Cancer Chemother Pharmacol (1982) 8:73–75

Cancer Chemotherapy and Pharmacology

Treatment of Patients with Refractory Myelogenous Leukemia with BCOMM [1,3-bis-chloro(2-chloroethyl)-1-nitrosourea (BCNU), Oncovin (Vincristine), Cyclophosphamide, High-dose Methotrexate and Methyl-glyoxal bis-guanylhydrazone (MGBG)]

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Summary. *Ten patients with AML refractory to anthracyclines and cytosine arabinoside were treated with vincristine 1.4 mg/m^2 and methotrexate (MTX) 2.5 gm/m^2 by intravenous (IV) bolus on day 1 [citrovorum factor (CF) rescue began 24 h later], BCNU 80 mg/m^2, and cyclophosphamide 900 mg/m^2 IV 36 h after MTX and MGBG 300 mg/m^2 IV over 1–2 h on days 3, 4, and 5. Bone marrow aplasia was achieved in all patients by day 12. Five patients (50%) achieved complete remission (CR). Two patients died of sepsis during induction. The median duration of remission was 24 weeks (range 8–38). Maintenance therapy was employed in three patients (high-dose MTX-CF in 2 and MGBG plus BCNU in 1), but did not appear to significantly increase the duration of remission. Nausea and vomiting occurred in eight patients. Five patients developed moderate stomatitis and one developed a modereately severe cutaneous reaction. This pilot experience demonstrates that patients with refractory AML can achieve CR after aggressive treatment with so-called second-line drugs, and may indicate that collateral sensitivity to MTX exists in cells which have become resistant to anthracyclines, a situation we previously described in an experimental cell line.*

Introduction

Complete remission (CR) can be induced in 60%–80% of patients with acute myelogenous leukemia (AML) by drug combinations containing both an anthracycline antibiotic and cytarabine [3, 5, 7]. Unfortunately, the median duration of remission is usually reported to be in the range of 13–15 months, and resistance to these agents is then often observed. We have previously described collateral sensitivity to methotrexate (MTX) in an in vitro cell line with induced resistance to adriamycin [10]. Collateral sensitivity is a biological change in a cell population, conferring increased resistance to one anticancer agent, which results in increased sensitivity to another. Since few examples of this sort of interaction have been described we used this association as a starting point in designing a combination of five drugs to treat patients whose AML was resistant to anthracyclines and cytarabine.

The drugs chosen, vincristine, MTX, 1,3-bis-chloro(2-chlor-ethyl)-1-nitrosourea (BCNU), cyclophosphamide and methyl-glyoxal-bis-guanylhydrazone (MGBG) all have demonstrated activity in acute leukemia [1, 4, 8, 11, 13]. It was our hypothesis that treatment with vincristine and high-dose MTX on day 1 would result in a substantial kill of S phase cells (especially in an anthracycline resistant population). Vincristine was used both because of its own activity in leukemia [8] and because it may increase net uptake of MTX [15]. Administration of substantial doses of BCNU and cyclophosphamide (which may have synergistic cytotoxicities [14]) on day 2 was intended to effect non-cycling cells. It was thought that after a large cell kill had 'recruited' resting cells into cycle, the S-phase-active drug MGBG would be maximally effective on days 3, 4, and 5. It was our

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0344-5704/82/0008/0073/$ 01.00

intention to use doses of drugs that were high enough to cause marrow aplasia rapidly and thus minimize the need for retreatment, which prolongs hospitalization and increases the risk of complications due to inadequate blood counts.

Patients and Methods

All ten patients treated had myelogenous leukemia (9 acute, 1 chronic in blast crisis) demonstrated both morphologically and by cytological staining characteristics [9]. The median age of the patients was 22 years (range 8–61), and six patients were male. Four patients were febrile with presumed sepsis prior to treatment. Six patients had pretreatment platelet counts below 20,000 per mm^3. All patients had been previously treated with an anthracycline drug and cytarabine at standard doses and had failed either reinduction [7] or primary induction [3]. In seven instances use of the anthracycline and cytarabine directly preceded BCOMM therapy, and bone marrow examinations revealed regrowth with leukemia blasts.

The BCOMM drug regimen is outlined in Table 1. Oncovin (vincristine) 1.4 mg/m^2 (maximum dose 2.0 mg) was given by IV bolus on day 1. After 30 min to 1 h MTX 2.5 g/m^2 was also given by IV bolus. Prior to MTX administration and for 48 h thereafter the urine of patients was alkalinized to a pH $\geq$ 7.0 with sodium bicarbonate PO or IV. Patients were also actively hydrated during this period. Citrovorum factor (CF) rescue at either 10 mg/m^2 IV every 6 h for 12 doses or 100 mg/m^2 every 3 h for 32 doses was begun 24 h after MTX. The lower dose was given if serum creatinine did not increase by 50% or more over baseline and the serum MTX level was less than 1×10^{-6} *M* at 24 h. If either of these conditions occurred higher-dose CF rescue was administered. This regimen is similar to that reported by Frei et al. [6].

At 36 h after MTX, patients were given BCNU 80 mg/m^2 and cyclophosphamide 900 mg/m^2, both by IV bolus. Approximately 24 h after BCNU and cyclophosphamide (day 3), MGBG 300 mg/m^2 IV was given over 1–2 h and repeated on days 4 and 5.

Results

Five of ten patients (50%) achieved CR after treatment with BCOMM. All complete responders were patients who had relapsed from an initial CR induced with anthracycline drugs and cytarabine. None of the three patients who were primarily resistant to these agents entered CR, although two of these patients attained good partial responses and one entered CR after further treatment with 4-(9-acridinylamino)-methanesulfon-*m*-anisidide(AMSA).

The bone marrow examinations of all patients showed aplasia with less than 5% blasts by 12 days after the beginning of therapy. In the five patients entering CR, the median time to bone marrow recovery (neutrophil count $\geq$ 1200 per mm^3 and platelet count $\geq$ 100,000 per mm^3) was 25 days (range 21–40) after the start of therapy.

Median duration of CR was 24 weeks (range 8–38) following the attainment of bone marrow recovery. Maintenance therapy was employed in three patients (high-dose MTX with CF rescue in 2 and MGBG and BCNU in 1), but an assessment of benefit is not possible with these small numbers. Median survival of all patients from the beginning of treatment was 32 weeks (40 weeks for patients attaining CR and 10 weeks for patients not entering CR. Two patients died of sepsis after treatment (1 patient with recurrent leukemia and 1 patient during marrow aplasia). The other three patients who failed to obtain a CR received alternative treatments. It was especially gratifying that one patient who attained CR survived for 112 weeks and another for 70 weeks because the induction of further remissions proved possible when resistance to BCOMM occurred.

No unexpected toxicities associated with this regimen were noted. Significant nausea and vomiting occurred in eight patients, being most severe on day 2 after administration of BCNU and cyclophosphamide. Stomatitis of a moderate degree was observed in five patients. One patient developed a generalized erythematous cutaneous reaction (but with minimal blistering or ulceration) like that previously described with the use of MGBG [13]. It is interesting that this patient had been sunbathing 3–4 days prior to treatment.

Table 1. Outline of BCOMM [BCNU, cyclophosphamide, Oncovin (vincristine), high-dose MTX, and MGBG] regimen

Drug[a]	1	2	3	4	5
Oncovin[b]	1.4 mg/m^2				
MTX[c]	2.5 g/m^2				
BCNU		80 mg/m^2			
Cyclophosphamide		900 mg/m^2			
MBGB			300 mg/m^2	300 mg/m^2	300 mg/m^2

[a] All drugs were given by IV bolus except MGBG, which was administered over 1–2 h IV

[b] Maximum dose 2.0 mg

[c] Prior alkalinization of urine, hydration and CF rescue as described by Frei et al. [6] was used with high-dose (see text for details)

Discussion

We were able to induce a CR in five of ten patients with AML refractory to anthracycline drugs and cytarabine by utilizing a combination of so-called second-line drugs. The population of patients we have studied has often been treated with single agents new to clinical testing. The highest reported response rates for such treatments even with drugs like AMSA and rubidazone have been in the range of 28%–30% [2, 12], and much lower rates have often been reported. The duration of remission has also typically been brief. The combination of agents we have utilized seems capable of producing a higher proportion of CRs, which are also of longer duration than is possible for single agents, although, admittedly, our sample size is small. Whether the effectiveness of this combination is substantially due to collateral sensitivity to MTX in cells with induced resistance to anthracyclines or to our scheduling of drugs cannot be determined from this study design, but the superiority of multiple-drug over single-agent treatment is not surprising to us. Obviously the effectiveness of new agents against leukemia needs to be tested until highly curative treatments can be developed. The optimum timing of such trials relative to the clinical course of patients, however, may need to be re-evaluated. Certainly for patients who become refractory to first-line treatment and are treated by physicians who do not have access to phase II agents, BCOMM seems to offer a reasonable expectation of attaining a CR with acceptable side-effects.

Acknowledgements. This work was supported in part by Public Health Service Grant CA 17094 from the National Cancer Institute and by Veterans Administration Research Support.

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Received September 3/Accepted November 24, 1981