Relapse and death during first remission in acute myeloid leukemia

Many papers have discussed the advisability of administering *intensive* chemotherapy to older patients with untreated acute myeloid leukemia (AML).[1-5] More specifically, several studies have attempted to identify patients at particularly high risk of induction death following such therapy.[6,7] However, the issue of chemotherapy-induced death once patients are in complete remission (CR) has received less attention. Unlike untreated patients, patients who have entered CR have already shown some evidence of sensitivity to chemotherapy. Clinicians may, therefore, be more reluctant to abandon chemotherapy in these patients than in untreated patients. Under the assumption that the decision to give such chemotherapy is conditioned by the risk of relapse versus the risk of death in CR we compare these two risks in patients at relatively high risk of death in CR.

Besides its clinical relevance, the topic of *death in CR* is also of analytic a interest. Therefore, many analyses of outcome in CR emphasize *relapse-free survival (RFS)*, in which both relapse and death in CR are considered events, rather than *remission duration*, in which patients who die in CR are considered *censored*. This practice follows from the principle, fundamental to Kaplan-Meier analysis, that censoring should only be carried out if the covariates associated with the outcome of interest (e.g. remission duration) and with the censoring event (e.g. death in CR) are mutually independent. While it could be presumed that the covariates associated with relapse and with death in CR would differ, there is little evidence in literature to confirm this. Therefore, we also examined whether patients who die in CR are more similar to patients who relapse or to patients who remain alive in CR. If the former is the case, empirical support would be provided for using RFS as an endpoint rather than remission duration.

Adults diagnosed with AML (≥20% blasts, acute promyelocytic leukemia excepted) at the M. D. Anderson Cancer Center (MDA) from 1991 to 2003 were included if their initial treatment contained cytarabine and if such treatment produced CR defined by standard criteria.[8] The 3% of patients who received allogeneic hematopoietic stem cell transplantation during first CR were excluded, because *decision to transplant* and relapse are not independent of each other. A total of 935 patients were eligible for analysis. Although dose reductions of post-remission therapy were made according to toxicity during the previous courses, therapy did not depend on risk of relapse. This study was approved by the MDA Institutional Review Board (IRB), and patients were treated in accordance with the Declaration of Helsinki. Waivers of informed consent and authorization were granted by the IRB. Cytogenetics were considered best [inv(16)/t(16;16) or t(8;21) with or without other abnormalities], worst (abnormalities of chromosomes 5 and/or 7 or complex karyotype defined as ≥3 aberrations) or intermediate (others). Antecedent hematologic disorder (AHD) was defined as documented abnormality in blood count for more than one month before MDA presentation. Groups were compared using the Fisher's exact test for categorical variables, and the Wilcoxon rank-sum test for numerical variables. To calculate the rates of relapse and death in CR, we divided the number of each event by the total observation time (patient-years) from CR to the first occurrence of relapse, death in CR or last contact.[9] Of the 935 patients, 637 relapsed at a median of 8.0 months from CR date, 108 died in first CR, and 190 remain alive in first CR with a median follow-up of 5.1 years (range, 0-14.3 years). Fifty-percent of the 108 patients died in the first three months from CR date, and we considered their deaths related to chemotherapy. The characteristics of these patients and those who died in CR later were essentially identical, leading us to combine the 2 groups. It is of particular interest that patients who died in CR were much more similar to patients who relapsed than to patients who remain alive in CR (Table 1). For example, the oldest

Table 1. Patients' characteristics.

	Continuous CR N=190	*p value**	*Death in CR N=108*	*p value***	*Relapse N=637*
Age Median (range)	49 (16-82)	<0.001	66 (26-86)	<0.001	57 (16-82)
Sex Male/Female	98/92 (52%/48%)	0.183	65/43 (60%/40%)	0.529	359/278 (56%/44%)
PS at CR achievement 0-1/2-4	151/25 (86%/14%)	<0.001	63/34 (65%/35%)	0.001	476/115 (81%/19%)
Cytogenetic risk Best/Intermediate/Worst	55/112/15 (30%/62%/8%)	<0.001	11/66/26 (11%/64%/25%)	0.751	54/375/169 (9%/63%/28%)
AHD Present/absent	41/149 (22%/78%)	0.003	41/67 (38%/62%)	0.746	230/407 (36%/64%)
Prior chemo/radiotherapy Present/absent	13/177 (7%/93%)	<0.001	24/84 (22%/78%)	0.006	76/561 (12%/88%)
Year 1991-1997/1998-2003	81/109 (43%/57%)	0.040	60/48 (56%/44%)	0.467	328/309 (51%/49%)

*CR: complete remission; PS: performance status; AHD: antecedent hematologic disorder. *Comparison between patients with continuous CR1 and patients with death in CR1. **Comparison between patients with death in CR1 and patients with relapse.*

Table 2. Outcome of patients at various risk of death in complete remission.

Age	PS at CR achievement*	N. of patients/ relapse/death in CR	Rate of relapse**	Rate of death in CR**	Relapse/ death in CR ratio
≥60	2-4	120/81/27	51.7	17.2	3.0
≥60	0-1	262/188/44	46.0	10.8	4.3
<60	2-4	54/34/7	22.3	4.6	4.8
<60	0-1	428/288/19	25.9	1.7	15.2
≥70	2-4	71/52/17	67.3	22.0	3.1
≥70	0-1	102/70/23	41.5	13.6	3.1
<70	2-4	103/63/17	27.2	7.3	3.7
<70	0-1	588/406/40	30.0	3.0	10.0

*PS: performance status; CR: complete remission. *Information was available in 864 patients. **N. of events per 100 patient-year follow-up.*

patients were those who died in CR and the next oldest were those who relapsed, and this same order applied to performance status at the time of CR. Twenty-eight percent of patients who relapsed and 25% of those who died in CR, but only 8% of those alive in CR, had worst cytogenetics. Similar trends were observed when only patients aged 60 or older were considered. Given these findings it seems inadvisable to perform analyses of remission duration in which patients who die in CR are censored.

A further aim was to identify patients at high risk of death in CR and compare their risk of death in CR and their risk of relapse. A problem with performing the usual multivariate analysis was how to consider patients who relapsed. Certainly it would not be logical to censor them given their resemblance to patients who die in CR. Ignoring them is also problematic since it ignores large amounts of data. We therefore simply chose to consider age and performance status at CR as principal predictors of relapse. Table 2 examines the rates of relapse and death in CR per 100 patient-year follow-up in each of several groups defined by age and performance status. Even in patients aged 70 and above, with Zubrod performance 2-4, there were three times as many relapses as deaths in CR. This finding emphasizes that the major threat to a patient who has just entered CR is relapse not death in CR. While the value of post-remission therapy in older patients has been questioned,[10-12] our findings suggest that a decision to discontinue chemotherapy once a patient is in CR is not advisable unless there is evidence that chemotherapy will not prevent relapse. This view could also guide other clinical decisions, e.g. how much dose reduction should occur and how long a course of chemotherapy should be delayed. Certainly, there is no proof that dose reduction or a delay in starting a post-remission course will make relapse more likely. But it could be presumed that, given the greater risk of relapse than of death in CR, the decision to reduce or delay such treatment could be questioned should relapse occur.

Masamitsu Yanada, Guillermo Garcia-Manero, Gautam Borthakur, Farhad Ravandi, Hagop Kantarjian, Elihu Estey

Department of Leukemia, University of Texas M. D. Anderson Cancer Center, Houston, USA

Key words: acute myeloid leukemia, complete remission, relapse, death in remission.

Correspondence: Masamitsu Yanada, Department of Leukemia, University of Texas M. D. Anderson Cancer Center, Unit 428, 1515 Holcombe Blvd, Houston, TX, 77030 USA. Phone: international +713.5631276. Fax: international +713.5637746. E-mail: myanada@mdanderson.org

References

1. Lowenberg B, Zittoun R, Kerkhofs H, Jehn U, Abels J, Debusscher L, et al. On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group. J Clin Oncol 1989;7:1268-74.
2. Tilly H, Castaigne S, Bordessoule D, Casassus P, Le Prise PY, Tertian G, et al. Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly. J Clin Oncol 1990;8:272-9.
3. Stone RM. The difficult problem of acute myeloid leukemia in the older adult. CA Cancer J Clin 2002;52:363-71.
4. Estey E. Acute myeloid leukemia and myelodysplastic syndromes in older patients. J Clin Oncol 2007;25:1908-15.
5. Baz R, Rodriguez C, Fu AZ, Jawde RA, Kalaycio M, Advani A, et al. Impact of remission induction chemotherapy on survival in older adults with acute myeloid leukemia. Cancer 2007;110:1752-9.
6. Kantarjian H, O'Brien S, Cortes J, Giles F, Faderl S, Jabbour E, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer 2006;106:1090-8.
7. Etienne A, Esterni B, Charbonnier A, Mozziconacci MJ, Arnoulet C, Coso D, et al. Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. Cancer 2007;109:1376-83.
8. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21:4642-9.
9. Kahl C, Storer BE, Sandmaier BM, Mielcarek M, Maris MB, Blume KG, et al. Relapse risk in patients with malignant diseases given allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. Blood 2007;110:2744-8.
10. Lowenberg B, Suciu S, Archimbaud E, Haak H, Stryckmans P, de Cataldo R, et al. Mitoxantrone versus daunorubicin in induction-consolidation chemotherapy--the value of low-dose cytarabine for maintenance of remission, and an assessment of prognostic factors in acute myeloid leukemia in the elderly: final report. European Organization for the Research and Treatment of Cancer and the Dutch-Belgian Hemato-Oncology Cooperative Hovon Group. J Clin Oncol 1998; 16: 872-81.
11. Stone RM, Berg DT, George SL, Dodge RK, Paciucci PA, Schulman PP, et al. Postremission therapy in older patients with de novo acute myeloid leukemia: a randomized trial comparing mitoxantrone and intermediate-dose cytarabine with standard-dose cytarabine. Blood 2001;98:548-53.
12. Gardin C, Turlure P, Fagot T, Thomas X, Terre C, Contentin N, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. Blood 2007;109:5129-35.

Citation: Yanada M, Garcia-Manero G, Borthakur G, Ravandi F, Kantarjian H, Estey E. Relapse and death during first remission in acute myeloid leukemia. Haematologica 2008 Apr; 93(4):633-634. doi: 10.3324/haematol.12366