Leukemia Long-Term Survival: Collaborative Task Force Review and Analysis

Supplement to ***Cancer***

Long-Term Follow-Up of Three Randomized Trials Comparing Idarubicin and Daunorubicin as Induction Therapies for Patients with Untreated Acute Myeloid Leukemia

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BACKGROUND. Most clinical trials for acute leukemia have reported results after 2–3 years of follow-up. Comparisons between the original data and longer-term follow-up data may be of interest, particularly with regard to promising new therapies.

METHODS. In 1996, survival data were updated from three prospective, randomized comparisons of idarubicin and daunorubicin that began in 1984 and 1985. These were trials of the Memorial Sloan-Kettering Cancer Center (MSKCC), the U.S. Multicenter Study Group, and the Southeastern Cancer Study Group (SEG). The original results of these trials were reported in 1991 and 1992.

RESULTS. The original results of the SEG trial demonstrated no significant difference between idarubicin and daunorubicin. The updated survival analysis showed similar results. The MSKCC trial revealed a significant advantage of idarubicin compared with daunorubicin in both the original and the updated analyses. The U.S. Multicenter trial found a significant difference favoring idarubicin in the original analysis, but the difference was not significant in the updated analysis.

CONCLUSIONS. It is essential that the median length of follow-up be clearly stated in any clinical trial. When the results obtained with a particularly promising new drug or procedure are presented early in the course of study (within 1–2 years), the investigators should strongly consider a repeat evaluation after an additional 3–5 years of follow-up. ***Cancer*** **1997;80:2181–5.** © *1997 American Cancer Society.*

KEYWORDS: acute myeloid leukemia, daunorubicin, idarubicin.

Because the median survival of patients treated for acute leukemia with chemotherapy has generally been in the range of 12–18 months, most clinical trials have reported results after 2–3 years of follow-up. In general, this time period allows for evaluation that is sufficient to enable the clinician to decide whether a significant advance in treatment has been made. Occasionally, a clinical trial does not report the length of follow-up; in such a case, it is mandatory that the survival curves show the actual data points so that the reader can determine where in the course of follow-up the majority of patients are.

Idarubicin (IDR), an anthracycline similar in structure to daunorubicin (DNR) but lacking a methoxy group at position 4 of the chromophore ring, first entered clinical leukemia trials in 1982. This particular compound was of interest because of the pharmacologic properties of its active metabolite idarubicin-ol[1] and the activity against

TABLE 1
U.S. Randomized Trials: Idarubicin vs. Daunorubicin

Trial	IDR dose (mg/m^2)	DNR dose (mg/m^2)	Ara-C dose (mg/m^2)	Patient age (yrs)	Patients with prior MDS	Consolidation	Maintenance
U.S. Multicenter	13 × 3	45 × 3	100 × 7	>18	Yes	Yes: ×2	No
SEG	12 × 3	45 × 3	100 × 7	>18	Yes	Yes: ×3	Yes: 4 courses[a]
MSKCC	12 × 3	50 × 3	200 × 7	18–60	No	Yes: ×2	Minimal

IDR: idarubicin; DNR: daunorubicin; ara-C: cytosine arabinoside; MDS: myelodysplastic syndrome; SEG: Southeastern Cancer Study Group; MSKCC: Memorial-Sloan Kettering Cancer Center.
[a] Withdrawn after 47 patients.

TABLE 2
Idarubicin/Ara-C vs. Daunorubicin/Ara-C Remission Incidence in Three Trials

	MSKCC			U.S. Multicenter			SEG		
	IDR	DNR	*P* value	IDR	DNR	*P* value	IDR	DNR	*P* value
Patients entered (n)	60	60		97	111		105	113	
Complete remission									
(n)	48	35	0.005	68	65	0.08	75	65	0.032
(%)	80%	58%		70%	59%		71%	58%	

Ara-C: cytosine arabinoside; MSKCC: Memorial Sloan-Kettering Cancer Center; SEG: Southeastern Cancer Study Group; IDR: idarubicin; DNR: daunorubicin.

multidrug-resistant leukemia cells demonstrated by both the parent compound and idarubicin-ol.[2,3] When IDR was used as a single agent, response rates of 18–38% were noted in heavily pretreated patients.[4–6] Beginning in 1984 and 1985, three U.S. study groups (the Memorial Sloan-Kettering Cancer Center [MSKCC], the U.S. Multicenter Study Group, and the Southeastern Cancer Study Group [SEG]) began to compare this drug with standard therapy in the treatment of patients with newly diagnosed acute myeloid leukemia (AML). Results were published separately by all three groups between 1991 and 1992.[7–9] To determine whether long-term follow-up altered the original results, all three trials were updated as of October 1996. These updated data are the basis of this report.

MATERIALS AND METHODS

Study Designs

Eligibility criteria differed somewhat among the three trials. For example, the MSKCC trial excluded patients who were older than 60 years or had prior myelodysplastic syndrome, whereas the U.S. Multicenter and SEG trials did not. In addition, doses of IDR and cytosine arabinoside (ara-C) varied slightly among the three centers. The differences among the protocols are shown in Table 1.

Survival Analysis

Survival data on the patients enrolled in protocols at MSKCC or at centers participating in the U.S. Multicenter and SEG trials were updated as of October 1996. The 10 patients who were entered in the original MSKCC trial but considered inevaluable were included in this analysis (5 in each treatment arm). Kaplan–Meier curves were then generated based on the updated data and were compared for statistical significance by the log rank test.

RESULTS

Between 1984 and 1989, a total of 574 adult patients with newly diagnosed AML were randomized to receive either IDR or DNR in combination with ara-C as induction chemotherapy. The incidence of remission for all evaluable patients in the three trials is shown in Table 2. The *P* values shown are from the original publications.[7–9] In the MSKCC and SEG trials, a significant difference in remission incidence was noted, with more patients randomized to the IDR/ara-C arm achieving complete remission. In the U.S. Multicenter trial, no significant difference was noted between the 2 arms; however, when analyzed by age, significantly more patients younger than 50 years who were randomized to the IDR/ara-C arm achieved complete remission.[8] Finally, in each of the three trials, significantly more patients randomized to the DNR/ara-C arm demonstrated primary refractory disease compared with patients randomized to the IDR/ara-C arm.[2]

Figures 1, 2, and 3 show both the original and the

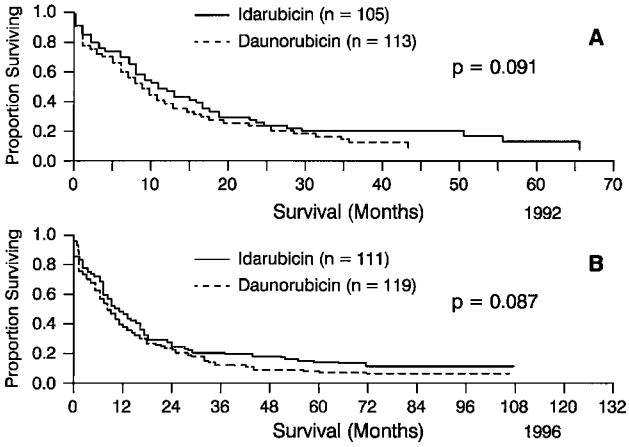

FIGURE 1. (A) The original survival curve published by Vogler et al.[9] in 1992 (representing evaluable patients) is shown. (B) The same data updated as of 1996 (representing all patients) is shown. The original curve is reprinted with the authors' permission and with the permission of the publisher, W. B. Saunders Company.

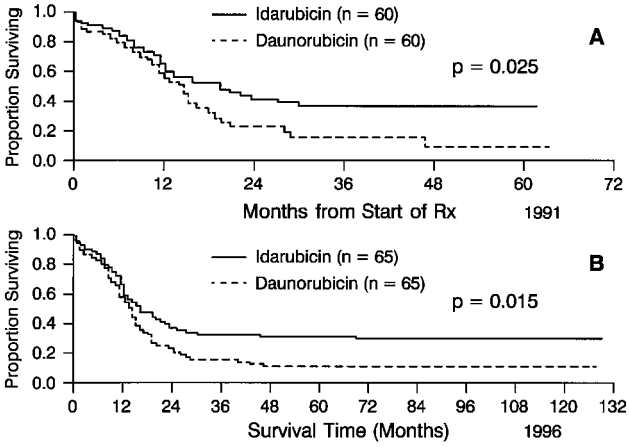

FIGURE 2. (A) The original survival curve published by Berman et al.[7] in 1991 (representing evaluable patients) is shown. (B) The same data updated as of 1996 (representing all patients) is shown. The original curve is reprinted with the permission of the publisher, W. B. Saunders Company.

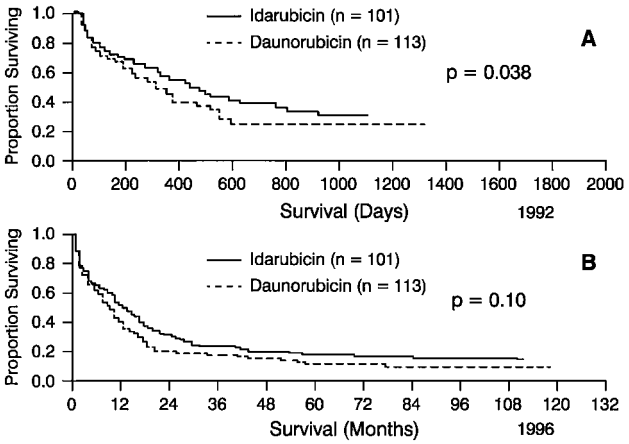

FIGURE 3. (A) The original survival curve published by Wiernik et al.[8] in 1992 (representing all patients) is shown. (B) The same data updated as of 1996 (representing all patients) is shown. The original curve is reprinted with the authors' permission and with the permission of the publisher, W. B. Saunders Company.

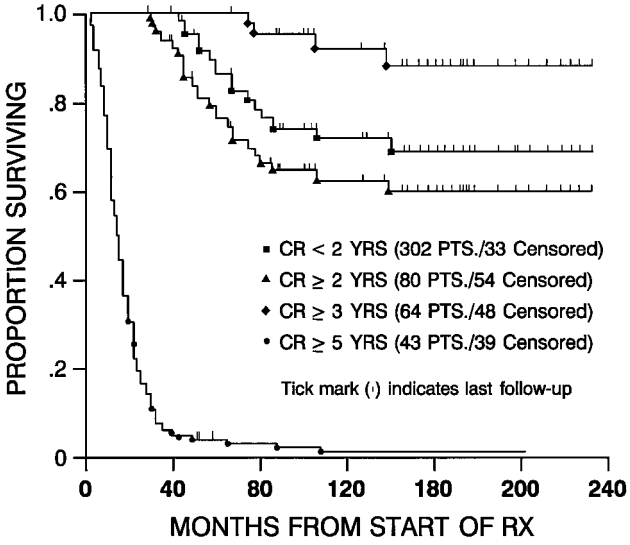

FIGURE 4. Long-term survival after 5 years of follow-up is shown for patients with previously untreated acute myelogenous leukemia treated at Memorial Sloan-Kettering Cancer Center on various protocols. Patients continued to relapse up to 10 years, although the rate of relapse was very low. CR: complete remission. From: Clarkson et al.[10] Reprinted by permission of the authors and the publisher, Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

updated survival curves for each of the three trials. In the originally published SEG trial (Fig. 1A), the difference between the two arms was not significant (P = 0.091). The updated data show similar results (P = 0.087; Fig. 1B). When originally published, the MSKCC trial showed a significant difference (P = 0.025; Fig. 2A). The updated data continue to show a significant difference in survival, favoring the IDR/ara-C arm (P = 0.015; Fig. 2B). However, in the U.S. Multicenter trial, the updated data differ from the original data. The original curves showed a significant difference in favor of the IDR arm (P = 0.038; Fig. 3A), whereas the updated data now show a P value of 0.10 (Fig. 3B).

The updated survival results of all three studies include all patients, whereas the originally published survival results were presented only for evaluable patients in the SEG and MSKCC trials. The updated survival results for evaluable patients in the SEG trial are similar (P = 0.14, data not shown) to the results shown

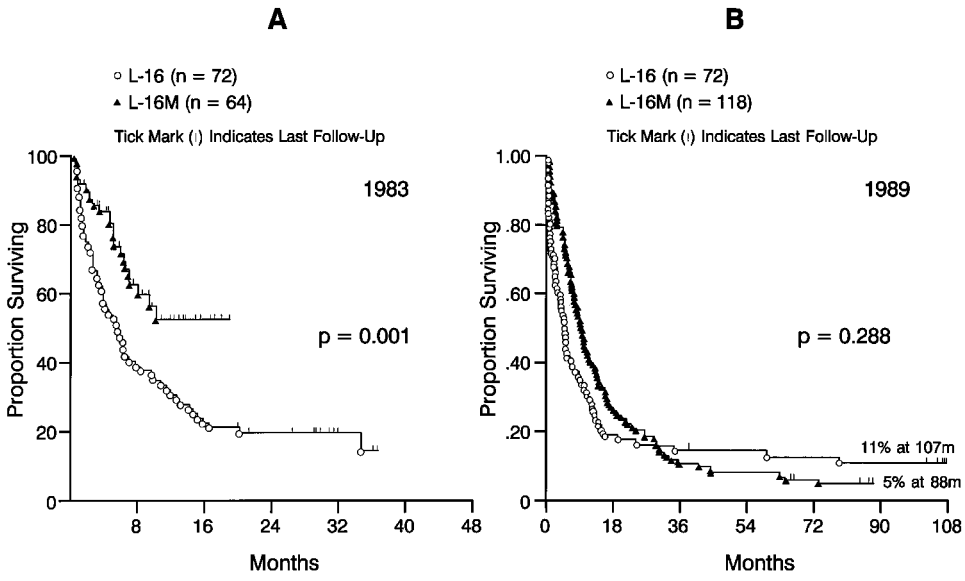

FIGURE 5. (A) An early analysis of two MSKCC protocols for patients with previously untreated acute myelogenous leukemia (protocols L-16 and L-16M) is shown. (B) The same data, analyzed 5 years later, is shown. From: Clarkson et al.[10] Reprinted by permission of the authors and the publisher, Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

in Figure 1B. Updated survival results of evaluable patients in the MSKCC trial are quite similar ($P = 0.14$, data not shown) to the curves shown in Figure 2B.

In the originally published survival analysis for the U.S. Multicenter trial, patients were censored after a bone marrow transplant. An updated survival analysis that also censored these patients yielded results ($P = 0.11$, data not shown) that are similar to the uncensored analysis shown in Figure 3B.

DISCUSSION

Most clinical studies in acute leukemia have reported results after a median of 2–3 years of follow-up, although it is not unusual to present data after only 1 year of patient accrual. However, because patients continue to relapse even after 5 years, it is important to update survival data periodically. Clarkson et al.[10] have provided 20-year follow-up data on more than 480 patients with this disease who were followed at the MSKCC. As shown in Figure 4, patients have continued to relapse 6–10 years after completing treatment, although the frequency of this occurrence is very low.

With such periodic reevaluation, we found, on one occasion, a marked difference in survival after a longer follow-up period than initially published.[10] In 1981, we began a randomized trial, the L-16 protocol, comparing amsacrine, ara-C, and 6-thioguanine (6-TG) with DNR, ara-C, and 6-TG in the treatment of adult patients with previously untreated AML. Because of unexpected toxicity, the doses of amsacrine, DNR, and ara-C were modified in the subsequent protocol, L-16M. An early comparison between the two protocols, performed in 1983, showed what appeared to be a highly significant difference in survival (Fig. 5A). However, when the two trials were again compared 5 years later in 1989, the survival curves were superimposable (Fig. 5B).

The current study updated three trials that compared two induction regimens for the treatment of adult AML. Two of the studies (MSKCC and SEG) showed very similar outcomes 4–5 years after original publication (Figs. 1 and 2). Follow-up of the U.S. Multicenter trial originally showed improved survival with IDR versus DNR ($P = 0.038$); however, the updated curves now show no statistically significant difference between the two agents ($P = 0.10$; Fig. 3). Based on these findings, two general recommendations can be made. First, it is essential that the median length of follow-up be clearly stated in any clinical study. Second, when results obtained with a particularly promising drug or procedure are presented early in the course of study (i.e., within 1–2 years), the authors should seriously consider a repeat evaluation after an additional 3–5 years of follow-up.

For the particular question posed by the introduction of IDR into the treatment regimen for AML, accumulated data from all series published to date and analyzed in an overview presented in a preliminary form by Wheatley et al.[11] suggest that survival is improved compared with survival achieved by standard therapy with DNR or other anthracyclines. Our long-term follow-up of three trials suggests a similar trend, although only one trial (the MSKCC trial) maintains statistical significance.

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