Long Term Follow-Up of Patients with Acute Myelogenous Leukemia Who Received the Daunorubicin, Vincristine, and Cytosine Arabinoside Regimen

Yves Beguin, M.D., Ph.D.
Brieuc Sautois, M.D.
Patricia Forget, M.D.
Jean Bury, M.D.
Georges Fillet, M.D., Ph.D.

Department of Medicine, Division of Hematology, University of Liège, Liège, Belgium.

Yves Beguin is a Senior Research Associate of the National Fund for Scientific Research (FNRS), Belgium. Brieuc Sautois is supported by a Télévie Research Fellowship from the FNRS.

Address for reprints: Yves Beguin, M.D., Ph.D., Department of Hematology, University of Liège, CHU Sart-Tilman, 4000 Liège, Belgium.

Received August 12, 1996; revision received November 26, 1996; accepted November 26, 1996.

BACKGROUND. In 1985, the authors published a study of acute myelogenous leukemia (AML) patients treated with a chemotherapeutic regimen that was then considered intensive. Ten years later, the authors reanalyzed the same cohort to determine whether the very promising actuarial results observed at 5 years held after longer follow-up.

METHODS. Between 1977 and 1982, 61 patients with AML were treated with a protocol consisting of daunorubicin, vincristine, and cytosine arabinoside induction followed by consolidation and maintenance for a total of 2 years. The complete remission (CR) rate was 66%, 84% in males versus 47% in females ($P < 0.005$). At the time of the first analysis in 1984, the overall survival (OS) was 17%, the projected 5-year continuous CR rate (CCR) 32%, and the disease free survival (DFS) rate 29%, with the best results observed for males and for patients ages 40–60 years ($P < 0.05$).

RESULTS. When the data were reanalyzed 11 years later in 1995, the results were 14% OS, 23% CCR, and 16% DFS at 5 years. However, these figures dropped to 8%, 18%, and 11% at 10 years and to 8%, 12%, and 7% at 15 years, respectively. Among the 40 CR patients, 31 relapsed (up to 13 years after CR), and all died within 1.6 years after relapse. Nine patients were in CCR: 4 died of unrelated causes (suicide, alcoholic cirrhosis, acute peritonitis, or bladder carcinoma), 1 was lost to follow-up after 11 years, 2 were alive and well at 17 years at last follow-up, and 2 were transplanted in first CR and were doing well at 13 and 14 years at last follow-up. The survival advantage for males over females persisted ($P = 0.0197$), but the advantage for patients age 40–60 years did not hold.

CONCLUSIONS. These long term data indicate that actuarial analysis at 5 years may overestimate the cure rate of AML patients because a number of late relapses do occur. However, the picture is blurred by the incidence of death not related to leukemia or its treatment; and when these patients were censored at the time of death, 17% of CR patients were still projected to be alive and free of leukemia after 17 years. ***Cancer*** **1997;79:1351–4.** © *1997 American Cancer Society.*

KEYWORDS: acute myelogenous leukemia, chemotherapy, clinical trial, long term follow-up.

In 1985, the results that we obtained with the daunorubicin, vincristine, and cytosine arabinoside (DOA) regimen in the treatment of patients with acute myelogenous leukemia (AML) were published in Cancer.[1] The complete remission (CR) rate was 66 %, median survival was 21 months, and median remission duration was 13 months with a projected CR rate of 30 % at 5 years. These results were considered

very encouraging at that time. In the current study, we reanalyzed the same cohort of patients after more than 11 years of additional follow-up to examine whether the promising results observed at 6.5 years of follow-up would hold after a much longer period of observation.

PATIENTS AND METHODS

As previously published,[1] 61 patients (30 females and 31 males) were treated with the DOA protocol between 1977 and 1982. Age ranged from 12 to 76 years (median, 51 years), with only one patient over 70. Induction therapy consisted of daunorubicin (DNR) 60 mg/m^2 given intravenously (i.v.) on Days 1, 2 and 6; vincristine (VCR) 1 mg/m^2 i.v. on Day 2; and cytosine arabinoside (Ara-C) 3 $\times$ 80 mg/m^2 i.v. on Days 3–7. After 2 consolidation courses, patients underwent monthly maintenance and intensification courses for up to 2 years after diagnosis, as described previously.[1] Informed consent was obtained from the patients or their guardians. Data as of August 1, 1995, was analyzed and compared with the analysis performed previously on data obtained as of January 1, 1984. Actuarial remission and survival analyses were performed using the Kaplan-Meier product limit method. Comparison between survival curves were made using the log rank test. All survival analyses were carried out with Graphpad Prism software (Graphpad Software, San Diego, CA). Two patients undergoing bone marrow transplantation (BMT) while in their first complete remission (CR) were censored for CR duration and survival at the time of transplantation.

RESULTS

Complete Remission

The results of induction therapy were published previously.[1] Briefly, among 61 patients, 40 (66%) achieved CR after 1 (n = 30) or 2 (n = 10) courses of induction, whereas 9 (15%) died during aplasia and 12 (20%) experienced induction failure. CR was achieved among 84% of males versus 47% of females ($P < 0.005$) and among 82% of patients younger than 40 years versus 59% of older patients (not significant). No other prognostic factors were identified for response.

Relapses

Among the 40 CR patients, 31 (78%) relapsed. Seven (18%) relapsed within 6 months of CR, 11 (28%) between 6 months and 1 year, 9 (23%) between 1 and 2 years, and 4 (10%) at 2.5, 3, 6, and 13 years, respectively. Of the 31 relapses, 25 were reinduced and 13 (52%) achieved a second CR. Two of them underwent allogeneic BMT while in second relapse, and one of them underwent allogeneic BMT while in second CR.

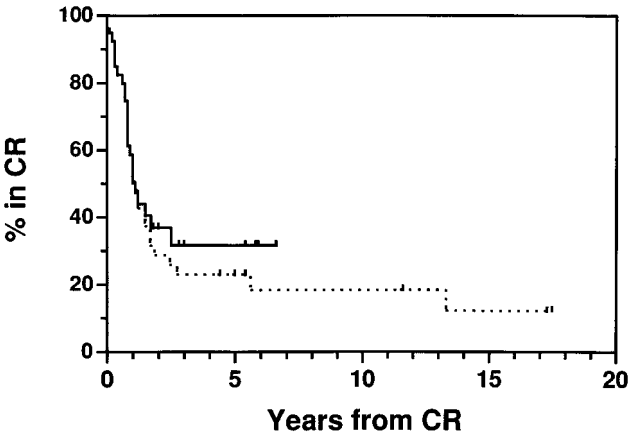

FIGURE 1. Duration of complete remission (CR) is shown. The analysis of the 1984 data (continuous line) is compared with the analysis of the 1995 data (broken line) for the same cohort of 40 CR patients (differences not significant).

All relapsed patients died within 1.6 years at a median of 0.4 years: 6 were not reinduced, 8 died during reinduction, 4 died of resistant disease, 4 died of complications while in second CR, 6 died while in second relapse, and 3 died after BMT.

Continuous Complete Remission

At last follow-up, nine patients (23 %) had been in continuous CR: 2 were alive and well more than 17 years after CR, 1 was lost to follow-up after more than 11 years, and the 2 patients who underwent BMT while in first CR were well 13 and 14 years later. However, four patients died while in CR of unrelated causes, i.e., suicide, alcoholic cirrhosis, postoperative peritonitis, and bladder carcinoma.

Duration of Response

Data analyzed as of January 1, 1984, gave a median CR duration of 1.1 years, with 32% of patients projected to be still in CR at 5 years. When the data as of August 1, 1995, were analyzed, the median CR duration did not change, but the CR rate dropped to 23% at 5 years, 18% at 10 years, and 12% at 15 years (Fig. 1). Although the 1984 analysis identified age 40–60 years as a favorable prognostic factor for CR duration (52% at 5 years vs. 10% for younger or older patients, $P = 0.0335$), the difference disappeared completely in the 1995 analysis. However, the significant advantage of male gender (median CR duration, 1.7 vs. 1.0 years, and CR rate at 5 years, 35% vs. 0%, $P = 0.0197$) confirmed previous findings. No other prognostic factor was identified. Although a plateau of continuous remission was apparent in the 1984 analysis, the occurrence of late relapses sent the curve several steps downward.

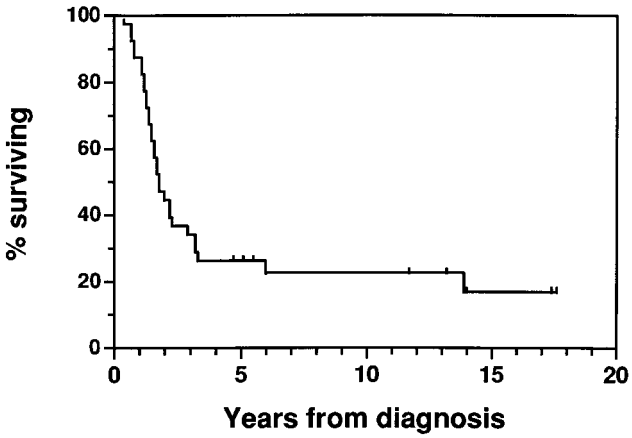

FIGURE 2. Overall survival of patients in complete remission is shown. Patients who died of causes unrelated to leukemia or its treatment were censored at the time of death.

Survival

Overall survival among the 61 patients was 59% at 1 year, 30% at 2 years, 15% at 5 years, 10% at 10 years, and 7% at 15 years, with a median of 1.3 years. Survival of CR patients was better, with 88 %, 43%, 23%, 15% and 11% survival at 1, 2, 5, 10, and 15 years, respectively, and a median of 1.7 years. Censoring for BMT in first CR further decreased survival of CR patients to 19% at 5 years, 11% at 10 years, and 7% at 15 years. This produced disease free survival rates of 16%, 11%, and 7% at 5, 10, and 15 years, respectively, with a median of 1.1 years. When patients dead from unrelated causes were censored at the time of death, overall survival of CR patients increased to 26% at 5 years, 23% at 10 years, and 17% at 15 years (Fig. 2). However, censoring for BMT in first CR made these values drop by 5%. Male gender bore a favorable prognosis as compared with female gender for survival of all patients ($P = 0.0005$), disease free survival ($P = 0.0239$) and overall survival of CR patients ($P = 0.0287$). Other factors, including age, did not show prognostic significance for survival.

DISCUSSION

In the current study, we updated results initially published in 1985,[1] with only 1 patient lost to follow-up after 11 years. Follow-up ranged from 11 to 17 years, the longest published for any AML trial (a few other studies have had follow-up extending to a maximum of 12.5 years). The CR rate of 18% at 10 years and the overall survival of 10% at 10 years are quite similar to long term results from large multicenter studies performed during the same period.[2,3] The range of 8–15% overall survival at 7–10 years in these studies is the same as the one reported for studies performed earlier[4] and later.[5–7] Only one other recent study, in which high dose Ara-C was used for consolidation, reported a better outcome of about 25% survival at 10 years, but only patients younger than 50 years with de novo AML were selected.[8]

In our study, 18% of CR patients relapsed within 6 months, 28% between 6 months and 1 year, 23% between 1 and 2 years, and 10% after 2 years. The relapse rate was still 40% among patients who did not undergo BMT and were still in CR after 2 years, and 29% among those still in CR at 5 years. Because of relapses occurring up to 13 years after CR, the CR rate dropped from 32% at 5 years in the 1984 analysis to 23% at 5 years and only 12% at 15 years in the current analysis. As discussed by Preisler et al,[9] early relapses may represent the regrowth of leukemic cells present at diagnosis and late relapses caused by the overgrowth of rare drug-resistant or quiescent cells. The current study indicates that because relapses indeed occur very late, a true plateau may never exist in acute nonlymphocytic leukemia (ANLL). As the existence of a plateau is often used as an indication of cure, this observation may give the depressing message that cure may not be certain even after very long follow-up. More specific treatment, i.e., with monoclonal antibodies or differentiating agents, may thus be needed in addition to chemotherapy.

Another factor contributing to poor survival is death from causes thought to be unrelated to leukemia or its treatment, i.e., postoperative peritonitis, bladder carcinoma, alcoholic cirrhosis, and suicide, all occurring within 6 years of CR. However, these deaths may not be totally unrelated to leukemia, as prolonged relative immunosuppression may cause a higher susceptibility to infections, chemotherapy may induce secondary cancers, and the strenuous experience of leukemia and its treatment may produce or aggravate behavioral or psychologic disorders. Nonetheless, the rate of death from unrelated causes may have been particularly high in our study and has not been reproduced in larger trials.

Another effect of longer follow-up on the results is the disappearance of any advantage for patients age 40–60 years as compared with younger or older patients. On the other hand, contrary to most other studies, female gender remained a significant adverse prognostic factor for CR rate and duration. This was not explained by the association of female gender with other classical adverse prognostic factors. We must acknowledge that this particular finding is probably due to small numbers. However, we cannot rule out the possibility that female gender truly is an adverse prognostic factor when patients are treated with the

DOA regimen but is no longer an adverse factor when patients receive more effective induction and consolidation therapy, as in our more recent trials (data not shown).

The overall survival rate of 7% at 15 years obtained in this study, which was initiated in the late 1970s and early 1980s, of course does not take into account significant advances in the treatment of ANLL that have occurred since that time.[10] The application of idarubicin for induction[11] and the use of intermediate/high dose cytosine arabinoside for induction,[12] consolidation,[13] or both[14] are very encouraging but await confirmation after longer follow-up. The increasing use of autologous or allogeneic BMT will certainly have a profound effect on the outcome of ANLL patients.[15] However, our study indicates that the final impact of newer approaches in the treatment of ANLL must always be evaluated after very long periods of observation.

REFERENCES

1. Beguin Y, Bury J, Fillet G, Lennes G. Treatment of acute nonlymphocytic leukemia in young and elderly patients. *Cancer* 1985;56:2587–92.
2. Morrison FS, Kopecky KJ, Head DR, Athens JW, Balcerzak SP, Gumbart C, et al. Late intensification with POMP chemotherapy prolongs survival in acute myelogenous leukemia: results of a Southwest Oncology Group study of rubidazone versus adriamycin for remission induction, prophylactic intrathecal therapy, late intensification, and levamisole maintenance. *Leukemia* 1992;6:708–14.
3. Bennett JM, Andersen JW, Cassileth PA. Long term survival in acute myeloid leukemia: the Eastern Cooperative Oncology Group (ECOG) experience. *Leuk Res* 1991;15:223-7.
4. Keating MJ, McCredie KB, Bodey GP, Smith TL, Gehan E, Freireich EJ. Improved prospects for long-term survival in adults with acute myelogenous leukemia. *JAMA* 1982; 248:2481–6.
5. Bandini G, Zuffa E, Rosti G, Battista R, D'Emilio E, Leoni F, et al. Long-term outcome of adults with acute myelogenous leukaemia: results of a prospective, randomized study of chemotherapy with a minimal follow-up of 7 years. *Br J Haematol* 1991;77:486–90.
6. Ghaddar HM, Plunkett W, Kantarjian HM, Pierce S, Freireich EJ, Keating MJ, et al. Long-term results following treatment of newly-diagnosed acute myelogenous leukemia with continuous-infusion high-dose cytosine arabinoside. *Leukemia* 1994;8:1269–74.
7. Volger WR, Weiner RS, Moore JO, Omura GA, Bartolucci AA, Stagg M. Long-term follow-up of a randomized postinduction therapy trial in acute myelogenous leukemia: a Southeastern Cancer Study Group trial. *Leukemia* 1995; 9:1456–60.
8. Heil G, Mitrou PS, Hoelzer D, Freund M, Link H, Ehninger G, et al. High-dose cytosine arabinoside and daunorubicin postremission therapy in adults with de novo acute myeloid leukemia: long-term follow-up of a prospective multicenter trial. *Ann Hematol* 1995;71:219–25.
9. Preisler HD, Anderson K, Rai K, Cuttner J, Yates J, Du Pre E, et al. The frequency of long-term remission in patients with acute myelogenous leukaemia treated with conventional maintenance chemotherapy: a study of 760 patients with a minimal follow-up time of 6 years. *Br J Haematol* 1989;71:189–94.
10. Rowe JM, Liesveld JL. Treatment and prognostic factors in acute myeloid leukemia. *Clin Haematol* 1996;9:87–105.
11. Wiernik PH, Banks PL, Case DC Jr., Arlin ZA, Periman PO, Todd MB, et al. Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. *Blood* 1992;79:313–9.
12. Bishop JF, Matthews JP, Young GA, Szer J, Gillett A, Joshua D, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. *Blood* 1996;87:1710–7.
13. Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med* 1994;331:896–903.
14. Phillips GL, Reece DE, Shepherd JD, Barnett MJ, Brown RA, Frei-Lahr DA, et al. High-dose cytarabine and daunorubicin induction and postremission chemotherapy for the treatment of acute myelogenous leukemia in adults. *Blood* 1991;77:1429–35.
15. Zittoun RA, Mandelli F, Willemze R, De Witte T, Labar B, Resegotti L, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. *N Engl J Med* 1995;332:217–23.