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Association between prolonged neutropenia and reduced relapse risk in pediatric AML: A report from the children's oncology group

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Cancer Epidemiology

Objective was to describe the relationship between the number of sterile site infections and duration of neutropenia during the first four cycles of chemotherapy and the risk of recurrence and overall survival in children with newly diagnosed acute myeloid leukemia (AML). AAML0531 was a Children's Oncology Group randomized phase 3 clinical trial that included 1022 children with *de novo* AML. For this analysis, we focused on non-Down syndrome favorable and standard risk patients who completed at least 4 cycles of chemotherapy without recurrence or withdrawal during protocol therapy. Those receiving hematopoietic stem cell transplantation in first remission were excluded. Five hundred and sixty-nine patients were included; 274 (48.2%) were favorable risk. The median cumulative time with neutropenia between Induction II to completion of Intensification II was 96 (range 54–204) days. Number of sterile site infections did not influence the risk of relapse or overall survival. However, longer duration of neutropenia was associated with a lower risk of relapse (hazard ratio 0.81 per 20 days neutropenia, $p = 0.007$). Longer duration of neutropenia was associated with a reduced risk of relapse for children with favorable and standard risk AML. Toxicity may be influenced by pharmacogenomics suggesting that individualized chemotherapy dosing may be an effective strategy.

Current therapies for pediatric acute myeloid leukemia (AML) are intensive; these children commonly experience infections and prolonged duration of neutropenia.[1,2] However, there is great variability in these outcomes even among children receiving identical therapy. Pharmacogenomics has been proposed as one mechanism, which may, in part, explain observed heterogeneity.[3] If this hypothesis is correct, then children with more toxicity may have relatively greater chemotherapy exposure compared with children with less toxicity. In this case, it is possible that relapse outcomes may be inversely related to the degree of toxicity although this potential relationship has never been well explored. Such an observation would provide support toward individualized dose intensity of chemotherapy, perhaps depending on specific genotypic variants.

AAML0531 was a Children's Oncology Group (COG) randomized phase 3 clinical trial that included children with *de novo* AML.[4] This trial provided an ideal platform in which to evaluate the relationship between toxicity and disease outcomes. Because infection and neutropenia are two common and clinically significant toxicities, we focused on those two side effects of therapy.

The objective was to describe the relationship between the number of sterile site infections and duration of neutropenia during the first four cycles of chemotherapy and the risk of recurrence and overall survival in children with newly diagnosed AML.

Methods

Subjects

Inclusion criteria for AAML0531 were age ≥ 1 month to ≤ 30 years with *de novo* AML. Infants aged <1 month with

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What's new?
Treatment responses vary considerably among children with acute myeloid leukemia (AML), leaving some children at risk of severe toxicity and others at risk of suboptimal systemic exposure. The present study shows that for children and young adults with favorable and standard risk AML, variations in treatment response significantly impact risk of disease relapse. In particular, duration of neutropenia during the first four cycles of chemotherapy was found to be inversely associated with relapse risk. The degree of neutropenia experienced may be influenced by genetic factors, suggesting that individualized chemotherapy dosing may be an effective strategy in pediatric AML.

progressive disease, and children with isolated chloromas and Down syndrome > 4 years were also eligible. The following patients were excluded from AAML0531: acute promyelocytic leukemia, AML as a second malignancy and myelodysplastic syndrome unless there were karyotypic abnormalities characteristic of *de novo* AML or the unequivocal presence of megakaryoblasts. For this analysis, we focused on favorable and standard risk patients who completed at least 4 cycles of chemotherapy without recurrence or withdrawal during protocol therapy. Down syndrome patients, high risk patients and those receiving hematopoietic stem cell transplantation (HSCT) in first remission were excluded from the analysis.

Trial description

The study enrolled patients between August 14, 2006 and June 15, 2010. The study was approved by each institutional review board and all parents/participants provided written informed consent and assent as appropriate. Favorable risk patients were those with favorable cytogenetics irrespective of response after Induction I. Favorable cytogenetics were inv(16), or t(8;21). High risk patients were those with: (*i*) monosomy 5, monosomy 7 or del5q cytogenetics; (*ii*) >15% blasts at end of Induction I in the absence of favorable cytogenetics; or (*iii*) FLT3/ITD high allelic ratio (only for patients enrolled later during the trial). Standard risk patients were those having neither low nor high risk features.

Chemotherapy was the same for all participants with the exception of the randomized assignment of gemtuzumab ozogamycin (GMTZ) and allocation to HSCT after Intensification I depending on risk status and donor availability. The treatment protocol consisted of 5 cycles of intensive chemotherapy based on the United Kingdom Medical Research Council 12 study.[5] Enrolled patients were randomized to receive or not receive GMTZ at 3 mg/kg/dose once on Day 6 during Induction I and Day 7 of Intensification II. Induction I consisted of cytarabine 100 mg/m^2/dose intravenous (IV) every 12 hr on days 1–10; daunorubicin 50 mg/m^2/dose IV on days 1, 3 and 5; and etoposide 100 mg/m^2/dose IV daily on days 1–5 (ADE 10 + 3 + 5). Induction II consisted of the same chemotherapy as Induction I except that cytarabine was administered for 8 days (ADE 8 + 3 + 5). Intensification courses were as follows: Intensification I: cytarabine 1 g/m^2/dose IV every 12 hr on days 1–5 and etoposide 150 mg/m^2/dose IV daily on days 1–5; Intensification II: cytarabine 1 g/m^2/dose IV every 12 hr on days 1–4 and mitoxantrone 12 mg/m^2/dose IV daily on days 3–6; and Intensification III: cytarabine 3 g/m^2/dose IV every 12 hr on days 1, 2 and 8, 9 and *E. coli* L-asparaginase 6,000 international units/m^2/dose intramuscularly on days 2 and 9. Best allogeneic donor HSCT was recommended for high risk patients. Matched family donor HSCT was recommended for standard risk patients if a donor was available.

The treatment protocol recommended that patients should progress to the next cycle of chemotherapy when the absolute neutrophil count (ANC) was > 1,000/μL, the platelet count > 75,000/μL, and active infections were controlled. Supportive care guidelines were provided and included empiric systemic antibiotics for patients with fever and neutropenia. Broad-spectrum antibiotics with activity against viridians group streptococci, *Pseudomonas aeruginosa,* and other Gram-negative organisms were recommended. Guidance related to antibacterial or granulocyte-colony stimulating factor prophylaxis was not provided. Fluconazole prophylaxis was recommended to prevent invasive fungal infection. Hospitalization following chemotherapy until the ANC was rising and at least 200/μL was recommended but was not mandated.

Outcomes

For this analysis, the outcomes were the cumulative incidence of relapse and overall survival from completion of Intensification II among patients who survived and completed at least 4 cycles of protocol therapy failure free. This approach was chosen to ensure comparable chemotherapy exposure given that the rate of infections varies widely between different chemotherapy courses.[6] We did not require patients to complete Intensification III as previous data suggested that the fifth cycle of therapy does not influence survival[5] and many patients were withdrawn after Intensification II because of prolonged neutropenia and severe infections.

Exposure variables and potential confounders

The primary exposure variables were the number of microbiologically documented sterile site infections during the first 4 cycles of chemotherapy, the number of Gram positive and negative sterile site infections during this time frame, and the cumulative time to neutrophil recovery between Induction II and completion of cycle 4 (Intensification II). Induction I

Table 1. Children with favorable and standard risk AML who completed 4 cycles of chemotherapy on AAML0531

	All patients ($N = 569$)	
Characteristic	***N***	**%**
Gender		
Female	290	51.0
Male	279	49.0
Age (years)		
0–1	106	18.6
2–16	408	71.7
≥17	55	9.7
Race		
Caucasian	408	71.7
Asian	26	4.6
African American	66	11.6
Other	41	7.2
Unknown	28	4.9
Weight group		
Underweight	40	7.0
Middleweight	376	66.1
Overweight	98	17.2
Unknown	55	9.7
Risk group		
Favorable	274	48.2
Standard	295	51.8
Gemtuzumab allocation		
Yes	289	50.8
No	280	49.2

was not included in the cumulative duration of neutropenia calculation since many centers did not wait for neutrophil recovery before starting Induction II.

Infections were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0[7] and grades 3 and 4 were included in the analysis. Infection data were collected prospectively by institutional clinical research associates and the data were monitored by two central reviewers (LS and RA) in real-time to optimize reporting accuracy. Only sterile site infections were included in this analysis. In order to calculate the cumulative duration of neutropenia for Induction II, Intensification I and Intensification II, the times between start of chemotherapy until neutrophil recovery (defined as ANC > 500/μL following the nadir) were calculated and summed. In the event that neutrophil recovery did not occur prior to start of the next cycle of chemotherapy, date of start of subsequent chemotherapy was used instead.

Potential confounders explored for this analysis were gender, age, race, weight group, risk group and allocation to GMTZ. Body mass index percentile at diagnosis was categorized as underweight, middleweight and overweight as previously described.[8] Patients were not stratified by receipt of GMTZ.

Statistical analysis

Data from AAML0531 were analyzed as of March 31, 2014. Relationships between exposure variables and outcomes were evaluated using the Cox proportional hazards model for overall survival and competing risk regression model for the cumulative incidence of relapse in univariate and multiple regression models. Both analyses began from the end of Intensification II. Overall survival was defined as time until death. The cumulative incidence of relapse was defined as time until relapse where any death without relapse was considered a competing event. Patients were otherwise censored at the last date of contact. Multiple regression included potential confounders significantly associated with survival in univariate analysis. A trend analysis of proportions was used to compare the proportions of sterile site infections by course. All tests of significance were two-sided and the alpha level was set at 0.05.

Results

There were 1 022 non-Down syndrome eligible children and young adults enrolled on AAML0531. Of these, 569 patients were favorable or standard risk; completed Intensification II without withdrawal or relapse; and did not receive HSCT on protocol therapy. Table 1 illustrates the demographics of the patient population; 279 (49.0%) were male and 274 (48.2%) were favorable risk.

Table 2 describes the number of sterile site infections occurring during each cycle of chemotherapy by type of infection. There were a total of 1 116 infections with the risk of infections significantly increasing with each successive cycle (p for trend <0.001). The median cumulative time with neutropenia between Induction II and completion of Intensification II was 96 (range 54–204) days. The number of patients who proceeded to Intensification I, II and III without achieving an ANC of 500/μL were 66, 66 and 70, respectively.

Table 3 illustrates the univariate and multivariable analyses of infection and duration of neutropenia and their associations with the risk of relapse and overall survival. In univariate analysis, longer duration of neutropenia was associated with a lower risk of relapse. The hazard ratio (HR) per each 20 day increase in the duration of neutropenia was 0.81 [95% confidence interval (CI) 0.70 to 0.94; $p = 0.007$]. Figure 1 illustrates the cumulative incidence of relapse by duration of neutropenia dichotomized at the median value. Longer duration of neutropenia was associated with a significantly lower risk of relapse ($p = 0.013$). However, Table 3 and Figure 2 illustrate that the duration of neutropenia was not associated with overall survival. There was no association between the number of infections and relapse risk or overall survival. There was no difference in median duration of

Table 2. Characteristics of infections occurring during first 4 cycles of chemotherapy on AAML0531 ($N = 569$)

Phase of therapy	All	Ind I	Ind II	Int I	Int II
Number sterile site infections	1 116	150	181	287	498
Bacteria					
Gram positive	814[1]	111	132	210	361
Viridans group streptococci	412	42	62	105	203
Enterococcus species	50	4	7	12	27
CoNS	202	34	33	58	77
Staphylococcus aureus	20	6	3	4	7
Mycobacteria	7	1	1	2	3
Other Gram positive	125	24	26	30	45
Gram negative	235	19	39	65	112
Enterobacter species.	37	3	8	5	21
Klebsiella species.	77	3	13	24	37
Pseudomonas species.	39	7	7	11	14
Escherichia coli	49	3	5	13	28
Other Gram negative	33	3	6	12	12
Fungi	38[2]	14	3	8	13
Yeasts	24	10	3	5	6
Molds	13	4	0	2	7
Other	29	6	7	4	12

Abbreviation: CoNS: coagulase negative staphylococci.
Number of infections occurring during each course of therapy where each patient could experience multiple infections.
[1]Two patients had both viridans group streptococci and *Enterococcus species* reported.
[2]One patient had fungi not otherwise specified.

Table 3. Relationship between infections and cumulative duration of neutropenia on risk of relapse and overall survival

	HR (95% CI)	*p* Value	Adjusted HR[1] (95% CI)	Adjusted *p* Value[1]
Relapse Risk				
Total infections[2]	0.94 (0.85 − 1.04)	0.247	0.97 (0.87 – 1.08)	0.599
Gram positive	0.96 (0.86 − 1.07)	0.457	0.98 (0.88 – 1.11)	0.792
Gram negative	0.87 (0.69 − 1.09)	0.227	0.91 (0.72 – 1.14)	0.402
Duration neutropenia[3] ($n = 563$)	0.81 (0.70 − 0.94)	0.007	0.88 (0.75 – 1.02)	0.096
Overall Survival				
Total infections[2]	1.02 (0.92 − 1.14)	0.705	1.06 (0.95 – 1.18)	0.274
Gram positive	0.99 (0.87 − 1.12)	0.856	1.03 (0.91 – 1.16)	0.687
Gram negative	1.10 (0.87 − 1.38)	0.431	1.14 (0.91 – 1.44)	0.255
Duration neutropenia[3] ($n = 563$)	0.90 (0.75 − 1.07)	0.229	0.98 (0.82 – 1.18)	0.855

Abbreviations: HR: hazard ratio; CI: confidence interval.
[11]After adjusting for African American race, favorable cytogenetics and gemtuzumab allocation.
[2]Infections reflect the number of sterile site infections occurring during cycles 1 to 4.
[3]Duration of neutropenia reflect cycles 2 to 4 with 563 patients having known duration times for all 3 courses with median = 96 days, range: 54–204 days. HR reflects the relative risk of a 20 day increase in duration.

neutropenia or overall survival for patients in the analysis versus those who withdrew at the end of Intensification 1 (data not shown).

For multiple regression analysis, the results of the Supplemental File were considered; this table illustrates the relationship between baseline characteristic and GMTZ allocation with the outcome variables. Since African-American race, risk group and GMTZ allocation were identified as potential confounders, they were included in the adjusted models illustrated in Table 3. The adjusted HR per

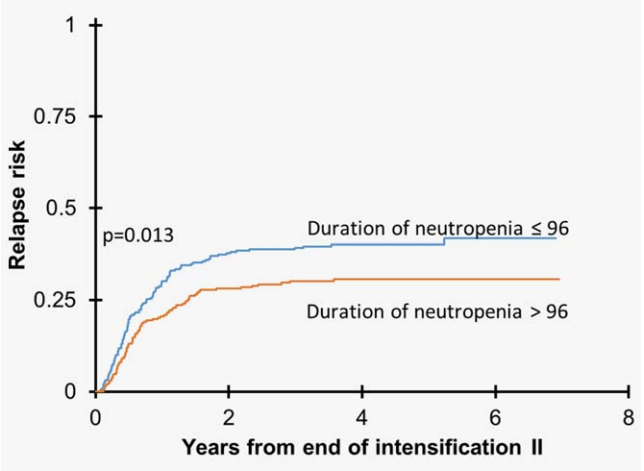

Figure 1. Cumulative incidence of relapse by duration of neutropenia. Cumulative incidence of relapse dichotomized by the median duration of neutropenia (>96 *vs.* ≤ 96 hr) for Induction II, Intensification I and Intensification II. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

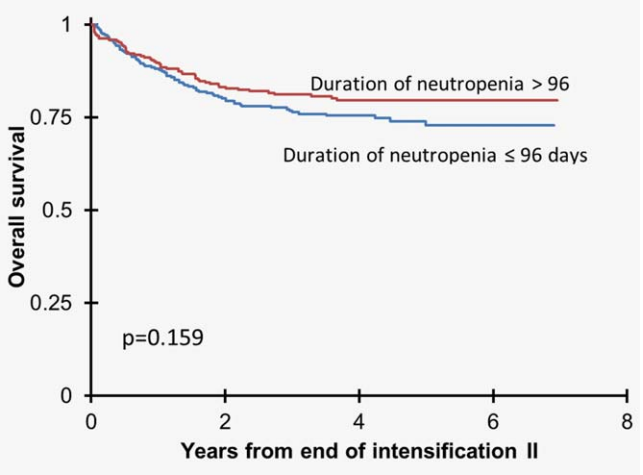

Figure 2. Overall survival by duration of neutropenia. Overall survival dichotomized by the median duration of neutropenia (>96 *vs.* ≤ 96 hr) for Induction II, Intensification I and Intensification II. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

each 20 day increase in the duration of neutropenia was 0.88 (95% CI 0.75 to 1.02; $p = 0.096$).

Discussion

We observed that among favorable and standard risk children and young adults with AML, the risk of relapse was inversely related to the duration of neutropenia; patients who had more prolonged neutropenia had lower relapse rates. This observation is important as it provides some evidence that there is a link between toxicity of therapy and disease control.

As one potential explanation of our findings, patients may have differential abilities to metabolize chemotherapy and patients whose pharmacodynamics results in greater drug exposure may have fewer relapses. This hypothesis requires there to be a relationship between intensity of therapy and disease outcome. Such a relationship has been observed in AML where patients treated with intensive timing induction had better survival and lower relapse rates compared to patients treated with standard timing induction.[9] Further, there is some evidence that pharmacogenomics is an important determinant of disease outcomes in AML.[3,10,11] This hypothesis also requires there to be an association between pharmacogenomics and toxicity. There is evidence that pharmacogenomics can predict cytarabine-related toxicity in the AML context.[12] Outside the AML setting, genotypic variation has been associated with the duration of chemotherapy-induced neutropenia.[13–15]

However, there are alternate explanations for our findings. First, clinicians may treat high risk patients more urgently and may be less likely to wait for neutrophil recovery before starting the next cycle of chemotherapy. To address this issue, we did not include neutrophil duration during Induction I since we know that many clinicians do not wait for neutrophil recovery to begin Induction II. Further, we limited our analysis to favorable and standard risk groups and thus, excluded high risk patients. In addition, the adjusted analysis did account for risk group.

The second possible alternate explanation is that our analysis may be influenced by other confounders. In particular, GMTZ may in part be confounding our results since GMTZ was associated with better outcomes and is associated with prolonged neutropenia. This hypothesis is supported by the increased HR in the adjusted model with an upper 95% CI of 1.02. Nonetheless, GMTZ does not appear to explain the association entirely based upon the adjusted HR of 0.88, a clinically meaningful decrement in the HR.

If our findings are replicated by others, these results suggest that individualizing chemotherapy dose intensity to each patient may be a potential strategy toward improving disease control and maintaining toxicities within an acceptable range. This strategy may be particularly important in diseases such as AML where therapies are currently at the limits of acceptable toxicity. Such approaches could include studying pharmacokinetics within individual patients with subsequent dose adjustments. Alternatively, as the study of pharmacogenomics matures, drug doses may be based on specific genotypes in drug metabolism enzymes.

We found that neutropenia duration influenced the risk of relapse but not overall survival. In clinical trials, it is relatively common to find interventions that can influence relapse but not survival for a few reasons. First, deaths are typically rarer than relapses and thus, it is more difficult statistically to show differences in overall survival. Second, more relapses do not always translate into more deaths as some children can be salvaged. Third, reduction in relapse may be

offset by more treatment-related mortality. All of these possibilities may be applicable to our study.

The strengths of our report include the homogeneity of treatment in a large number of children and young adults with AML. However, our results must be interpreted in light of its limitations. While achievement of a specific neutrophil count was recommended on AAML0531, there was heterogeneity in how clinicians decided when to begin the next cycle of chemotherapy. Furthermore, there was heterogeneity in supportive care although we know that only about 20% of COG sites routinely use prophylactic granulocyte-colony stimulating factor in this disease.[16]

In conclusion, in children and young adults with favorable and standard risk AML, longer duration of neutropenia was associated with a lower relapse risk. This finding suggests that individual variation in drug metabolism may contribute to explaining toxicity and disease control. Future work should consider the role of pharmacokinetics and pharmacogenomics to individualize AML chemotherapy dosing.

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