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AMSA Toxicity in Patients with Abnormal Liver Function

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Abstract—*4'-(9-Acridinylamino) methanesulfon-m-anisidide AMSA) is a new antitumor drug effective in the treatment of acute leukemia and some solid tumors. Phase I and II studies showed myelosuppression to be its major toxicity. Preliminary pharmacological studies with AMSA revealed prolongation of half-life and delayed clearance in patients with compromised liver function. In this study, we have correlated pretreatment liver function abnormalities with myelosuppressive toxicity of AMSA in patients with leukemia and a variety of solid tumors. In patients with solid tumors and elevated serum bilirubin levels, the degree of myelosuppression was unpredictable. Since some patients experienced excessive toxicity it is advisable to begin therapy with a 25–30% reduction in the starting dose of AMSA for patients with elevated bilirubin values. In leukemia patients with a serum bilirubin level up to 3 mg/dl dose reduction is not indicated, but longer duration of hypoplasia may occur. It may, however, be advisable to start at a 25% lower dose, especially if the bilirubin level is greater than 3 mg/dl. Additional pharmacokinetic studies are necessary to clarify the relationship between liver dysfunction, plasma clearance of AMSA and the degree of myelosuppression.*

INTRODUCTION

THE ACRIDINE derivative AMSA, a new antitumor drug, has been shown to be effective against acute leukemia, lymphoreticular neoplasms and some solid tumors [1–4]. The maximum tolerated dose of AMSA for patients with solid tumors is 40 mg/m²/day for 3 days or 120 mg/m² as a single dose repeated every 21 days. Dose-limiting toxicity is myelosuppression, which is usually brief, reversible and noncumulative. At the recommended dose level of AMSA, the degree of myelosuppression in a recently reported phase II study was modest with a median WBC count of 2500/μl and a median granulocyte count of 1400 μl [5]. One third of the patients had inadequate myelosuppression with AMSA dose of 40 mg/m²/day for 3 days and accordingly tolerated AMSA dose level of 50–75 mg/m²/day for 3 days. Other less common side effects of AMSA include nausea, vomiting, stomatitis, dizziness and possible neurologic and cardiac rhythm abnormalities [6].

For patients with acute leukemia, the optimum dose schedule of AMSA is 75–90 mg/m² daily for 7 days. The median duration of myelosuppression with this dose level is approximately 4 weeks [4].

We observed that with the usual dose of AMSA, myelosuppression was more pronounced in some patients with abnormal liver function. This retrospective review was undertaken to evaluate the relationship of AMSA dose to myelosuppression in patients with abnormal liver function and to derive guidelines for dose adjustment.

PATIENTS AND METHODS

Twenty-one patients with abnormal liver function treated with AMSA were evaluated. Fifteen patients had solid tumors and six had acute leukemia.

Patients with solid tumors

Primary tumors included colon and rectal adenocarcinoma, 7; melanoma, 4; breast adenocarcinoma, 1; teratocarcinoma, 1; and

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adenocarcinoma—unknown primary, 2. All patients had significant abnormalities of liver function with elevated serum bilirubin or transaminase concentrations or both, prior to treatment with AMSA. All patients had hepatomegaly with liver scan evidence of liver metastases. Renal function was normal, except in one patient who had mild impairment. Patient characteristics, including prior treatment and the degree of myelosuppression, are outlined in Table 1.

AMSA was given intravenously at a dose of 20–50 mg/m^2/day for 3 days dissolved in 250 ml of 5% dextrose in water. Courses were repeated every 21 days, provided myelosuppression had resolved. Complete blood counts, including a platelet count, were obtained prior to treatment and usually once weekly thereafter. Blood chemistries, including bilirubin and serum glutamic oxaloacetic transaminase (SGOT), were obtained prior to each course and as often as clinically indicated. Seventeen courses of AMSA were evaluated. Myelosuppression was graded as follows: mild, lowest WBC count greater than 2500/μl, lowest granulocyte count greater than 1000/μl or lowest platelet count greater than 1000,000/μl; moderate, lowest WBC count 1500–2500/μl, lowest granulocyte count 500–1000/μl or lowest platelet count 50,000–100,000/μl; and severe, lowest WBC count less than 1000/μl, lowest granulocyte count less than 500/μl or lowest platelet count less than 50,000/μl.

Liver function abnormalities were graded as follows: mild, elevated SGOT* level (one to three times normal) but a normal serum bilirubin level (0.1–1 mg/dl); moderate, elevated SGOT level (more than four times normal) or serum bilirubin level 1–3 mg/dl or both; severe, bilirubin level greater than 3 mg/dl.

Leukemia patients

Six patients with acute leukemia had elevated serum bilirubin levels and were treated with AMSA. The dose of AMSA varied among different patients partly because of the design of the study and partly because the dose was reduced due to elevated bilirubin levels in some patients. All patients had received prior chemotherapy with multiple agents but were in relapse at the time of AMSA treatment. AMSA dose per course, liver functions and AMSA toxicity are detailed in Table 2. All patients were treated as in-patients and were monitored with frequent bone marrow examinations, daily blood counts and repeated blood chemistry determinations, as indicated.

†Normal range for SGOT: 10–50 mU/ml.

RESULTS

Patients with solid tumors

The relationship of myelosuppression to the degree of liver function abnormality is summarized in Table 3. Since the dose of AMSA received by individual patients was variable, it is difficult to be certain about an absolute relationship between the degree of liver dysfunction and the severity of myelosupression. Nevertheless, there is a strong suggestion that patients with abnormal liver function were at higher risk of severe myelosuppression when given full dose of AMSA. Among patients with elevated SGOT levels but normal serum bilirubin levels, the degree of myelosuppression with AMSA was similar to that expected with the usual dose of AMSA. Among the patients with moderate liver function abnormalities, 6 of 12 developed severe myelosupression, and this was fatal in 2 patients. Four patients had modest myelosuppression, but 2 had received 25–50% reduction in AMSA dose because of elevated bilirubin levels. Two patients were able to tolerate full doses of AMSA in spite of elevated bilirubin levels, indicating that the correlation between hyperbilirubinemia and myelosuppression was not strong. Of the 6 patients who had a 25–30% reduction in AMSA dose because of elevated bilirubin level, only one had severe myelosuppression. Other parameters of liver disease, such as the level of serum alkaline phosphatase or the extent of hepatomegaly, did not provide any additional guidelines in making a prediction for the severity of myelosuppression.

Leukemia patients

Table 2 details the toxicity of AMSA related to the degree of serum bilirubin elevation. A total of 10 courses of AMSA were given to six patients who had elevated bilirubin secondary to their illness or related complications. Three patients died from systemic infections during the period of myelosuppression following AMSA therapy, two of them in the 2 weeks after treatment. The third patient died of prolonged hypoplasis (41 days) and had no evidence of residual leukemia at autopsy. She had obstructive jaundice from gallbladder calculi. Among the remaining patients, five of six AMSA courses were given in the presence of elevated bilirubin levels. In spite of full doses of AMSA the mean time to recovery from myelosuppression was five weeks (range 3–7 weeks), which was approximately one week

Table 1. Patient characteristics and AMSA toxicity—patients with solid tumors

Patient no.	Age (yr)	Primary tumors	Prior therapy	Pretreatment Bilirubin mg/dl	Pretreatment SGOT mU/ml	AMSA dose mg/m² for 3 days	Lowest counts/μl WBC	Lowest counts/μl Granulocyte	Lowest counts/μl Platelets	Comment
1	27	Melanoma	None	1.0	155	50	3.9	2.3	315	Bilirubin increased to 1.2 mg.
2	38	Melanoma	None	0.9	73	40	4.2	1.7	278	Received 2nd course of AMSA at same dose
3	41	Colon	5-FU, VCR Bruceantin	1.0	115	40	1.5	0.5	119	Second course at 30 mg/m²/day
4	44	Colon	5-FU, Vindesine	0.8	184	40	1.6	0.2	145	No complications from therapy
5	32	Testis	VLB, CDDP, Bleo	5.1	92	30	0.5	0.0	11	Died on day 12 from sepsis. Pretreatment elevation BUN/creat. (33/1.3)
6	47	Colon	5-FU, VCR,	4.9	162	30	4.8	—	160	No myelosuppression. Bilirubin rose to 7 mg during therapy
7	47	Colon	5-FU	10	210	20	4.3	2.9	150	Dose reduced because of elevated bilirubin. Received 2 courses
8	42	Colon	5-FU, VCR, XRT, Vindesine	2.0	159	25	2.5	1.9	166	No complications despite prior radiotherapy to spine
9	55	Breast	5-FU, Adr, CYT	(a) 0.3	116	30	0.9	0.0	14	No complications secondary to myelosuppression
			Tamoxifen	(b) 0.6	250	20	0.7	1.0	13	
10	68	Melanoma	None	3.9	198	40	1.9	0.8	10	Death related to severe myelosuppression and bleeding
11	43	Colon	Adr, VCR, 5-FU, Mito-C, MeCCNU	4.0	85	40	5.1	3.1	160	Received 2nd course of AMSA at 50 mg/m² daily for 3 days without incidence
12	69	Melanoma	None	1.7	154	30	2.2	0.9	180	Also received DTIC 800/m² concurrently
13	60	Pancreas	5-FU, VCR, MeCCNU	1.3	28	40	0.7	0.0	100	Death from progressive disease
14	53	Rectum	5-FU, VCR	1.3	32	37.5	0.7	0.0	23	Bilirubin increased to 3 mg/dl by day 7. Developed Gm-ve sepsis
15	55	Colon	5-FU, VCR	(a) 1.1	49	30	3.0	1.7	176	No complications
			MeCCNU	(b) 2.8	57	40	2.2	1.0	100	

Abbreviations: 5-FU, 5-fluorouracil; VCR, Vincristine; VLB, velban; Bleo, bleomycin; Mito-C, mitomycin C; MeCCNU, methyl CCNU; Adr, adriamycin; XRT, radiotherapy; CDDP, *cis* platinum: CYT, cyclophosphamide.

Table 2. AMSA therapy in leukemia patients with liver dysfunction

Patient no.	Age (yr)	Course no.	Serum bilirubin Pretreatment	Serum bilirubin Maximum (day)	AMSA dose mg/m² (× no. of days)	Duration of marrow hypoplasia	AMSA Toxicity Stomatitis	AMSA Toxicity Infection	Liver histology on autopsy	Outcome
1	22	1	0.7	18(9)	75×7	18	none	*Escherichiacoli* sepsis	Extensive necrosis around central veins	Died from infection and progressive leukemia
		2	3.4	10(16)	75×7	26	none	Pneumonia	Moderate fatty metamorphosis	
2	54	1	0.8	4(9)	50×7	16	none	F.U.O.	Mild fatty change	Died from infection and myelosuppression on day 15
		2	1.9	10(15)	75×7	15+	++	*Candida* sepsis		
3	25	1	5.0	10(15)	75×4	32	none	Gm-ve sepsis	No autopsy	Died from progressive leukemia
		2	5.8	24(25)	75×7	24	++	Gm-ve sepsis		
4	26	1	1.9	7(36)	90×7	36	none	No sepsis	No autopsy	CR
		2	2.8	10(44)	75×7	51	none	*Candida* sepsis		Progressive leukemia
5	70	1	1.5	21(41)	75×5	41+	none	F.U.O.	Mild fatty change and bridging fibrosis	Death from sepsis and liver failure due to obstructive jaundice
6	68	1	3.4	9(9)	90×5	14+	++	Gm-ve sepsis	Mild fatty change, Lymphoma infiltration	Died of sepsis on day 14

Table 3. Hematologic toxicity by AMSA dose and liver function: patients with solid tumors

Liver function abnormality	No. of courses	Myelosuppression		
		Mild	Moderate	Severe
Mild	5	3(30, 40, 50)*	1(40)	1(30)
Moderate	7	1(25)	2(30, 40)	4(20, 40, 40, 40)
Severe	5	3(20, 30, 40)	—	2(30, 40)

*(dose in mg/m^2/day × 3 days).

longer than that expected for patients with normal bilirubin levels.

All ten courses of AMSA were accompanied by rises in serum bilirubin levels following the treatment. In seven patients in whom reversibility could be evaluated, bilirubin level fell significantly, usually to near pretreatment levels. The serum transaminase levels were normal in seven courses and remained unchanged during treatment despite significant rises in serum bilirubin levels.

Four patients had a liver examination at autopsy. Three showed intrahepatic cholestasis and fatty metamorphosis. The cholestasis was more severe in the central portions of the lobules than in the portal areas. Three patients showed severe hemosiderosis and had no evidence of liver cell necrosis or significant inflammatory infiltration. The fourth patient had no evidence of cholestasis but showed marked necrosis around the central veins, as well as evidence of moderate fatty metamorphosis. The relationship of AMSA to the central hepatic necrosis in this patient is uncertain because she was also afflicted with respiratory failure and septicemia.

Moderately severe stomatitis was seen in 3 of 10 courses with AMSA dose levels that ordinarily would not cause stomatitis. It was more severe in patients whose pretreatment liver function status was worse than that of other patients.

DISCUSSION

The pharmacologic disposition of AMSA in rats and mice was studied by Cysyk *et al.* [7]. Using [^{14}C]-labeled AMSA they found that radioactivity was selectively localized in the liver, mainly as metabolites of AMSA. Greater than 50% of the administered dose was excreted in the bile in the first two hours. They also observed a bile-to-plasma AMSA concentration ratio of 400:1, suggesting an active transport. Greater than 80% of the administered dose was excreted via the biliary route into the feces, with the remaining radioactivity being recovered in the urine. Pharmacokinetic studies of AMSA in humans have also shown that biliary excretion plays a significant role in the elimination of this agent [8]. Severe hepatic dysfunction leads to a significant prolongation of plasma half-life of AMSA and a delay in the total body and plasma clearance [8, 9].

Because hepatic metabolism and biliary excretion are the major routes of excretion of AMSA, the accumulation of AMSA and its metabolites in patients with abnormal liver function may result in greater toxicity.

Our data from solid tumor patients suggest that in patients with abnormal liver function the usual dose of AMSA can cause severe myelosuppression, and therefore a dose reduction should be considered. We suggest a 25–30% reduction in the AMSA dose if the serum bilirubin level is elevated or if SGOT is greater than four times normal values. Adjustment of dose in subsequent courses should depend upon the degree of myelosuppression observed with the first course of therapy. It should, however, be pointed out that two of our patients with serum bilirubin values greater than 3 mg/dl tolerated full doses of AMSA with modest myelosuppression. This points out that the myelosuppressive toxicity of AMSA in patients with abnormal liver function is not always predictable, that the recommendations suggested above should be used only as guidelines and that the decision regarding dose reduction should be based on the overall clinical condition of the patient.

In leukemia patients with elevated serum bilirubin levels, AMSA therapy was associated with some increase in the duration of bone marrow hypoplasia. Our limited data suggest that no significant decrease in dose is needed with serum bilirubin below 3 mg/dl. However, bone marrow hypoplasia may be prolonged and aggressive hematologic support is needed. If the general condition of the patient allows, a 25% reduction in the starting AMSA dose may be desirable, especially if the serum bilirubin is greater than 3 mg/dl.

Among leukemia patients with elevated pretreatment bilirubin levels, we observed a further increase in the bilirubin levels following AMSA therapy. This was not surprising since hyperbilirubinemia has been observed in leukemia patients even when the pretreatment bilirubin was normal [4]. Although sepsis occurring during marrow hypoplasia may have been responsible for the rise in bilirubin, it is conceivable that AMSA or its metabolites may interfere with bilirubin metabolism or excretion or both. Based on the animal toxicology studies done at the National Cancer Institute, there is concern that the vehicle used to dissolve AMSA may be a contributory factor in the etiology of hyperbilirubinemia. The lack of concomitant increase in SGOT suggests lack of any direct hepatocellular toxicity. This is confirmed by the absence of any evidence of hepatitis or other drug-induced hepatocellular damage on autopsy examination of the liver in three of our patients. We therefore believe that AMSA has no direct hepatotoxicity and that the basis of hyperbilirubinemia during AMSA therapy is not entirely clear at the present time.

In conclusion, AMSA toxicity in patients with compromised liver function is unpredictable and can be excessive. Certain guidelines have been suggested for the use of AMSA in this group of patients. Further studies of AMSA pharmacology will be of interest and may help establish proper guidelines for dose adjustment.

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