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Successful Treatment of a Patient with Acute Nonlymphoblastic Leukemia (ANLL) and Anthracycline Cardiomyopathy with 4′(9-Acridinylamino) Methanesulfon-*M*-Anisidide (AMSA)

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Summary. *A patient with acute nonlymphoblastic leukemia in relapse and anthracycline cardiomyopathy was treated with AMSA in combination with cytosine arabinoside and thioguanine (AAT). Induction of remission was accomplished after one course of therapy without development of congestive heart failure. Radionuclide studies done prior to and subsequent to the reinduction with AAT revealed that the combination did not induce further deterioration of myocardial function. Although the exact risk of AMSA causing additional cardiac damage will require more extensive experience, this case suggests that AMSA may be safely given to patients with anthracycline cardiomyopathy and may be the treatment of choice for this group of patients.*

Introduction

Cardiomyopathy is a recognized complication of therapy with anthracyclines and may be a limiting factor in the treatment of ANLL. AMSA, an acridine derivative, is also an effective agent for ANLL [3, 4, 8]. Toxic effects reported include dose-related marrow suppression, nausea and vomiting, stomatitis, and hepatic dysfunction. Cardiac dysrhythmias after administration of AMSA have been documented in patients with electrolyte disturbances [9, 10, 15], and there are rare reports [11, 12] of congestive heart failure occurring in patients who have previously received anthracyclines. A patient with ANLL in relapse and anthracycline cardiomyopathy was successfully treated with AMSA in combination with cytosine arabinoside (Ara-C) and 6-thioguanine (6-TG) without further deterioration of cardiac function.

Case Report

G. C. is a 41-year-old woman whose erythroleukemia (FAB classification: M6) was diagnosed in 1978. She achieved complete remission in August 1978 after two induction courses of daunomycin, Ara-C, and 6-TG (Memorial Hospital L-14 Protocol; [2]), receiving a total of 360 mg daunomycin/m^2. She was then given 1 year of intensification therapy, including an additional 275 mg daunomycin/m^2 and 180 mg of adriamycin/m^2.

Before receiving chemotherapy, the patient had a blood pressure of 140/80 and a normal physical examination except for a grade II/IV mitral regurgitation murmur. Electrocardiogram (ECG) and X-ray findings in the chest were normal.

Two months after completion of intensification therapy, the patient developed exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Physical examination revealed a blood pressure of 80/40, tachycardia, tachypnea, jugular venous distention, a third heart sound, pulmonary rales, hepatomegaly, and lower extremity edema. The ECG showed decreased voltage in the precordial leads and an X-ray of the chest revealed cardiomegaly, pulmonary vascular congestion, and bilateral pleural effusions. Blood counts, hepatic and renal function tests, and urine analysis were normal, and bone marrow aspiration documented continued remission. An ultrasound examination of the heart demonstrated normal valvular apparatus and excluded a pericardial effusion. Left atrial and ventricular dimensions were at the upper limits of normal, but poor wall motion and a reduced ejection fraction were noted.

The patient improved with digoxin, furosemide, and nitrates but remained unable to do more than light housework. A radionuclide cineangiogram obtained 1 year later (August, 1980) revealed an ejection fraction of 27% with chamber enlargement and generalized hypokinesis. She was hospitalized in September, 1981 with anemia, leukocytosis, thrombocytopenia, and worsening symptoms of congestive heart failure; bone marrow aspiration documented relapse of erythroleukemia. After diuresis and red cell transfusion, she was treated with AMSA 120 mg/m^2 IV daily for 5 days, Ara-C 200 mg/m^2 IV daily by infusion for 5 days, and 6-TG 100 mg/m^2 PO every 12 h for 10 doses, and achieved a complete remission in 21 days without cardiac complications. A repeat radionuclide cineangiogram 6 weeks after therapy was unchanged. Following induction of remission, the patient has received AMSA 120 mg/m^2 every 3 weeks for a total of six doses without developing further evidence of congestive heart failure.

Discussion

The management of patients with ANLL and anthracycline cardiomyopathy may become a more common clinical problem as survival in this disease improves. Congestive heart failure occurs in 5%–10% of patients treated with 550 mg adriamycin/m^2 [14] or 900 mg daunomyocin/m^2 [19], and is lethal in 60%–80% of affected patients. The most satisfactory method for monitoring left ventricular function in patients receiving anthracyclines is radionuclide cineangiography [5]. This technique mode it possible to document a reduced ejection fraction which persisted for many months in 30%–50% of patients who

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had received less than 550 mg adriamycin/m^2 and had no evidence of congestive heart failure [1, 7]. These studies suggest that clinically evident cardiomyopathy may be averted by discontinuing anthracyclines in those patients who develop a reduced ejection fraction.

AMSA in combination with Ara-C and 6-TG is capable of inducing remission in 32% of patients with ANLL in relapse [4]. Dysrhythmias temporally related to administration of the drug have been reported in patients with hypokalemia, hypocalcemia, and hypomagnesemia [9, 10, 15]. A recent report [12] documented decreased myocardial contractility by echocardiography in 8 of 21 children who were studied before and after therapy with AMSA, and two of these developed clinical congestive heart failure. All had received prior therapy which included anthracyclines for a median of 21 months before treatment with AMSA. In another report [11], a patient with ANLL in relapse died of sepsis and unexplained congestive heart failure after induction therapy with AMSA. This patient had previously received 450 mg adriamycin/m^2.

Cardiac toxicity from AMSA has not been encountered in experimental animals [6] and our experience in this patient suggests that AMSA may be given to patients with anthracycline cardiomyopathy without further impairment of left ventricular function.

References

1. Alexander J, Dainiak N, Berger HJ, Goldman L, Johnstone D, Reduto L, Duffy T, Schwartz P, Gottschalk A, Zaret BL (1979) Serial assessment of doxyrubicin cardiotoxicity with quantitative radionuclide angiography. N Engl J Med 300: 278–283
2. Arlin ZA, Gee TS, Fried J, Koenigsberg E, Wolmark N, Clarkson B (1979) Rapid induction of remission in acute non-lymphocytic leukemia (ANLL). Proc AACR/ASCO 20: 112
3. Arlin ZA, Sklaroff RB, Gee TS, Kempin SJ, Howard J, Clarkson BD, Young CW (1980) Phase I and II trials of 4′(9-acridinylamino) methanesulfon-m-anisidide (AMSA) in patients with acute leukemia. Cancer Res 40: 3304–3306
4. Arlin ZA, Flomenberg N, Gee TS, Kempin SJ, Dellaquila C, Mertelsmann R, Strauss DJ, Young CW, Clarkson BD (1981) Treatment of acute leukemia in relapse with 4′(9-acridinylamino) methanesulfon-m-anisidide (AMSA) in combination with cytosine arabinoside and thioguanine. Cancer Clin Trials 4: 317–321
5. Conference on Long-term Normal Tissue Effects of Cancer Treatment (1981) Summary of cardiac portion of cardiopulmonary workshop. Cancer Clin trials 4 [Suppl]: 53–59
6. Cysyk RK, Shoemaker D, Adamson RH (1977) The pharmacologic disposition of 4′(9-acridinylamino) methanesulfon-m-anisidide (AMSA) in mice and rats. Drug Metab Dispos 5: 579–590
7. Gottdiener JS, Mathisen DJ, Borer JS, Bonow RD, Myers CE, Barr LH, Schwartz DE, Bacharach SL, Green MV, Rosenberg SA (1981) Doxorubicin cardiotoxicity: assessment of late ventricular dysfunction by radionuclide cineangiography. Ann Intern Med 94: 430–435
8. Legha SS, Gutterman JU, Hall SW, Benjamin RS, Burgess MA, Valdivesco M, Bodey GP (1978) Phase I clinical investigation of 4′(9-acridinylamino) methanesulfon-m-anisidide (AMSA), a new acridine derivative. Cancer Res 38: 3712–3716
9. Legha SS, Latreille J, McCredie KB, Bodey GP (1979) Neurologic and cardiac rhythm abnormalities associated with 4′(acridinylamino) methanesulfon-m-anisidide (AMSA) therapy. Cancer Treat Rep 63: 2001–2003
10. Riela AR, Kimball JC, Patterson RB (1981) Cardiac arrhythmia associated with AMSA in a child: a Southwest Oncology Group study. Cancer Treat Rep 65: 1121–1123
11. Slevin ML, Shannon MS, Prentice HG, Goldman AJ, Lister TA (1981) A Phase I and II study of m-AMSA in acute leukaemia. Cancer Chemother Pharmacol 6: 137–140
12. Tan C, Wollner N, Steinherz P, Steinherz L, Meyers P, Sorell M, Miller D (1981) Acridinylamino-anisidide (AMSA) in children with leukemia and lymphoma. Proc Am Assoc Cancer Res 22: 169
13. Von Hoff DD, Rosenweig M, Layard M, Slavik M, Muggia FM (1977) Daunomycin-induced cardiotoxicity in children and adults: a review of 110 cases. Am J Med 62: 200–208
14. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rosenweig M, Muggia FM (1979) Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 91: 710–717
15. Von Hoff DD, Elson D, Polk G, Coltman C Jr (1980) Acute ventricular fibrillation and death during infusion of 4′(9-acridinylamino) methanesulfon-m-anisidide (AMSA). Cancer Treat Rep 64: 356–358

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