Published in final edited form as:
Cancer. 2009 March 1; 115(5): 1100–1108. doi:10.1002/cncr.24107.

INFECTIONS AND ASSOCIATION WITH DIFFERENT INTENSITY OF CHEMOTHERAPY IN CHILDREN WITH ACUTE MYELOID LEUKEMIA

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Abstract

Background—The objectives were to compare infections during different intensities of therapy in children with acute myeloid leukemia (AML).

Methods—Subjects were children enrolled on CCG 2891 with AML. In Phase 1 (induction), patients were randomized to intensive or standard timing. In Phase 2 (consolidation), those with a family donor were allocated allogeneic stem cell transplantation (SCT); remainder were randomized to autologous SCT or chemotherapy. This report compares infections between different treatments on an intent-to-treat basis.

Results—During Phase 1, intensive timing was associated with more bacterial (57.7% vs. 39.4%, *P*<0.001), fungal (27.4% vs. 9.9%, P<.001) and viral (14.0% vs. 3.9%, P<.001) infections compared to standard timing. During Phase 2, chemotherapy was associated with more bacterial (56.5% vs. 40.1%, P=.005), but similar fungal (9.5% vs. 6.1%, P=1.000) and viral (4.2% vs. 12.9%, P=.728) infections compared with allogeneic SCT. No differences between chemotherapy and autologous SCT infections were seen.

Fatal infections were more common during intensive compared with standard timing induction (5.5% vs. 0.9%; P=.004). Infectious deaths were similar between chemotherapy, autologous SCT and allogeneic SCT.

Conclusions—Prevalence of infection varies depending on the intensity and type of treatment. This information sheds insight into the mechanisms behind susceptibility and outcome of infections in pediatric AML.

Keywords

infections; children; acute myeloid leukemia

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There are no financial disclosures.

BACKGROUND

Infections are an important cause or morbidity and mortality for children with acute myeloid leukemia (AML).[1-5] These patients are at particularly high risk of infection, likely related to the intensity of their therapy and the therapy's focus upon the myeloid compartment resulting in repeated episodes of prolonged and profound neutropenia. In previous pediatric AML trials, 29% to 60% of children experienced at least one microbiologically documented infection.[2, 4] Infections not only contribute to mortality but also impact by prolonging hospitalization, compromising subsequent chemotherapy delivery, affecting quality of life and increasing health care utilization.

We know clinically that children receiving different intensity of chemotherapy will experience different frequencies of infectious complications. However, rarely are different therapies administered to similar, contemporaneous populations with the same disease, and thus, it has been difficult to understand whether therapy, disease, host or environmental characteristics are most influential in infection risks. Understanding the prevalence and characteristics of invasive bacterial, fungal and viral infections according to different types of anti-cancer therapy in similar populations may shed insight into mechanisms behind susceptibility and outcome of infections by different pathogens.

Given this consideration, we wished to explore bacterial, fungal and viral infections in children enrolled on Children's Cancer Group (CCG) 2891; in this protocol, infection data were prospectively collected during treatment phases of differing intensity. This trial included a randomization between intensive timing and standard timing induction chemotherapy in Phase 1. During Phase 2, those with a suitable family donor were allocated to allogeneic stem cell transplantation (SCT) while those without a donor were randomized to autologous SCT or chemotherapy. Therefore, the design of this trial allowed us to examine among comparable groups of patients how intensive timing affects the prevalence of infection in Phase 1 and how different types of treatment affect the prevalence of infection in Phase 2. We focused on microbiologically documented infections since these are the most objective to classify. We hypothesized that the prevalence of infections would be higher in intensive timing versus standard timing during Phase 1 and that for Phase 2, the prevalence of infection would be highest for allogeneic SCT given the intensity of conditioning and contribution of graft-versus-host disease to infection outcomes.

The objectives of this study were to compare the prevalence and characteristics of microbiologically documented bacterial, fungal and viral infections during different intensities of anti-cancer therapy in children with AML enrolled on CCG 2891.

PATIENTS AND METHODS

Patients

The patients included in this report were those enrolled on CCG 2891.[6, 7] Children less than 21 years of age with newly diagnosed AML, and acute undifferentiated or biphenotypic leukemia with evidence of myeloid differentiation, were eligible. Patients with acute promyelocytic leukemia became ineligible in April 1992. For this report, patients with Down's syndrome, AML as a second malignancy, myelodysplastic syndrome or isolated chloroma were excluded. We also excluded 15 patients who started with standard timing and whose protocol was changed to intensive timing when an analysis revealed the superiority of intensive timing.

The specific therapy of this trial consisted of two phases of therapy. Phase 1 contained four cycles of induction chemotherapy. Initial treatment consisted of two cycles of a five-drug regimen of chemotherapy administered over four days: dexamethasone, cytarabine, 6-

thioganine, etoposide and rubidomycin (DCTER). Patients were randomized to receive the second cycle of DCTER either with intensive timing after a 6 day rest period irrespective of bone marrow status or hematological recovery, or to standard timing in which bone marrow was examined on day 14. Those in whom the day 14 marrow demonstrated good leukemia response had their second DCTER administered when the blood counts recovered whereas those with > 40% blasts on their day 14 bone marrow proceeded to the second DCTER at that time. The next two cycles of induction chemotherapy were then administered, which consisted of two cycles of DCTER given either as intensive or standard timing according to the initial randomization. All patients in both arms received identical amounts of total induction chemotherapy. Those in remission after four DCTER cycles with an appropriate family donor were allocated to allogeneic SCT. All others were randomized between autologous SCT versus intensive chemotherapy. Intensive chemotherapy consisted of four courses of three chemotherapy regimens. Course 1 consisted of high dose, intensively-timed cytarabine and L-asparaginase, courses 2 and 3 consisted of 6-thioguanine, vincristine, cytarabine, cyclophosphamide and 5-azacytidine, and course 4 consisted of cytarabine, daunorubicin, etoposide, 6-thioganine and dexamethasone (a modified DCTER). Collectively, either SCT or the four courses of intensive chemotherapy were referred to as Phase 2. As only course 1 was composed of intensive chemotherapy, the description of infections during Phase 2 chemotherapy was limited to this course. Initially, the use of hematopoietic growth factors was not permitted except for granulocyte-macrophage colony stimulating factor which was allowed for poor engraftment following SCT. However, in an attempt to reduce infection outcomes, prophylactic granulocyte colony stimulating factor was introduced in 1993 in a non-randomized fashion. Results of this intervention have previously been reported.[8] Other than for these indications, the use of prophylactic colony stimulating factor was discouraged. All children received trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis jiroveci*. Either nystatin or clotrimazole troches were recommended for fungal prophylaxis.

Those allocated to allogeneic or autologous SCT were conditioned using four days of oral Busulphan and four days of cyclophosphamide. For autologous SCT recipients, bone marrow was harvested with 4-hydroperoxycyclophosphamide ex vivo purging. For allogeneic SCT recipients, graft versus host disease prophylaxis consisted of 15 mg/m^2 of methotrexate on day 1 followed by 10 mg/m^2 on days 3, 6 and 11 and weekly until day 100. This trial was open to patient accrual from October 1989 to May 1995.

The two main comparisons for this report were in Phase 1 between those randomized to intensive timing and standard timing induction chemotherapy, and in Phase 2 between those with a matched family donor (allogeneic SCT) and those randomized to autologous SCT or chemotherapy.[7] These comparisons all were conducted in an intent-to-treat fashion to overcome biases inherent in an analysis by treatment received.

Outcomes and Potential Predictors

Infections were prospectively collected by the institutional clinical research associates using a standardized data collection form. This report focuses on microbiologically documented bacterial, fungal and viral infections, which were defined as any positive culture although data managers were instructed to not report positive surveillance cultures. Reporting of fungal infection was limited to microbiologically documented infections because insufficient clinical information were available to classify fungal infections according to the Mycoses Study Group/ European Organization for Research and Treatment of Cancer guidelines.[9] Microbiologically documented infections were considered in a similar fashion as previously described.[10] Episodes with the same organisms within the same phase of therapy were counted as different infections if they occurred more than 7 days apart. In the case of common contaminants such as coagulase-negative staphylococci and Gram-positive bacilli, insufficient clinical

information was available to distinguish between likely contaminants versus invasive infections and in this study; positive cultures were included as infectious episodes. Multiple organisms from the same child within the same phase of therapy were considered separate infections.

Potential predictors of infection outcomes that were examined were regimen assigned in induction (intensive versus standard timing) and type of therapy in Phase 2 (intensive chemotherapy during course 1, autologous SCT and allogeneic SCT). In addition, we examined age (at study entry) and ethnicity as potential predictors of infections. Because of the potential for an interaction between these variables and treatment, we only performed these regressions in the intensive timing group for Phase 1 and in the course 1 chemotherapy group for Phase 2.

Statistical Analysis

The number of infections was expressed as the prevalence within a given phase of therapy and it is a simple fraction of the number of patients experiencing at least one given infection compared to all patients undertaking the same therapy. The time period at risk was during on study chemotherapy administration or SCT and did not include time following removal from study for any reason, or relapse. For most children, the time period at risk began on the day chemotherapy was initiated and extended until the day prior to initiation of the next course of chemotherapy except for SCT. The follow-up period for SCT was 100 days following transplantation. The prevalence of infection between different treatment types was compared using the Chi square test. In order to determine whether the number of infections varied according to age or ethnicity irrespective of type of therapy, the incidence (per 100 patient days of therapy) of infection was modeled either using Poisson or negative binomial regression depending roughly on the observed variance (what is called *over-dispersion*) of the average incidence rates. Effects were expressed as the incidence rate ratio (IRR). The IRR expresses the increase in risk of an outcome for a one-unit change in the covariate and can be considered analogous to a relative risk. This analysis was restricted to those randomized to intensive timing in Phase 1 and those randomized to chemotherapy in Phase 2.

The analysis of infectious deaths by type of treatment censored patients at relapse or death.

Statistical analyses were performed using SAS software (version 8.2, SAS Institute Inc., Cary, NC.) or Stata software (StataCorp. 2005 Stata Statistical Software Releases 8, 9, College Station TX). All tests of significance were two-sided and statistical significance was defined as $P < .05$.

RESULTS

A total of 872 patients were enrolled on CCG 2891. Details of the demographics have previously been published.[6] Of these 872 patients, 678 were randomized to intensive versus standard timing induction and 452 were allocated or randomized to chemotherapy, autologous SCT or allogeneic SCT in Phase 2. For the induction question, 194 non-randomized patients were allocated to intensive timing when an analysis revealed better disease outcome with intensive timing. The non-randomized patients are not included in the following analyses. Compliance with randomization and allocation was excellent. Of the subjects randomized to standard versus intensive timing allocation, only 15 children did not receive the randomized treatment. Compliance with consolidation therapy, either randomized or allocated, was 88% overall.

Table 1 illustrates the number of patients having at least one bacterial, fungal or viral infection during the specified phases of therapy and the most common species of Gram positive and Gram negative infections during Phase 1 and Phase 2 treatments. During Phase 1, intensive

timing was associated with more bacterial infections compared with standard timing (57.7% vs. 39.4%, *P*<0.001). We noted either significant or non-significant tendencies for more infections during intensive timing with most Gram positive and negative pathogens. In particular, there was a significance increase in viridans group streptococcal infections associated with intensive timing induction. In contrast, infections with coagulase negative Staphylococci and *Staphylococcus aureus* occurred at a similar frequency in the intensive and standard timing groups (Table 1). Fungal infections also were more common in intensive timing for both yeasts (19.0% vs. 8.4%, P<.001) and molds (11.7% vs. 1.5%, P<.001). Finally, viral infections occurred more frequently during intensive timing (14.0% vs. 3.9%, P<.001). During intensive timing, viral infections consisted of herpes simplex (n=25), rotavirus (n=6), cytomegalovirus (n=5), influenza (n=4), herpes zoster (n=3), parainfluenza (n=3), adenovirus (n=2) and respiratory syncytial virus (n=2). During standard timing, viral infections consisted of herpes simplex (n=7), herpes zoster virus (n=3), influenza (n=1), parainfluenza (n=1) and rotavirus (n=1).

Table 1 also demonstrates that during Phase 2, chemotherapy was associated with more bacterial infections (56.5% vs. 40.1%, P=.005) and more viridans group streptococcal bacteremia (16.1% vs. 2.7%; P<.001) compared with allogeneic SCT. Conversely, chemotherapy and allogeneic SCT were associated with similar risks of fungal infections (9.5% vs. 6.1%, P=1.000) and viral infections (4.2% vs. 12.9%, P=.728). We may have overestimated infections in the allogeneic SCT arm since infections were collected to 100 days following SCT compared to the start of next phase of treatment in the chemotherapy arm. Thus, we also compared the incidence of infections per 100 days in chemotherapy relative to allogeneic SCT recipients and the same pattern of greater infections with chemotherapy was seen (data not shown). No differences between bacterial, fungal or viral infections were noted between Phase 2 chemotherapy and autologous SCT. The prevalence of infections during Phase 2 may be affected by the length of the reporting period for each type of therapy. In Phase 2, the median duration of course 1 chemotherapy was 44 days (range 1, 253 days) while the median duration for autologous SCT was 110 days (range 20, 162 days) and the median duration for allogeneic SCT was 111 days (range 2, 410 days). The prevalence of infections during Phase 2 chemotherapy, autologous SCT and allogeneic SCT were not higher in those who had received Phase 1 intensive timing compared to those who had received standard timing (data not shown).

Table 2 illustrates the affect of age on the risk of various infections during Phase 1 and 2. During Phase 1, infections did not vary depending upon patient age. Conversely, children greater than 10 years of age had a higher risk of fungal infections in Phase 2 (IRR 2.763, 95% CI 1.221, 6.253; P=.012). Table 3 demonstrates that ethnicity had little impact on infections other than black children having less fungal infections in Phase 2 (IRR 0.00; P=.005).

Table 4 illustrates that there were 33 fatal infections. Bacterial were responsible for 19 (58%) infection deaths while molds were responsible for 11 (33%) fatal infections. Table 5 illustrates the number of children who died of infection according to intensity of induction therapy (intensive versus standard timing) or type of consolidation (chemotherapy, autologous SCT and allogeneic SCT). In addition, infectious deaths in consolidation are illustrated according to the type of induction received. Infection deaths were significantly more common during intensive timing in induction (5.5% vs. 0.9%; P=.004) whereas deaths were similarly distributed between chemotherapy, autologous SCT and allogeneic SCT (Table 5).

DISCUSSION

We found that on CCG 2891, a phase III pediatric AML trial, more bacterial, fungal and viral infections were associated with intensive timing compared with standard timing and more infectious deaths were associated with intensive timing. However, this increase did not occur

uniformly and infections with *Staphylococcus* species occurred at a similar frequency. In contrast to our expected finding, more bacterial infections and more viridans group streptococcal bacteremia were associated with Phase 2 chemotherapy compared with allogeneic SCT. We also found that Gram negative organisms and molds continue to contribute to fatal infections in pediatric AML.

Our data are unique for several reasons. We have reported infection data for the largest cohort of children with AML to date and because of the design of the trial, we have comparable groups of children treated with different intensities of therapy (intensive versus standard timing) as well as different types of treatment (chemotherapy, autologous SCT and allogeneic SCT). This design provides an opportunity to gain insight into how the prevalence of bacterial infection varies depending on treatment.

We found that the prevalence of infection was higher with intensive timing compared to standard timing induction, which was expected. However, during Phase 2, bacterial infections and viridans group streptococcal infections were less common with allogeneic SCT compared to chemotherapy. Similar finds were seen when infections only with alpha haemolytic *Streptococcus* were examined on this same trial.[11] The finding of more infections with chemotherapy compared with allogeneic SCT was surprising. It is possible that the risk of infection is indeed greater with chemotherapy. However, other possible explanations for this finding include the use of antibacterial prophylaxis[12, 13] or hematopoietic colony-stimulating factors during allogeneic SCT[14], since these interventions can reduce the risk of infections. However, use of these interventions should have been minimal since the protocol discouraged prophylactic use of colony stimulating factors during SCT and the only antibiotic prophylaxis proscribed by the protocol was trimethoprim-sulfamethoxazole. Unfortunately, data on these interventions were not collected. In addition, since the difference in prevalence of infections in chemotherapy relative to allogeneic SCT appeared to be related to more viridans group streptococci with chemotherapy, this finding provides further evidence that high dose cytarabine is a specific risk factor for infections with viridans group *Streptococcus* since all these types of consolidation would be expected to cause severe mucositis.[11] Even with less infections occurring during allogeneic SCT, the risk of treatment related mortality was higher with allogeneic SCT, which occurred in 14% of such patients compared with 4% in chemotherapy arm and 5% in autologous SCT arm.[7]

In spite of more fatal infections with intensive timing induction, event-free survival at 3 years was significantly better with intensive timing (42±7%) compared with standard timing (27 ±6%, P=.0005).[6] Consequently, the increased infectious deaths were off-set by improved disease control. Nonetheless, given a better understanding of increased infections with intensive timing, strategies to reduce those infectious deaths may continue to improve survival associated with intensive induction treatment.

Some may argue that the findings from this study are less important since therapy similar to CCG 2891 is not currently commonly used to treat children with AML. While this is true, the principles of our findings of the high risk of bacterial infections, the association between the risk of infections and type of treatment, role of Gram negative organisms and predictors of infections and infectious deaths should hold true for other trials as well. Furthermore, many of the elements within CCG 2891 are used in many AML trials including anthracycline based cycles and the use of high dose, often intensively timed cytarabine, thus emphasizing the rationale for carefully examining the risk of infections during Phase 2 chemotherapy in this report. Furthermore, this report is important because we have very little knowledge about risk factors for infection from randomized studies. Almost all of our knowledge is based on observational studies which may be difficult to interpret because of potential biases and confounders. Given our findings, we believe that prevention of invasive fungal infections

should be a priority since more than a quarter of children during intensive timing induction had a microbiologically documented infection. Second, prevention of invasive viral infections also is important since the risk increases with intensity of therapy. Third, initial efforts to reduce infections in patient with AML should be targeted at chemotherapy recipients in addition to SCT recipients since those receiving chemotherapy are at higher risk of such infections compared with those undergoing allogeneic SCT.

Our study has important limitations. For example, we do not know whether children received antibacterial prophylaxis (in addition to co-trimoxazole) and if so, what type of prophylaxis they received. Patients who receive antibacterial prophylaxis are expected to have reduced bacterial infections[12, 13] and thus, this may have biased some of our findings. Second, we did not have data on body mass index on this trial. Since others have found obesity a risk factor for increased treatment related mortality in children with AML,[15] our finding of more fungal infections with older children may in fact reflect an association between adverse outcomes and obesity. Finally, the use of a specific form to collect information was newly introduced for this study and thus, we may have underestimated the prevalence of infections if some infections were not reported using this form.

In conclusion, the prevalence of infection varies depending on the type of treatment with the highest risk of infections being associated with intensive timing induction and chemotherapy consolidation. These findings provide insight into the mechanisms behind susceptibility to infections in pediatric AML.

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TABLE 1

NUMBER OF PATIENTS EXPERIENCING AT LEAST ONE TYPE OF BACTERIAL INFECTION ACROSS DIFFERENT PHASES OF CHEMOTHERAPY

	Phase 1			Phase 2				
	Std Timing	**Int Timing**	**P value**	**Course 1 Chemo**	**Auto SCT**	**P* value**	**Allo SCT**	**P* value**
Number of Patients	335	343		168	137		147	
Bacteria	132 (39.4%)	198 (57.7%)	<0.001	95 (56.5%)	69 (50.4%)	0.300	59 (40.1%)	0.005
All Gram positive bacteria	107 (31.9%)	159 (46.4%)	<0.001	63 (37.5%)	47 (34.3%)	0.632	40 (27.2%)	0.055
CoNS	41 (12.2%)	53 (15.5%)	0.266	18 (10.7)%	17 (12.4%)	0.719	18 (12.2%)	0.724
Viridans group *Streptococcus*	28 (8.4%)	53 (15.5%)	0.005	27 (16.1%)	19 (13.4%)	0.632	4 (2.7%)	<0.001
Enterococcus species	15 (4.5%)	24 (7.0%)	0.188	3 (1.8%)	6 (4.4%)	0.308	5 (3.4%)	0.480
Staphylococcus aureus	14 (4.2%)	17 (5.0%)	0.714	3 (1.8%)	3 (2.2%)	1.000	3 (2.0%)	1.000
All Gram negative bacteria	46 (13.7%)	91 (26.5%)	<0.001	48 (28.6%)	34 (24.8%)	0.517	32 (21.8%)	0.195
Pseudomonas species	13 (3.9%)	32 (9.3%)	0.005	11 (6.5%)	12 (8.8%)	0.517	10 (6.8%)	1.000
Klebsiella species	12 (3.6%)	21 (6.1%)	0.153	9 (5.4%)	7 (5.1%)	1.000	4 (2.7%)	0.271
Escherichiae coli	11 (3.3%)	16 (4.7%)	0.434	12 (7.1%)	7 (5.1%)	0.635	9 (6.1%)	0.822
Enterobacter species	5 (1.5%)	13 (3.8%)	0.092	4 (2.4%)	3 (2.2%)	1.000	3 (2.0%)	1.000
Fungi	33 (9.9%)	94 (27.4%)	<0.001	16 (9.5%)	11 (8.0%)	0.690	9 (6.1%)	1.000
Yeasts	28 (8.4%)	65 (19.0%)	<0.001	12 (7.1%)	9 (6.6%)	1.000	6 (4.1%)	0.301
Molds	5 (1.5%)	40 (11.7%)	<0.001	5 (3.0%)	2 (1.5%)	0.465	3 (2.0%)	0.332
Viruses	13 (3.9%)	48 (14.0%)	<0.001	7 (4.2%)	12 (8.8%)	0.151	19 (12.9%)	0.728

Abbreviations: std - standard; int - intensive; chemo - chemotherapy; auto - autologous; allo -allogeneic; CoNS - coagulase negative *Staphylococcus*

*P values relative to course 1 chemotherapy in Phase 2

TABLE 2

INCIDENCE OF INFECTIONS AND COMPARISON BY AGE DURING INTENSIVE TIMING IN PHASE 1 AND CHEMOTHERAPY IN PHASE 2

Phase		Age Group	Rate/100 Days	95% CI	IRR*	95% CI	P Value
1 N=343	Bacteria	0 to < 2 Years	**1.250**	0.939, 1.664	**1.221**	0.885, 1.684	**0.227**
		2 to 10 Years	**0.936**	0.757, 1.157	**0.806**	0.615, 1.057	**0.118**
		> 10 Years	**1.118**	0.908, 1.376	**1.080**	0.825, 1.413	**0.576**
	Gram Neg	0 to < 2 Years	**0.433**	0.301, 0.623	**1.452**	0.956, 2.205	**0.091**
		2 to 10 Years	**0.295**	0.220, 0.395	**0.863**	0.596, 1.249	**0.431**
		> 10 Years	**0.302**	0.226, 0.403	**0.895**	0.619, 1.293	**0.553**
	Gram Pos	0 to < 2 Years	**0.801**	0.578, 1.108	**1.139**	0.790, 1.641	**0.489**
		2 to 10 Years	**0.642**	0.505, 0.815	**0.825**	0.609, 1.118	**0.214**
		> 10 Years	**0.767**	0.609, 0.966	**1.108**	0.821, 1.498	**0.502**
	Fungi	0 to < 2 Years	**0.239**	0.146, 0.390	**0.708**	0.418, 1.198	**0.180**
		2 to 10 Years	**0.302**	0.226, 0.403	**0.906**	0.627, 1.311	**0.600**
		> 10 Years	**0.374**	0.288, 0.485	**1.324**	0.924, 1.897	**0.128**
	Viruses	0 to < 2 Years	**0.209**	0.124, 0.353	**1.556**	0.848, 2.854	**0.169**
		2 to 10 Years	**0.151**	0.100, 0.227	**1.034**	0.605, 1.766	**0.904**
		> 10 Years	**0.118**	0.074, 0.187	**0.700**	0.399, 1.230	**0.207**
2 N=168	Bacteria	0 to < 2 Years	**0.926**	0.650, 1.320	**1.152**	0.760, 1.746	**0.506**
		2 to 10 Years	**0.755**	0.550, 1.036	**0.855**	0.577, 1.265	**0.430**
		> 10 Years	**0.854**	0.628, 1.161	**1.034**	0.703, 1.521	**0.866**
	Gram Neg	0 to < 2 Years	**0.332**	0.209, 0.526	**1.009**	0.593, 1.718	**0.974**
		2 to 10 Years	**0.323**	0.220, 0.474	**0.968**	0.600, 1.563	**0.895**
		> 10 Years	**0.334**	0.232, 0.481	**1.025**	0.641, 1.637	**0.919**
	Gram Pos	0 to < 2 Years	**0.581**	0.379, 0.892	**1.289**	0.776, 2.140	**0.332**
		2 to 10 Years	**0.421**	0.283, 0.628	**0.805**	0.492, 1.317	**0.384**
		> 10 Years	**0.482**	0.328, 0.708	**0.990**	0.612, 1.602	**0.968**
	Fungi	0 to < 2 Years	**0.092**	0.038, 0.221	**0.771**	0.289, 2.053	**0.593**

Phase	Age Group	Rate/100 Days	95% CI	IRR*	95% CI	P Value
	2 to 10 Years	**0.050**	0.019, 0.132	**0.333**	0.114, 0.971	**0.024**
	> 10 Years	**0.184**	0.113,0.301	**2.763**	1.221, 6.253	**0.012**
Viruses	0 to < 2 Years	**0.092**	0.038, 0.221	**1.713**	0.574, 5.110	**0.349**
	2 to 10 Years	**0.062**	0.026, 0.149	**0.972**	0.326, 2.902	**0.960**
	> 10 Years	**0.046**	0.017, 0.123	**0.622**	0.195, 1.983	**0.408**

* IRR - incidenc rate ratio. IRRs and p-values compare each age group to all other age groups combined, for example, 0 to < 2 years versus ≥ 2 years.

TABLE 3

INCIDENCE OF INFECTIONS AND COMPARISON BY ETHNICITY DURING INTENSIVE TIMING IN PHASE 1 AND CHEMOTHERAPY IN PHASE 2

Phase		Ethnicity	Rate/100 Days	95% CI	IRR*	95% CI	P Value
1 N=343	Bacteria	White	1.031	0.881, 1.207	0.888	0.666, 1.185	0.420
		Black	0.959	0.624, 1.474	0.888	0.566, 1.395	0.606
		Hispanic	1.310	0.889, 1.930	1.259	0.834, 1.901	0.275
	Gram Neg	White	0.315	0.254, 0.390	0.919	0.624, 1.354	0.671
		Black	0.282	0.156, 0.509	0.861	0.463, 1.601	0.629
		Hispanic	0.394	0.237, 0.653	1.253	0.729, 2.152	0.979
	Gram Pos	White	0.706	0.592, 0.842	0.927	0.671, 1.281	0.648
		Black	0.645	0.396, 1.051	0.884	0.530, 1.474	0.635
		Hispanic	0.841	0.547, 1.293	1.189	0.752, 1.880	0.462
	Fungi	White	0.307	0.247, 0.382	0.873	0.594, 1.284	0.495
		Black	0.333	0.193, 0.574	1.046	0.588, 1.861	0.878
		Hispanic	0.446	0.278, 0.718	1.461	0.874, 2.442	0.166
	Viruses	White	0.148	0.108, 0.202	0.999	0.558, 1.787	0.997
		Black	0.128	0.053, 0.308	0.853	0.340, 2.140	0.730
		Hispanic	0.263	0.141, 0.488	1.948	0.982, 3.866	0.076
2 N=168	Bacteria	White	0.876	0.694, 1.107	1.141	0.772, 1.686	0.507
		Black	0.588	0.339, 1.018	0.670	0.374, 1.200	0.172
		Hispanic	0.821	0.485, 1.390	0.980	0.557, 1.721	0.943
	Gram Neg	White	0.330	0.247, 0.440	1.001	0.622, 1.610	0.997
		Black	0.124	0.047, 0.330	0.340	0.124, 0.932	0.013
		Hispanic	0.483	0.280, 0.832	1.567	0.860, 2.854	0.162
	Gram Pos	White	0.519	0.390, 0.690	1.216	0.745, 1.982	0.432
		Black	0.460	0.246, 0.860	0.940	0.479, 1.843	0.856
		Hispanic	0.336	0.159, 0.708	0.663	0.302, 1.454	0.292
	Fungi	White	0.129	0.081, 0.205	1.511	0.631, 3.617	0.341

Phase	Ethnicity	Rate/100 Days	95% CI	IRR*	95% CI	P Value
	Black	0.000		0.000		0.005
	Hispanic	0.186	0.077, 0.446	1.808	0.678, 4.816	0.265
Viruses	White	0.050	0.024, 0.105	0.588	0.206, 1.675	0.323
	Black	0.031	0.004 0.220	0.451	0.059, 3.451	0.390
	Hispanic	0.186	0.077, 0.446	4.017	1.346, 11.987	0.023

* IRR - incidence rate ratio. IRRs and p values compare white versus non-white children, black versus non-black children and hispanic versus non-hispanic children

TABLE 4

CAUSES OF FATAL INFECTIONS IN PHASE 1 OR PHASE 2 TREATMENT

		Number of Fatal Infections (N=33)*
Infection Type	**Bacteria**	**19 (57.6%)**
Gram Positive Bacteria	All Gram positive bacteria	11 (33.3%)
	CoNS	0
	Viridans group streptococci	4 (12.1%)
	Enterococcus species	2 (61%)
	Staphylococcus aureus	0
	Pneumococcus	0
	Others	5
Gram Negative Bacteria	All Gram negative bacteria	9 (27.3%)
	Pseudomonas species	4 (12.1%)
	Klebsiella species	0
	Escherichiae coli	1 (3.0%)
	Enterobacter species	1 (3.0%)
	Citrobacter species	0
	All other Gram negatives	3 (9.1%)
Fungi		14 (42.4%)
Yeasts		3 (9.1%)
Molds		11 (33.3%)
Viruses	Cytomegalovirus	1 (3.0%)

Abbreviations: CoNS - coagulase negative *Staphylococcus*

* Numbers do not add up to 33 because of multiple organisms associated with fatal infections

TABLE 5

COMPARISON OF PROPORTION OF FATAL INFECTIONS AND INTENSITY AND TYPE OF TREATMENT

		No. Patients	No. Fatal Infections	Proportion of Fatal Infections (95% CI)	P Value
Phase 1	Standard	335	3	0.9% (0.3, 2.4%)	0.004
	Intensive	343	19	5.5% (3.5, 8.3%)	
Phase 2*	Chemo Course 1	168	4	2.4% (0.8, 5.6%)	0.536[1], 0.505[2]
	Standard	65	1	1.5% (0.1, 7.4%)	0.577[3]
	Intensive	103	3	2.9% (0.8, 7.6%)	
	Autologous SCT	137	5	3.6% (1.4, 7.8%)	0.228[4]
	Standard	44	2	4.5% (0.8, 13.7%)	0.677
	Intensive	93	3	3.2% (0.9, 8.4%)	
	Allogeneic SCT	147	2	1.4% (0.3, 4.4%)	
	Standard	52	1	1.9% (0.2, 9.0%)	0.655
	Intensive	95	1	1.1% (0.1, 5.2%)	

Abbreviations: CI - confidence interval; SCT - stem cell transplantation; No - number

[1] chemotherapy vs. autologous

[2] chemotherapy vs. allogeneic

[3] standard vs. intensive (Phase 2 fatal infections by induction)

[4] autologous vs. allogeneic

* Phase 2 therapy mortality also shown according to whether patient was randomized to standard versus intensive timing in induction