Establishment of baseline toxicity expectations with standard frontline chemotherapy in acute myelogenous leukemia

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The rates of expected serious adverse events in patients with acute leukemia on chemotherapy far exceed those in patients with solid tumors. Regulatory authorities require similar reporting criteria, which overburden the investigators and infrastructure with unnecessary documentation. To establish a baseline for expected toxicities before and during leukemia therapy, we reviewed 1534 adults with acute myeloid leukemia (AML; excluding acute promyelocytic leukemia) from 1990 to 2006 who received frontline intensive chemotherapy; 723 (47%) were 60 years or older. Prior to therapy, grade 3/4 cytopenias were observed in 86% of patients. All patients developed one or more grade 3/4 cytopenias during therapy, and more than 90% had a febrile episode. Admission to the intensive care unit, mechanical ventilation, and dialysis were required in 28%, 16%, and 7%, respectively. Mortality during induction, 2-week mortality, and 6-week mortality were 20%, 5%, and 16%, respectively. Grade 3/4 renal or hepatic toxicities were observed in 3% and 22% of patients, respectively. Other grade 3 or 4 toxicities were also common before treatment and during therapy. This paper establishes a baseline toxicity rate for patients with AML during induction therapy, and this could be used as a control group for future reference. Guidelines for reporting adverse events in leukemia studies should be revisited. (Blood. 2007;110:3547-3551)

Introduction

In evaluating the toxicities of new agents or regimens, the regulatory agencies often consider similar sets of criteria for solid tumors and leukemias. Patients with acute leukemia invariably present with a compromised bone marrow status, severe myelosuppression, and cytopenias; receive intensive chemotherapy; and frequently have infections requiring hospitalizations and affecting organ functions (particularly pulmonary, hepatic, and renal). These preexisting or expected complications are often required to be submitted as adverse or serious adverse events. This requirement results in several problems: (1) overburdening the investigators and regulatory agencies with unnecessary documentation, thus taxing the physical and economic infrastructures; (2) diverting time and attention from potentially important drug- or treatment-associated significant issues; and (3) attributing toxicities to a drug or treatment when that toxicity is not treatment related.

To establish baseline expectations of toxicities before and during therapy in acute leukemia, we reviewed our experience in newly diagnosed patients with acute myelogenous leukemia (AML) receiving induction therapy. Since older patients are expected to have perhaps worse baseline organ functions and to tolerate intensive chemotherapy less well (therefore to have more frequent organ complications), we analyzed the data also in the younger versus the older patient subgroups.

Patients and methods

Adults with a diagnosis of AML or high-risk myelodysplastic syndrome (MDS) referred to the Leukemia Department at M. D. Anderson Cancer Center from 1990 to 2006, and who received frontline intensive chemotherapy on current protocols, were reviewed.[1-5] Patients with acute promyelocytic leukemia were excluded. Informed consent was obtained according to institutional guidelines and in accordance with the Declaration of Helsinki, and Institutional Review Board approval was granted by the University of Texas M. D. Anderson Cancer Center (MDACC).

We analyzed the incidence of grade 3 or 4 toxicities both at baseline and during induction therapy within each age group and regimen.

For the purpose of the study, 3 end points for mortality were considered: (1) 6-week mortality, defined as any death occurring in the first 6 weeks regardless of disease status or cause of death; (2) early mortality, defined as death in 14 or fewer days; and (3) total induction death, defined as death occurring without a documented complete remission at any time during induction. The latter is more subjective than the other 2 definitions, since the decision and timing of a second induction course are variable. Variables were compared by the chi-square test.

Results

Patient characteristics and baseline grade 3 or 4 toxicities

The patient characteristics are shown in Table 1; 1543 patients were identified; their median age was 60 years (range, 16 to 87 years); 644 (42%) were females. The treatment programs were summarized in previous reports.[1-5] The numbers of patients on each treatment are summarized in Table 2. We then analyzed the incidence of baseline events considered to be grade 3 or 4 by the National Cancer Institute, Cancer Therapy Evaluation Program (NCI-CTEP) criteria version 3.0. Grade 3 or 4 anemia was noted in

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Table 1. Presenting adverse features of the study group with age younger than 60 years (n = 811) versus age 60 years or older (n = 723)

	Percentage			
Parameter/category	**All**	**Age, younger than 60 y**	**Age, 60 y or older**	***P***
Percent of total [n]	100 [1534]	53 [811]	47 [723]	
Sex, female	42	48	34	<.001
Diagnosis				
AML	88	90	85	
MDS	12	10	15	.008
Hemoglobin level, g/L, lower than 80	50	51	50	NS
Granulocyte count, × 10^9/L				
0.5 to less than 1.0	14	14	14	NS
Less than 0.5	34	33	34	NS
Platelet count, × 10^9/L				
50 to 99	28	28	27	NS
20 to 49	36	39	33	.01
Less than 20	16	14	19	.01
Karyotype				
t(8;21), inversion 16	9	14	3	<.001
Normal	36	33	40	.01
5 or 7 abnormalities	25	23	27	NS
Other abnormalities	26	25	26	NS
IM/not done	5	5	5	NS
Fever				
FUO	16	18	13	.007
Pneumonia	12	12	12	NS
Other infections	8	9	8	NS
Creatinine, mg %				
Over 2	3	2	5	.001
1.3 to 2	15	9	21	<.001
Bilirubin, mg %				
Over 2	3	3	3	NS
1.3 to 2	7	7	7	NS
Fatal bleeding, yes (n)	<1(10)	<1 (4)	<1 (6)	NS
Admission to ICU, yes	9	9	10	NS

AML indicates acute myeloid leukemia, MDS, myelodysplastic syndrome; FUO, fever of unknown origin; IM, insufficient metaphases; and NS, not statistically significant, $P > .05$.

50%; neutropenia, in 48%; and thrombocytopenia, in 52%. Febrile episodes with or without a documented infection were noted in 36%. Baseline elevations of creatinine (> 176.8 μM [2 mg/dL]) and bilirubin (> 34.2 μM [2 mg/dL]) were observed in 3% and 3%, respectively. Admission to the intensive care unit was needed in 9%. Those baseline incidences tended to be higher in older patients (Table 1). The distribution of patients in different treatment groups based on age and karyotype was different due to the study inclusion criteria. The more standard idarubicin and cytarabine studies involved mostly better prognosis patients (younger; diploid karyotype) over the temporal course of our research programs. The more investigational studies were designed mostly for worse prognosis patients (older; unfavorable karyotype). This is demonstrated in Table 3. These differences could explain the differences in complete remission (CR) rates and survival, as previously reported.[4,5]

Table 2. Treatment regimens

Regimen	**No. (%)**
Idarubicin + cytarabine (IA)	438 (29)
Daunorubicin + cytarabine (DA)	149 (10)
Fludarabine + cytarabine (FA)	278 (18)
Fludarabine + cytarabine + idarubicin (FAI)	279 (18)
Topotecan + cytarabine (TA)	330 (21)
Clofarabine + cytarabine (CA)	60 (4)

Early, 6-week, and induction mortality

It is often difficult to distinguish mortality during induction by whether it is (1) treatment or drug related, (2) related to the

Table 3. Characteristics of the study group by therapy (percentage)

	Regimen						
	IA	**DA**	**FA**	**FAI**	**TA**	**CA**	***P***
Overall number	438	149	278	279	330	60	
Age, 60 y or older (%)	36	44	44	61	52	58	<.001
Karyotype (%)							
Favorable	8	5	22	1	6	0	<.001
Diploid	43	26	25	26	49	50	<.001
5 or 7 abnormalities	17	33	26	35	22	25	<.001
Others	27	30	22	32	20	23	.008
Insufficient metaphases	5	6	5	6	2	2	.2

Table 4. Mortality by regimen

Regimen	No. treated	Percentage mortality					
		Early mortality	*P*	Total induction mortality	*P*	6-wk mortality	*P*
IA	438	3	—	15	—	12	—
DA	149	6	NS	28	.001	23	.001
FA	278	9	.001	21	.03	18	.03
FAI	279	6	.054	33	<.001	23	.001
TA	330	5	NS	15	NS	13	NS
CA	60	0	NS	13	NS	8	NS
Total	1534	5	—	20	—	16	—

See Table 2 for abbreviations. *P* values compared with IA.
NS indicates not statistically significant, $P > .05$; —, not applicable.

baseline patient condition, or (3) related to ineffective therapy and poor leukemia control. Realistically, it is a combination of the 3 factors and should be evaluated as such. To establish the expected baseline mortality (for comparison with future investigational trials), we analyzed early (2-week), 6-week, and induction mortality by treatment regimen and within age groups. Table 4 shows the 3 mortality end point rates overall and by regimen. The overall induction mortality rate was 20%, and ranged from 13% to 33% by regimen. This range was mostly age dependent. Table 5 shows the mortality rates in younger versus older patients within each regimen. As expected, mortality rates were significantly higher in older patients. Survival also differed among the various regimens compared with the more standard idarubicin and cytarabine (IA) regimen. In previously published studies, using multivariate analyses, the CR and survival rates were similar with different regimens.[4,5]

Grade 3 or 4 toxicities during induction therapy

As expected, all patients developed one form or another of grade 3 or 4 myelosuppression (Table 6). Febrile episodes occurred in 94%, documented infections occurred in 64%, and admission to the intensive care unit was required in 28%. Other extramedullary toxicities included renal dysfunction in 3% and liver dysfunction in 22%. Respiratory support and dialysis were required in 16% and 7%, respectively. Of interest is the higher rate of dialysis than grade 3 or 4 renal toxicities. This is due to the definition of grade 3 toxicity that requires a creatinine level 3 to 6 times or more of the upper limit of normal (ULN). The ULN in our institution is 132.6 μM (1.5 mg/dL); a grade 3 toxicity is defined as a creatinine value higher than 397.8 μM (4.5 mg/dL), a level before which dialysis may have already been initiated. The rate of grade 2 renal toxicity varies from 12% to 20% according to regimen. The rates of

Table 5. Percentage mortality by regimen and within age groups

No. in regimen (<60 y/≥ 60 y)	2 wk		6 wk		Induction	
	Age, younger than 60 y	Age, 60 y or older	Age, younger than 60 y	Age, 60 y or older	Age, younger than 60 y	Age, 60 y or older
IA (281/157)	2	4	8*	18*	10*	23*
DA (84/65)	4	9	11*	40*†	19*	38*†
FA (155/123)	5*	15*†	8*	29*†	10*	35*†
FAI (108/171)	5	7	16*†	27*	28†	36†
TA (158/172)	5	5	10	16	11	18
CA (25/35)	0	0	0	14	8	17
Total (811/723)	4*	7*	10*	24*	10*	21*

See Table 2 for abbreviations.
*Statistically significant differences ($P \leq .05$) between younger than 60 years and 60 years or older age groups in a particular regimen.
†Statistically significant differences ($P \leq .05$) in a particular age group compared with IA.

Table 6. Percentage grade 3 or 4 toxicities during induction therapy

Grade 3 or 4 toxicity	Total	IA	DA	FA	FAI	TA	CA	*P*
Anemia	65	67	79	65	53	63	90	<.001
Thrombocytopenia	72	70	83	78	64	65	98	<.001
Neutropenia	91	94	91	93	91	82	98	<.001
Fever unknown origin	30	31	24	33	22	34	38	.006
Documented infection	64	61	72	55	77	60	55	<.001
Hospitalization	93	92	72	88	99	60	55	<.001
Renal	3	2	4	4	3	3	3	.7
Hepatic	22	22	27	22	24	18	18	.2
Cardiac	2	4	2	<1	<1	<1	3	.001
Dialysis	7	6	13	9	9	5	7	.22
Intensive care unit	28	27	44	37	41	24	12	<.001
Mechanical ventilation	16	14	27	27	22	12	7	.002
Hyponatremia	16	14	21	17	16	17	10	.2
Hypokalemia	33	38	36	23	36	32	30	.001

See Table 2 for abbreviations.

Table 7. Grade 3 or 4 toxicities during induction therapy by age group

Grade 3 or 4 toxicity	Percentage grade 3 or 4 toxicity by age, y		
	Age, younger than 60	Age, 60 y or older	*P*
Anemia	62	69	.007
Thrombocytopenia	70	74	.08
Neutropenia	90	91	NS
Fever of unknown origin	33	27	.008
Documented infection	58	70	<.001
Hospitalization	91	96	<.001
Renal	2	4	.03
Hepatic	20	24	.04
Cardiac	1	3	.04
Dialysis	4	9	.002
Admission to intensive care unit	22	34	<.001
Mechanical ventilation	11	20	<.001
Hyponatremia	14	19	.007
Hypokalemia	32	34	NS
Nausea and vomiting	3	2	NS
Diarrhea	9	4	<.001
Mucositis	4	4	NS

NS indicates not statistically significant, $P > .05$.

nonhematologic grade 3 or 4 toxicities were significantly higher, as expected, in older patients (Table 7). This was particularly relevant for organ dysfunctions such as pulmonary, hepatic, cardiac, and renal failure. This is likely due to the worse baseline organ dysfunction in older patients and/or their worse tolerance of chemotherapy.

Discussion

Reporting grade 3 or 4 toxicities on investigational regimens, which are not treatment related and not higher than baseline expectations, burdens heavily the infrastructures of regulatory organizations (Food and Drug Administration [FDA], NCI-CTEP) and investigators (who need to report within 24 hours or 7 days).[6,7] Such toxicities can still be reported and analyzed in the periodic (6-month or annual) reports and in the final study analysis/publication. Based on our experience, reporting a serious adverse event takes on average 1 to 3 hours of a research nurse/researcher at the site of investigation, as well as significant time and effort at the site of the regulatory organization. Others have reported a mean of 35 minutes and up to 6 hours for clinical trial documentation including serious adverse event reporting.[8]

This issue is of significance for tumors in which there is a baseline compromise of organs such as the bone marrow, and primarily concern 2 disciplines: leukemias (and perhaps some lymphomas with marrow involvement) and stem cell transplantation. Following the current FDA/NCI-CTEP guidelines, "serious adverse events" would have to be reported *before* starting any therapy in more than 50% of patients, and on therapy in more than 90% of patients. Reporting such serious adverse events may at times vary depending on the interpretations of the guidelines published by the FDA.[9]

In this study, the first of its kind, we aimed to establish baseline expectations for these serious adverse events in patients with AML, before therapy as well as during induction therapy. Although we analyzed this in a large cohort of patients (1534 patients), we recommend using the anthracycline-cytarabine regimens as the baseline comparator for future reference. We also realize that the incidence of some toxicities (eg, dialysis, ICU admission, or respiratory support) may differ from one institution to the other depending on the institutions' guidelines. However, we hope that this study would initiate a fruitful dialogue between leukemia researchers, regulatory bodies, and pharmaceutical companies interested in developing drugs in leukemia, as to what should really be reported. Based on our analysis, it appears that many of the grade 3 or 4 toxicities that some pharmaceutical companies insist on reporting to the FDA as serious adverse events are not truly so. Consequently, reporting them as serious adverse events overburdens the infrastructure of the investigators' institutional (Office of Protocol Research, Institutional Review Board [IRB]) and the government regulatory bodies. While the ratio of true to overall reported serious adverse events is unknown, we estimate, based on our reporting experience that of approximately 10 "serious adverse events" reported to the FDA in leukemia studies, perhaps only 1 is a true serious adverse event (ie, related to the drug or treatment). In another study, 31% of reported grade 3 to 5 toxicities were unrelated or unlikely to be related to the drug.[6]

Table 8. Adverse event (AE) reporting policy for leukemia phase 2 studies

(1) All deaths with possible, probable, or definite attribution to the study drug must have a written report submitted to the Institutional Review Board (IRB) via office of protocol research (OPR) within 24 hours (next working day) of knowledge of the event. All deaths not related to the study drug must have a written report submitted to the IRB within 5 working days.

(2) Unexpected life-threatening events will be reported to IRB within 5 working days of notification regardless of attribution to study drug. These events may include opportunistic infections, eg, CMV, pneumocystis, tuberculosis, or other unusual organisms or their presentations. Other unexpected life-threatening events, specifically events prompting initiation of life support and organ failure known not to be due to leukemia, will be reported.

Examples:

(a) Simple febrile neutropenia with hospitalization is not an expedited reportable event to the IRB but will be included in the annual report to the IRB, whereas febrile neutropenia complicated by Gram-negative bacteremia with shock or its complications is to be reported within 5 working days of notification.

(b) Thrombocytopenic epistaxis or bleeding from mucosal surfaces easily managed with platelet support is not an expedited reportable event to the IRB but will be included in the annual report to the IRB, whereas bleeding not controlled with platelet support within 48 hours of onset of the bleed, or resulting in significant clinical conditions (eg, CNS or pulmonary hemorrhage), will be reported within 5 working days of notification.

(3a) Prolonged myelosuppression following induction therapy defined as marrow cellularity 5% without evidence of leukemia 42 or more days from start of therapy and not due to use of additional antileukemia agents before day 42 will be reported within 30 days of notification.

(3b) Myelosuppression following postremission therapy will be reported if at 42 days after treatment marrow has not recovered to platelets $>20\,000\times10^9$/L or granulocytes $> 500\times10^9$/L. Myelosuppression and associated complications are expected events during leukemia therapy. Myelosuppression and associated simple complications such as fever, infections, bleeding, and related hospitalizations will, except as noted above, not be reported as individual AEs, but will be summarized in annual report to the IRB. Extramedullary toxicities (eg, renal, pulmonary, hepatic) will be reported according to the standard MDACC adverse event reporting policy

Because of these important concerns in centers where leukemia research is prominent, several senior faculty representing the leukemia research department met with colleagues who were members of the M. D. Anderson Institutional Review Board to develop formal guidelines for reporting adverse events on leukemia clinical studies. These are outlined in Table 8. These are the events that require individual case report forms and reporting within 24 hours or 7 days. All other grade 3 or 4 toxicities will also be reported in the periodic summaries as well as in the final analyses/reports. These proposals should be considered as a work-in-progress, and perhaps as a starting point for initiating discussions that will hopefully be beneficial to all parties involved including investigators, regulatory organizations, and pharmaceutical companies.

Authorship

Contribution: E.A. wrote the paper and analyzed the data; J.C. and S.O. reviewed the paper and made corrections; S.P. and M.B.R. collected and analyzed the data; E.E., M.M., M.K., and E.J.F. reviewed the paper and made corrections; and H.K. wrote the paper and analyzed the data.

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