 1, 142a.
32. Hines JD, Oken MM, Mazza JJ *et al.* High dose cytosine arabinoside and *m*-AMSA is effective therapy in relapsed acute nonlymphocytic leukemia. *J Clin Oncol* 1984, **2,** 545-549.
33. Johnson RK, Chitnis MP, Embrey WM, Gregory EB. *In vivo* characteristics of resistance and cross resistance of an adriamycin-resistant subline of P388 leukemia. *Cancer Treat Rep* 1978, **62,** 1535-1547.
34. Cabanillas F, Legha SS, Budey GP, Freireich EJ. Initial experience with AMSA as single agent treatment against malignant lymphoproliferative disorders. *Blood* 1981, **57,** 614-616.
35. Baguley BC, Falkenhaug EM, Rastrick JM, Marbrook J. An assessment of the immunosuppressive activity of the antitumor compound 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (*m*-AMSA). *Eur J Cancer* 1974, **10,** 169-171.
36. Legha SS, Latreille J, McCredie KB, Bodey GP. Neurologic and cardiac rhythm abnormalities associated with 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA) therapy. *Cancer Treat Rep* 1979, **63,** 2001-2003.
37. Grillo-Loez AJ, Hess F, Cardiotoxocity associated with Amsacrine. *Proc ASCO* 1983, **2,** 183.