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Maintenance therapy with decitabine in younger adults with acute myeloid leukemia in first remission: a phase 2 Cancer and Leukemia Group B study (CALGB 10503)

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CONFLICT OF INTEREST

The authors declare no conflicts of interests.

AUTHORSHIP CONTRIBUTIONS

WB was the Study Chair of the clinical trial. RAL was the Chair of the Leukemia group for the Alliance (formerly CALGB). GM also assisted in the design of the study. WB, RK, DJD, GU, BLP, WS, MRB, JEK, ESW, GM, RMS, and RAL enrolled patients, provided clinical management, and facilitated the conduct of the study. SG, BLS, and JK provided statistical support. EH and BLS managed the database. WB and RK audited the data case report forms. CDB provided support and oversight for molecular studies. KM assisted with data acquisition and interpretation, manuscript writing, and formatting. All authors reviewed the results and approved manuscript submission.

Abstract

In this prospective phase 2 clinical trial conducted by Cancer and Leukemia Group B (CALGB, now the Alliance), we studied decitabine as maintenance therapy for younger adults with acute myeloid leukemia (AML) who remained in first complete remission (CR1) following intensive induction and consolidation. Given that decitabine is clinically active in AML and with hypomethylating activity distinct from cytotoxic chemotherapy, we hypothesized that one year of maintenance therapy would improve disease-free survival (DFS) for AML patients <60 years who did not receive allogeneic stem cell transplantation (alloHCT) in CR1. After blood count recovery from final consolidation, patients received decitabine at 20mg/m^2 IV daily for 4–5 days, every 6 weeks for 8 cycles. One-hundred-thirty-four patients received decitabine, 85 (63%) had favorable risk AML. The median number of cycles received was 7 (range, 1–8), and the primary reason for discontinuation was relapse. DFS at 1-year and 3-years was 79% and 54%, respectively. These results are similar to the outcomes in the historical control comprised of similar patients treated on recent CALGB trials. Thus, maintenance with decitabine provided no benefit overall. Standard use of decitabine maintenance in younger AML patients in CR1 is not warranted. This trial was registered at www.clinicaltrials.gov as NCT00416598.

INTRODUCTION

Although most patients with acute myeloid leukemia (AML) achieve remission with initial therapy, especially those aged <60 years, the majority ultimately relapse and die of disease. Post-remission therapies such as transplantation or clinical trials with novel agents remain ongoing research priorities. The most effective post-remission therapy, allogeneic hematopoietic cell transplantation (alloHCT), provides a potentially lifelong graft-versus-leukemia effect for select patients. However, the toxicities may outweigh the benefits for patients in first remission who have intermediate or favorable risk disease. In contrast to transplantation, “maintenance therapy” has been traditionally defined as prolonged but relatively low toxicity treatment. Long-term maintenance therapy with conventional cytotoxic drugs improves survival in acute lymphoblastic leukemia. However, with the notable exception of arsenic trioxide and retinoic acid in acute promyelocytic leukemia, no maintenance therapy has proven effective in AML.[1–5] Given lack of benefit observed when conventional cytotoxic drugs have been used as maintenance in AML, agents with alternative mechanisms of action are appealing for investigation in this area.

Decitabine and azacitidine have epigenetic activities distinct from conventional chemotherapies.[6] Although the relationship between drug-induced DNA demethylation and clinical response to these agents remains incompletely understood, both can induce and maintain clinical responses in myelodysplastic syndromes (MDS) and in AML.[7–15] Both are now approved in the United States for treatment of patients with MDS, and they are frequently used as single agents for older AML patients even outside of clinical trials. Critical to successful therapy with these azanucleosides is the administration of repetitive cycles of treatment at regular intervals (e.g., 4–6 weeks), allowing efficient incorporation of drug into the newly synthesized nucleotides of myeloid blasts undergoing mitosis during each exposure. Such therapy is well tolerated.

Given these findings, we hypothesized that hypomethylating agents would be ideal candidates to test as maintenance therapy in AML. Indeed, preliminary data with decitabine maintenance have provided promising, albeit inconclusive, evidence of benefit.[15] Azacitidine or decitabine maintenance is now under study in several clinical trials (including after alloHCT). Furthermore, based on very limited published data, post-remission therapy with a hypomethylating agent is commonly utilized in clinical practice. To determine whether long-term maintenance with decitabine was feasible and beneficial for younger adults with AML in first remission, we conducted a phase 2 trial within the Cancer and Leukemia Group B (CALGB, now part of the Alliance for Clinical Trials in Oncology).

PATIENTS AND METHODS

Eligibility criteria and study design

Patients were enrolled on CALGB study 10503 at the initial diagnosis of AML and received uniform induction and risk-adapted consolidation therapies. Eligible patients were adults age ≥5 and <60 years, with an unequivocal histologic diagnosis of non-M3 AML. Patients with myelodysplastic features were eligible only if there was no evidence of MDS >3 months prior to enrollment. Patients with therapy-related AML (t-AML) were eligible if free of their primary disease with no chemotherapy for at least 2 years. No prior azacitidine or decitabine therapy was permitted. With the exception of including t-AML patients in the current effort, these inclusion criteria were the same as in recent studies (with alternative investigational maintenance or observation) within CALGB for the same population. Patients registered to maintenance on those studies served as the historical reference group for the current, non-randomized study of decitabine maintenance. Written informed consent and approval by institutional review boards were required at each participating institution.

Treatment: induction and consolidation

Induction and risk-adapted consolidation therapies were identical to the standard treatment arms of the historical reference CALGB studies in this patient population. Induction used daunorubicin 90mg/m^2/day IV on days 1–3, etoposide 100mg/m^2/day IV on days 1–3, and cytarabine 100mg/m^2/day continuous IV on days 1–7 (“3+3+7”). If necessary, a second induction course was given on a 2+2+5 schedule for those with persistent disease on day 14 (>5% blasts and at least 20% cellular marrow). Post-remission consolidation chemotherapy was assigned depending on molecular and/or cytogenetic risk. Patients requiring alloHCT were removed from study prior to receiving consolidation or maintenance, as feasible. Patients with core-binding factor (CBF) AML, that is patients with either t(8;21)(q22;q22)/*RUNX1-RUNX1T1* or inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB-MYH11* detected by cytogenetic and/or molecular methods,[17] received 3 cycles of high-dose cytarabine (HIDAC, 3 gm/m^2 over 3 hours, every 12 hours, on days 1, 3, and 5). All other patients underwent chemo-mobilization with HIDAC (2gm/m^2 every 12 hours for 8 doses) with etoposide (10 mg/kg/day IV continuous infusion days 1–4; total dose of 40 mg/kg) followed by filgrastim for collection of stem cells. These patients then received autologous hematopoietic stem cell transplantation (autoHCT) following high-dose busulfan and etoposide as previously described.[18,19] Patients ineligible for autoHCT received two

additional cycles of standard HIDAC consolidation following one cycle of HIDAC/etoposide.

Disease evaluation time points and follow-up during maintenance included bone marrow aspiration and biopsy every 3–4 months for 1 year after completion of consolidation therapy, then every 6 months for 2 years. These same time points were also used as previously done in the historical control which included patients who received investigational recombinant interleukin-2 (rIL-2) maintenance or observation during CR1 in prior CALGB trials.

Maintenance: treatment with decitabine

Patients remaining in complete remission (CR) after consolidation were scheduled to receive 8 cycles of decitabine IV over one hour at 20 mg/m^2/day for 5 days, every 6 weeks. To be eligible for maintenance, patients were required to have adequate recovery of neutrophils (>1x10^9/L) and platelets (>75x10^9/L) and be within 90 days of autoHCT or 60 days of last HIDAC, if no autoHCT. Patients were required to have blood count recovery (as noted above) prior to starting each subsequent cycle of decitabine as well. If necessary, a two week delay before the next cycle of decitabine was permitted to allow count recovery. For grade 4 neutropenia lasting more than two weeks or grade 4 thrombocytopenia lasting more than one week after decitabine therapy, one day of treatment was deleted from the subsequent cycle. However, a minimum of 3 days of decitabine per cycle was required in order to continue protocol therapy. The schedule of decitabine was shortened to 4 days for patients consolidated with autoHCT when pre-planned thresholds for prolonged neutropenia were exceeded after 20 patients were treated. Patients consolidated with only HIDAC chemotherapy (no auto-HSCT) continued on the original 5-day/cycle treatment schedule.

Criteria for response and toxicity

CR was defined as bone marrow biopsy ≥20% cellularity with <5% blasts at the time of hematologic recovery [neutrophils >1x10^9/L and platelets >100x10^9/L], following one or two cycles of induction. The NCI Common Toxicity Criteria (CTCAE 3.0) were used to grade adverse events.

Quality control, quality assurance and auditing

Patient registration, data collection, and all statistical analyses were carried out by the Alliance for Clinical Trials in Oncology Statistics and Data Center. The medical records of 91% of patients receiving decitabine maintenance were audited (additionally, 26% of all other patients enrolled on CALGB 10503 were audited); records from each participating institution were reviewed. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies.

Cytogenetic and molecular analyses

Pretreatment cytogenetic analyses were performed by the institutional cytogenetic laboratories and the results were confirmed by central karyotype review.[20] For the karyotype to be classified as normal, ≥20 metaphase cells from bone marrow specimens subjected to short-term culture must have been analyzed.[20] The presence or absence of *FLT3*-internal tandem duplication (*FLT3*-ITD),[21,22] and mutations in the *CEBPA*[23] and *NPM1*[24] genes

were evaluated centrally. The patients were categorized according to the European LeukemiaNet (ELN) classification.[25]

Statistical analysis

The primary endpoint of the study was 1 year disease-free survival (DFS) for non-CBF AML patients who registered for decitabine maintenance therapy. DFS was defined as the time from documented CR to time of relapse or death. Overall survival (OS) was calculated as the time from study entry (i.e., prior to induction treatment) to death from any cause. Event-free patients were censored at the time of their last follow-up. No interim analysis was planned. This study was designed with separate decision criteria for non-CBF AML patients and for CBF AML patients. Each of these subgroups was evaluated using phase 2 decision criteria that were calibrated to the historical reference group patients who were treated with the same induction and risk-adapted consolidation strategy as on prior CALGB trials for this patient population. The historical reference group was comprised of previous studies in this target population which included a maintenance component, namely rIL-2 or observation. Additional follow-up data for the reference group (specifically from CALGB 19808) became available during the course of the current trial, allowing further calibration of study results relative to the reference group including consideration of ELN-risk group assignment. For the non-CBF AML patients, the statistical design required 75 patients registered to receive decitabine maintenance to detect an increase of 0.15 in the true one-year DFS rate. Similarly, for the CBF AML patients, 32 patients were required to detect an increase of 0.20 in the one-year DFS rate relative to the reference cohort. Designs for each group provided at least 90% power and assumed a type I error constraint of 10%.

Patient characteristics were summarized using descriptive statistics. Comparisons of these characteristics between groups used either chi-square statistics for categorical variables or two-sample t-tests or one-way ANOVAs for continuous variables, or their nonparametric equivalents in the setting of non-normality and/or small subgroup numbers. DFS and OS were evaluated using the methods of Kaplan and Meier, and differences between groups were assessed using log rank statistics. DFS and OS rates and specific time points were based on estimates from the DFS and OS distribution through Kaplan-Meier analyses.

RESULTS

Patient characteristics

Five hundred forty-six newly diagnosed AML patients enrolled upfront on CALGB 10503 from January 23, 2007 thru July 30, 2010. The median age was 48 years (range, 17–60), and the median presenting white blood count (WBC) was 12.6 x 10^9/L (range, 0.3–380 x 10^9/L). Overall, 76% of patients achieved CR (414/546); 32% of the CR patients (134/414) subsequently received the investigational maintenance. Reasons for patients who achieved CR but did not ultimately receive the maintenance therapy included removal from study (especially for alloHCT), patient refusal, inadequate count recovery after consolidation, and early relapse, among others (Table 1).

Of the 134 patients who registered for maintenance, 46 (34%) had CBF AML of whom all had received consolidation with HIDAC. Among the remaining 88 patients, 74 had received consolidation with autoHCT, and 14 had received HIDAC-based consolidation. The median time from initial study registration to initiation of maintenance therapy was 6.3 months (range, 4.6–11.0). Patients receiving decitabine had a median age of 45 years (range, 18–60) and presenting WBC of 13.5 x 10^9/L (range, 0.4–221 x 10^9/L). Patients who received maintenance were in the following ELN genetic risk groups: favorable (63%), intermediate-I (10%), intermediate-II (12%), adverse (7%), and unknown (7%). This risk group breakdown is quite similar to that in the most contemporary part of the historical reference group for which molecular data was available (CALGB 19808, Table 2). Likewise, clinical characteristics were well matched (Supplemental Table 1) between the study group and 19808.

Feasibility

Treatment with decitabine was well tolerated and generally well accepted by patients and physicians. A total of 770 cycles of decitabine were given; the median number of cycles given per patient was 7 (range, 1–8). Forty-six percent of patients received all 8 planned cycles; relapse was the most common reason for treatment discontinuation. Seventy-five percent of patients received at least 4 cycles. Discontinuation due to patient refusal occurred in 13%. Grade 3 or higher adverse events are listed in Table 3 and are notable for the expected myelosuppression. Serious complications resulting from myelosuppression were rare. Considering the total of all cycles administered, 59% of cycles (456/770) resulted in grade 3 or higher neutropenia, but only 4% (28/770) had grade ≥3 infection.

Outcomes

For the patients who received post-remission maintenance with decitabine, 1-year and 3-year DFS were 79% (95% CI, 71–85%) and 54% (45–62%), and 1-year and 3-year OS were 96% (90–98%) and 68% (59–75%), respectively (see Figure 1). The median follow up for the study group with 95% confidence interval (CI) was 56.7 months (18.5-NE). For CBF AML patients, 1-year DFS was 80% (66–89%); for non-CBF AML patients, 1-year DFS was 78% (68–86%). The use of decitabine maintenance did not provide any apparent benefit for DFS or OS relative to the historical reference group, as a whole or within the CBF AML or non-CBF AML subsets, respectively. Likewise, the results with respect to DFS and OS from this study were virtually identical to those seen with comparable patients treated on the immediately preceding trial in this population CALGB 19808 (the only study in the historical control with adequate molecular characterization of *FLT3, NPM1,* and *CEBPA*; Supplemental Figure 1).

DISCUSSION

For AML patients in remission after intensive therapy, there are currently no compelling data to justify standard use of any long-term maintenance therapy. At least for conventional cytotoxic drugs, previous trials proved that prolonged low-dose maintenance is not better than intensive therapy,[26] yielding, at best, a modest improvement in DFS but not in OS.[27] The likelihood of achieving a second remission is reduced when relapses occur while

patients are receiving conventional maintenance therapy, suggesting the emergence of drug resistance. Thus, conventional maintenance therapy in AML has been largely abandoned due to lack of efficacy. Investigational use of drugs with alternative mechanisms of action remains of interest, but results have been disappointing with agents such as gemtuzumab ozogamicin[28,29] or, more recently, rIL-2 with or without histamine dihydrochloride.[16,30–36] One study with rIL-2/histamine dihydrochloride showed a statistically significant DFS benefit but no benefit for OS;[35] however, a recent meta-analysis, plus a subsequent report of a randomized trial from the Alliance, further dampen enthusiasm for use of rIL-2 in remission maintenance in AML.[16,36]

Hypomethylating agents, namely decitabine and azacitidine, may be useful to maintain or deepen AML/MDS responses. In a randomized phase III study for higher risk MDS, prolonged therapy with single-agent, low-dose azacitidine significantly improved OS compared with conventional care regimens, despite a low overall CR rate.[9] Notably, a subset of patients with low blast count AML (20–30% blasts) had a survival benefit with prolonged azacitidine treatment (median survival, 24.5 *v* 16.0 months for conventional care regimens).[10] Several schedules of prolonged therapy with low-dose decitabine have also shown promise for AML.[11–15] A low incidence of treatment related toxicity for these agents, beyond myelotoxicity, supported their development into trials of frontline therapy for “unfit” older AML patients and into maintenance therapy for a range of patients and disease states. Accordingly, the federal website *clinicaltrials.gov* currently lists nearly 20 active clinical trials that employ some form of investigational maintenance therapy with a hypomethylating agent.

Despite promise seen with decitabine maintenance in a small randomized study,[15] our trial found no benefit to 1 year of maintenance therapy in younger patients with AML in first CR compared with a well-matched and uniformly treated historical control. A number of factors could have contributed to this negative result. It is possible that the efficacy of the drug was diminished by a suboptimal schedule or dose, but this study included post-autoHCT patients who likely would not have tolerated a more intensive dose or more frequent schedule of decitabine maintenance therapy, at least in the early months following recovery from the transplant. It is possible, albeit unlikely, that an alternative dose, route, or schedule of decitabine, or with different intensive induction or post-remission strategies before maintenance, would yield different results.

There was a higher proportion of CBF AML patients who registered for maintenance therapy with decitabine than that in the previous rIL-2 maintenance trials conducted in the Alliance. Whether this difference in CBF AML patients was due to greater familiarity with and acceptance of decitabine (rather than rhIL-2) as maintenance for AML, or due to improved protocol compliance in successive investigational maintenance studies within the Group is unknown. Preliminary laboratory data showing a potential role for aberrant DNA methyltransferase activity in CBF AML,[37] and clinical cases of CBF AML that had achieved CR following treatment with single agent decitabine[12] bolstered our hypothesis that this subset would benefit from decitabine and may have also contributed to more robust recruitment of CBF AML patients. Though the study was not powered to detect small

differences in survival for CBF AML patients, there did not appear to be clinical benefit in this subset of patients from decitabine maintenance.

These results do not extinguish hope that maintenance therapy with a hypomethylating agent might prove useful in selected patient populations. Included among these areas of ongoing research interest are patients who are older, post-alloHCT for high-risk AML, or perhaps, with unique molecular features. Several ongoing studies should help to address these questions. Most notably among these, Eastern Cooperative Oncology Group (ECOG) is evaluating decitabine maintenance in older AML patients after either clofarabine or daunorubicin-based induction (NCT01041703), the Bone Marrow Transplant Clinical Trials Network recently completed accrual for azacitidine maintenance after alloHCT for AML in first CR (NCT01168219), and another trial is currently exploring the use of oral azacitidine maintenance in older AML patients (NCT01757535), respectively. Each study will provide important data in this area. However, our results suggest that use of hypomethylating agents for prolonged maintenance, following remission achieved by conventional means and with intensive consolidation therapy, should remain investigational.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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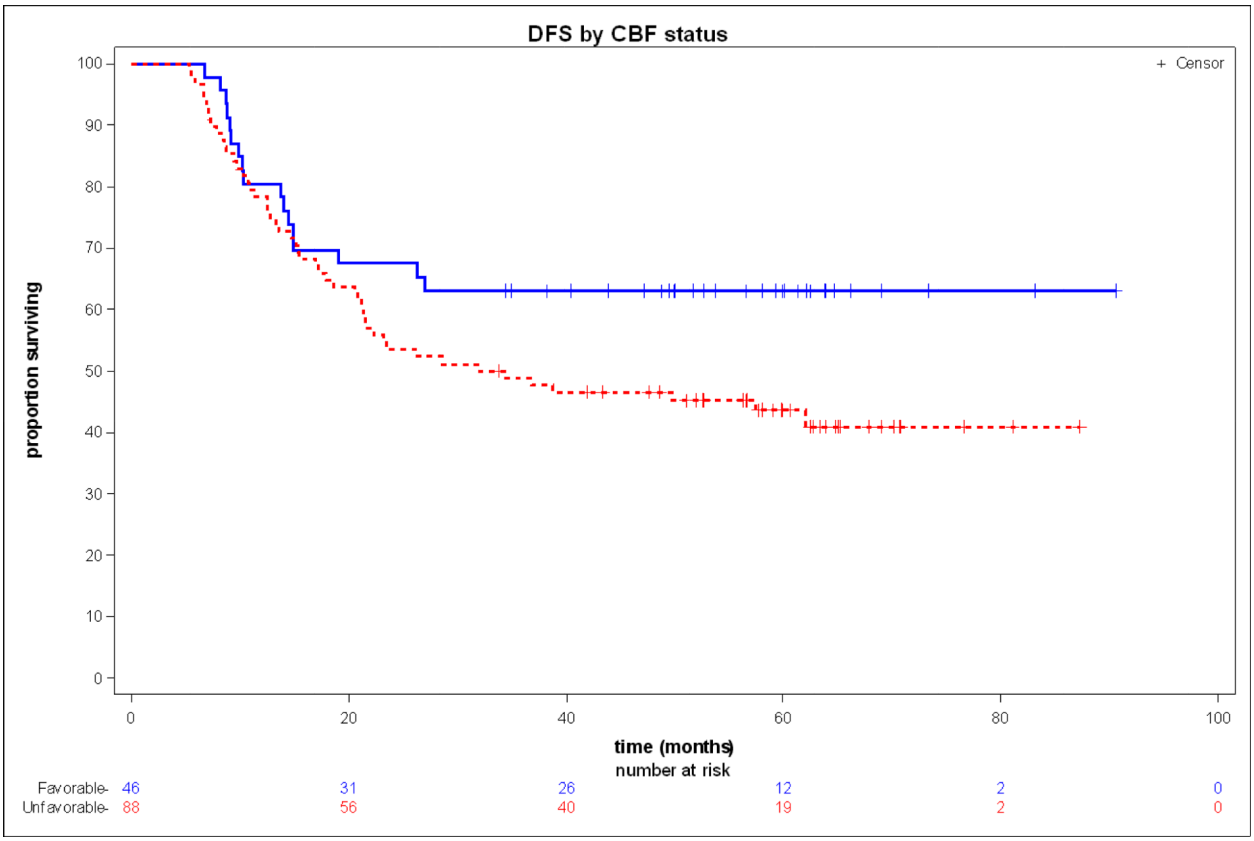

Figure 1.

Disease-free survival of patients with core-binding factor (CBF) AML (blue) or non-CBF AML (red) who received maintenance decitabine.

Table 1

Reasons for study discontinuation prior to decitabine maintenance therapy for patients who achieved complete remission

Treatment course	No.	% of CR patients
Achieved CR, received maintenance	134	32
Achieved CR, no maintenance	280	68
Reasons for no maintenance		
Early relapse	29	7
Withdrew for non-protocol therapy (alloHCT in CR1)	96 (86)	23 (21)
Patient refused	44	11
Unresolved toxicity after consolidation	33	8
Ineligible due to low counts (post autoHCT)	38	9
Death during consolidation	6	1
Insurance denial	4	<1
Other	30	7

Abbreviations: alloHCT, allogeneic hematopoietic stem cell transplantation; autoHCT, autologous hematopoietic stem cell transplantation; CR1, first complete remission.

Table 2

Patient risk (by ELN classification) and clinical outcomes for CALGB 10503 patients receiving maintenance were similar to those from the most recent CALGB trial in this population with alternative maintenance therapy (19808[*])

Characteristic	CALGB 10503	CALGB 19808	*P*-value[†]
ELN Genetic Group,[‡] no. (%)			.07
Favorable	85 (63)	94 (44)	
Intermediate-I	13 (10)	28 (13)	
Intermediate-II	16 (12)	36 (17)	
Adverse	10 (7)	10 (5)	
Unknown	10 (7)	46 (21)	
3-year OS, %	68	61/68	
3-year DFS, %	54	45/56	

[*] Patients randomized to observation/rhIL-2 maintenance.[16]

[†] *P*-value is from Fisher's exact test (not including unknowns).

[‡] The patients were categorized according to the European LeukemiaNet (ELN) classification[25] as follows: Favorable Genetic Group included patients with t(8;21) or inv(16)/t(16;16) and cytogenetically normal AML (CN-AML) patients who harbored mutated *CEBPA* and/or mutated *NPM1* without *FLT3*-ITD; Intermediate-I Group included the remaining CN-AML patients who had wild-type *CEBPA* and mutated *NPM1* with *FLT3*-ITD or wild-type *NPM1* with or without *FLT3*-ITD; Intermediate-II Group included patients with t(9;11) and those with all other chromosome abnormalities that were not classified as Favorable or Adverse; and Adverse Group included patients with inv(3)/t(3;3), t(6;9), t(v;11) (v;q23), −5 or del(5q), −7, abn(17p) and complex karyotype with ≥3 abnormalities.

Table 3

Adverse events Grade 3 or higher among 132 patients receiving decitabine maintenance therapy

Adverse Event[a]	Grade 3		Grade 4[b]	
	No.	%	No.	%
Neutropenia	16	12	103	79
Thrombocytopenia	43	33	52	40
Anemia	15	11	0	0
Febrile neutropenia	13	10	1	1
Infection with <Grade 3 ANC	3	2	0	0
Infection with ≥Grade 3 ANC	9	7	0	0
Fatigue[a]	9	7	0	0
Pain[a]	7	5	0	0
ALT[a]	4	3	0	0
Dyspnea*	4	3	0	0

Abbreviations: ANC, absolute neutrophil count; ALT, alanine aminotransferase.

[a]Non-hematologic toxicities include all Grade 3+ toxicities occurring in at least 3% of patients.

[b]No Grade 5 events occurred during maintenance therapy without relapse of leukemia (e.g., there was no fatal drug toxicity).