Experience with gemtuzumab ozogamycin ("mylotarg") and all-*trans* retinoic acid in untreated acute promyelocytic leukemia

Elihu H. Estey, Francis J. Giles, Miloslav Beran, Susan O'Brien, Sherry A. Pierce, Stefan H. Faderl, Jorge E. Cortes, and Hagop M. Kantarjian

We administered gemtuzumab ozogamycin ("mylotarg"; 9 mg/m² day 1 or 5) and all-*trans* retinoic acid (ATRA) to 19 patients with untreated acute promyelocytic leukemia (APL). There were 3 patients who also received idarubicin because of a white blood cell (WBC) count of more than 30 000/μL. In complete remission (CR), patients were to receive 8 courses of mylotarg (9 mg/m² every 4 to 5 weeks) and ATRA; idarubicin was added only for persistent or recurrent polymerase chain reaction (PCR) positivity. The CR rate was 16/19 (84%). All 12 patients tested to date were PCR-negative 2 to 4 months from CR date; none of the 7 patients evaluated subsequently have reverted to PCR positivity (median follow-up in CR was 5 months, up to 14 months). Mylotarg was well tolerated. A median of 5 post-CR courses have been given to date with 3 patients having currently received 8 post-CR courses, and 4 patients receiving 7 post-CR courses. Mylotarg appears active in APL, and repeated administration is feasible. (Blood. 2002;99:4222-4224)

Introduction

CD33 expression is essentially universal in acute promyelocytic leukemia (APL), and the APL cell's surface typically contains large amounts of the antigen. The anti–CD33 antibody (HuM195), although unattached to a cytotoxic agent, produced polymerase chain reaction (PCR) "negativity" in 11 out of 22 patients with APL who remained PCR "positive" in hematologic complete remission (CR).[1] Gemtuzumab ozogamicin ("mylotarg") combines an anti–CD33 antibody (hP 67.6) with calicheamicin, a cytotoxic agent that, given its similarities with anthracyclines,[2] might be expected to be particularly active in APL. These observations led to the trial described below.

Study design

After formal institutional review board approval, 19 patients, in each of whom the morphologic impression of APL was confirmed molecularly, were treated. Their median age was 50 years; all were ambulatory with a serum bilirubin less than 2.0 mg/mL. There were 18 patients with the characteristic t(15;17). The median initial white blood cell (WBC) count was 3700/μL (up to 101 000/μL) and the median initial platelet count 29 000/μL. There were 8 patients who were "high-risk," 5 who were "low-risk," and 6 who were "intermediate risk."[3]

Patients received all-*trans* retinoic acid (ATRA) (45 mg/m² daily) until CR, after which the same dose was administered using a 2-weeks-on, 2-weeks-off schedule. Mylotarg, 9 mg/m², was given on day 5 (day 1 if the presenting WBC count was > 10 000/μL). There were 3 patients with initial WBC counts of more than 30 000/μL who also received idarubicin (12 mg/m² daily, days 1-3). In CR, patients were to receive 9 mg/m² mylotarg once every 4 to 5 weeks provided platelet and neutrophil counts were more than 100 000/μL and more than 1000/μL, respectively. If counts had not recovered, the next course was to be delayed and the dose reduced; dose reduction was also permitted for extramedullary toxicity. Therapy was to be discontinued after administration of 8 postremission doses of mylotarg (ie, 9 total doses). PCR testing at a level of 10^{-4} was conducted every 2 to 4 months in CR. If the test was "positive," 3 cycles of idarubicin (12 mg/m² daily, days 1 and 2) were to be given, mylotarg discontinued, and ATRA continued.

Approval for the trial was provided by the M. D. Anderson institutional review board and informed consent was provided according to the Declaration of Helsinki.

Results and discussion

The CR rate was 16 out of 19 (84%; 95% confidence interval [CI], 60%-97%) and was 14 out of 16 (88%; 95% CI, 62%-98%) in patients given mylotarg and ATRA without idarubicin. These rates were essentially identical to those we previously observed with single-agent liposomal ATRA,[4] or oral ATRA and idarubicin,[5] as were the rates in high-risk patients (5/8 +/− idarubicin, 3/5 no idarubicin). The median time to hematologic CR (as usually defined) was 27 days, considering all patients or only those given ATRA and mylotarg without idarubicin. The 3 patients who did not achieve CR died (2 of hemorrhage, 1 of multiorgan failure) before antileukemic response was known. There were 2 episodes of possible ATRA syndrome; both resolved with conventional management. Veno-occlusive disease of the liver was not seen, although 7 patients developed asymptomatic self-limited increases in serum glutamic-pyruvic transaminase (SGPT) (up to 192 mg/mL) within one week of starting therapy. There were 2 additional patients (each also given idarubicin) who had asymptomatic self-limited rises in bilirubin (up to 4.1 mg/mL) within 13 days after beginning treatment.

From the Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston.

Submitted December 5, 2001; accepted January 17, 2002. Prepublished online as *Blood* First Edition Paper, April 30, 2002; DOI 10.1182/blood-2001-12-0174.

Reprints: Elihu H. Estey, Department of Leukemia, Box 428, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; e-mail: ehestey@mdanderson.org.

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Table 1. Postremission data

Patient	Idarubicin during induction	Number of post-CR courses of mylotarg to date	Interval (wks) between various courses	Dose per course in mg/m^2	Hematologic status
1	No	8	2*, 6, 5, 4, 6, 5, 4, 7	9 on all 8 courses	CR × 14 MOS +
2	No	8	0, 4, 8, 4, 5, 4, 4, 4	9 on courses 1 and 2; 3 on remaining 6 courses	CR × 12 MOS +
3	No	7	0, 5, 5, 5, 4, 6, 4, not given	9 on courses 1 through 3; 6 on courses 4 and 5; 4.5 on remaining 2 courses	CR × 12 MOS +
6	No	3	5, 4, 7	9 on all 3 courses	CR × 4 MOS +
7	No	7	1, 4, 5, 4, 5, 6, 5	9 on all 7 courses	CR × 7 MOS +
8	Yes	8	0, 4, 5, 4, 8, 4, 4, 4	9 on courses 1 through 5; 6 on courses 6 through 8	CR × 11 MOS +
9	No	7	1, 6, 4, 4, 5, 6, 5	9 on course 1; 5 on courses 2 through 7	CR × 7 MOS +
10	No	7	0, 4, 5, 4, 4, 4, 4	9 on all 7 courses	CR × 6 MOS +
11	Yes	3	0, 5, 5	9 on all 3 courses	CR × 2 MOS +
13	No	4	1, 5, 4, 4, not given	9 on all 4 courses	CR × 5 MOS +
14	No	5	1, 4, 5, 5, 5	9 on all 5 courses	CR × 4 MOS +
15	No	3	0, 4, 4	9 on all 3 courses	CR × 2 MOS +
16	No	1	1	7	CR × 1 MO +
17	No	2	2, 4	9 on both courses	CR × 2 MOS +
18	No	2	1, 4	9 on both courses	CR × 1 MO +
19	No	1	2	9	CR × 1 MO +

*In each case the first number represents the weeks between complete remission (CR) date and start of the first postremission course.

Of the 4 patients in whom sufficient time has passed, 3 have received all 8 planned post-CR courses.The fourth patient did not receive the eighth course (because of a self-limited, asymptomatic rise in bilirubin to 2.1 mg/mL on the preceding course). This patient and one with a negative PCR but a platelet count of 50 000/μL 9 weeks after post-CR course 4 have been the only patients in whom a post-CR course has been omitted. The number of post-CR courses given to date is as follows: 8 courses (3 patients), 7 courses (4 patients), 5 courses (1 patient), 4 courses (1 patient), 3 courses (3 patients), 2 courses (2 patients), 1 course (2 patients) (Table 1). A median of one week (range, 0-5 weeks) has elapsed between CR date and administration of the first postremission course, and a median of 5 weeks (range, 4-8 weeks) between subsequent courses. The interval between courses has not increased as therapy progresses. Reductions from the planned dose of 9 mg/m^2 have been carried out in 5 patients because of infection (3 patients), a lower extremity thrombus (1 patient), and infusion-related complications (1 patient). All 16 patients who entered CR remain alive in hematologic CR, although the median follow-up in CR is only 5 months (up to 14 months).

Of the 16 patients, 14 have become PCR-negative, including 6 who became negative after induction, and 2, 4, and 2 who became negative after 1, 2, and 3 post-CR courses, respectively. Given these data, there may be no need to give 8 post-CR courses of mylotarg. The 2 patients who remain PCR-positive have been in CR only 1 to 2 months and have not yet had follow-up PCRs. Of the 11 patients tested at time of CR, 6 were PCR-negative (5/10; 95% CI, 19%-82% among patients not given idarubicin) (Table 2). At 1 to 4 months from CR all 12 patients tested to date were PCR-negative (10/10; 95% CI, 69%-100% considering only patients not given idarubicin during induction). Of the 7 patients who had subsequent PCR testing, 5 were PCR-negative, with the most recent tests performed 5, 11, 12, 12, and 13 months, respectively, from CR date. In 2 patients, positive PCRs were detected 5 months from CR date but were likely falsely positive (Table 2). Thus the rates of PCR negativity are as follows: at 1 to 4 months, 12/12; at 5

Table 2. PCR data

Patient	Idarubicin during induction	PML-RARα isoform	PCR at CR*	Follow-up PCRs*
1	No	Long	Positive	Negative at 3, 7, 11, and 13 months† (after 3, 6, 8, and 8 post-CR courses)
2	No	Long	Negative	Negative at 3, 6, 9, and 12 months† (after 2, 5, 8, and 8 post-CR courses)
3	No	Short	Positive	Negative at 2, 4, 7, 10, and 12 months† (after 2, 4, 6, 8, and 8 post-CR courses)
6	No	Short	Not done	Negative at 2 and 4 months† (after 1 and 3 post-CR courses)
7	No	Long	Positive	Negative at 4 months† (after 3 post-CR courses)
8	Yes	Short	Negative	Negative at 2 months, positive at 5 months, negative at 9 and 11 months†,‡ (after 2, 4, 8, and 8 post-CR courses)
9	No	Long	Negative	Negative at 3, positive at 5 months, negative at 8 months†,§ (after 2, 4, and 6 post-CR courses)
10	No	Short	Not done	Negative at 2, 4, and 6 months† (after 2, 4, and 6 post-CR courses)
11	Yes	Variable	Not done	Negative at 1 month† (after 1 post-CR course)
13	No	Short	Inadequate	Negative at 2 and 5 months† (after 2 post-CR courses)
14	No	Unknown‖	Negative	Negative at 2 and 4 months† (after 2 and 4 post-CR courses)
15	No	Long	Not done	Negative at 2 months† (after 2 post-CR courses)

*At 10^{-4}; in addition patients 16 and 18 were negative at complete remission (CR) and patients 17 and 19 were positive; none of these patients received idarubicin and none have yet had follow-up polymerase chain reaction (PCR) tests.

†From CR date.

‡PCR showed the long isoform although at presentation only the short form was detected, suggesting that 5-month result was a false positive; the PCRs at 9 and 11 months were negative, adding credence to this suggestion.

§PCR showed the short isoform although at presentation only the long form was detected, suggesting that 5-month result was a false positive; the PCR at 8 months was negative, supporting this suggestion.

‖But t(15;17) present at diagnosis.

to 8 months, 7/7; and at 9 to 12 months, 4/4. Corresponding rates in patients given only ATRA and mylotarg during induction are 10/10, 6/6, and 3/3. Thus, no patients have yet received idarubicin in CR. Assuming a true 21% rate of PCR negativity with single-agent ATRA ("monotherapy") at 1 to 4 months as reported by Jurcic et al,[1] the probability of our data if mylotarg did not add to the effectiveness of ATRA is $(.21)^{10} = 0.0000002$. Assuming even a true 50% rate of PCR negativity, the probabilities of our data are 0.001, 0.016, and 0.125 at 1 to 4, 5 to 8, and 9 to 12 months, respectively. Thus we believe that our data reflect the addition of mylotarg to ATRA. While the above analysis cannot substitute for a control population given ATRA monotherapy and followed with our assay, such a population would be difficult to obtain given that Chinese data suggested a median CR duration of only 5 months in patients given ATRA monotherapy,[6] which is identical to what would result in the unlikely event that each of our 14 patients given only mylotarg and ATRA were to relapse within the next month. Indeed, the rates of PCR negativity that we observed are similar to those reported with ATRA and idarubicin in GIMEMA and American trials,[7,8] recognizing that we had many fewer patients and that their prognoses were possibly different from patients in these other trials. A randomized trial might address the comparative benefits of ATRA and idarubicin or ATRA and mylotarg in untreated patients at relatively high risk of relapse if given ATRA and idarubicin.[3]

Acknowledgment

The authors thank Angela Culler for her expert secretarial assistance.

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