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Original article

Infection-related complications during treatment for childhood acute lymphoblastic leukemia

Short title: Infection in children with ALL

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Background: Comprehensive studies on neutropenia and infection-related complications in patients with acute lymphoblastic leukemia (ALL) are lacking.

Patients and methods: We evaluated infection-related complications that were grade ≥3 on National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) and their risk factors in 409 children with newly diagnosed ALL throughout the treatment period.

Results: Of the 2420 infection episodes, febrile neutropenia and clinically or microbiologically documented infection were seen in 1107 and 1313 episodes, respectively. Among documented infection episodes, upper respiratory was the most common (*n*=389), followed by ear (*n*=151), bloodstream (*n*=147), and gastrointestinal (*n*=145) infections. These episodes were more common during intensified therapy phases such as remission induction and reinduction, but respiratory and ear infections, presumably viral in origin, also occurred during continuation phases. The 3-year cumulative incidence of infection-related death was low (1.0%±0.9%, *n*=4), including 2 from *Bacillus cereus* bacteremia. There was no fungal infection-related mortality. Age 1–9.9 years at diagnosis was associated with febrile neutropenia (*P*=0.002) during induction and febrile neutropenia and documented infection (both *P*<0.001) during later continuation. White race was associated with documented infection (*P*=0.034) during induction. Compared with low-risk patients, standard- and high-risk patients received more intensive therapy during early continuation and had higher incidences of febrile neutropenia (*P*<0.001) and documented infections (*P*=0.043). Furthermore, poor neutrophil surge after dexamethasone pulses during continuation, which can reflect the poor bone marrow reserve, was associated with infections (*P*<0.001).

Conclusions: The incidence of infection-related death was low. However, young age, white race, intensive chemotherapy, and lack of neutrophil surge after dexamethasone treatment were associated with infection-related complications. Close monitoring for prompt administration of antibiotics and modification of chemotherapy should be considered in these patients.

Clinical trials number: NCT00137111

Key words: acute lymphoblastic leukemia, children, infection

Key message: This study describes all infection-related complications throughout the treatment phases in children with ALL. Infection often occurs during intensive therapy phases such as induction and reinduction, but respiratory and ear infections occur throughout treatment. Younger age, white race, and lack of neutrophil surge after dexamethasone during continuation are risk factors for infection.

Introduction

The long-term survival of patients with acute lymphocytic leukemia (ALL) has increased to approximately 90% with risk-directed therapy and improved supportive care.[1] However, intensification and prolonged use of chemotherapeutic drugs are associated with the increased risk of infections.[2, 3] The frequency of treatment-related mortality in contemporary ALL trials is reported to be 2%–4%, mostly due to infections.[3, 4] Chemotherapy intensity, neutropenia, Down syndrome patients, and female gender are associated with a higher risk of infection-related deaths.[2-4] A minor modification in an intensive conventional induction regimen can lead to higher infection-related morbidity and mortality. For example, the substitution of prednisone (40 mg/m^2, daily) with dexamethasone (6 mg/m^2, daily) in an induction regimen resulted in a high incidence of sepsis (16 of 38 children with ALL, 42.1%) and in 4 toxic deaths (10.5%).[5] To prevent infection-related death, it is essential to evaluate the incidence and pattern of infection-related complications and associated risk factors in patients with ALL.

Therapy-induced infection-related complications in pediatric acute myeloid leukemia (AML) patients are well characterized.[6, 7] However, similar data on ALL patients are limited to those during induction therapy, and data throughout all treatment phases are lacking. We therefore evaluated the spectrum of and risk factors for infection-related complications throughout the entire treatment period in ALL patients treated with a contemporary regimen in a single protocol.

Methods and Patients

patients, treatment, and supportive care

This retrospective study was approved by the institutional review board and included ALL patients (*n*=409) treated in the Total XV study from June 2000 to October 2010 at St. Jude Children's Research Hospital (St. Jude).[8] Risk classification and treatment regimen are described elsewhere.[8] Patients received oral trimethoprim-sulfamethoxazole 3 days per week starting at day 15 of remission induction until 2 months off therapy for *Pneumocystis jiroveci* pneumonia prophylaxis. Apart from this, routine prophylactic antibiotics or antifungals or colony-stimulating factors were not administered. Patients were advised to wear a particulate filtration mask during the induction and reinduction phases or whenever ANC was $<0.5\times10^9$/L. All patients had a Port-a-Cath or central venous catheter, which was aseptically accessed as necessary for blood draw or drug infusion. Cefepime or ceftadizime was immediately administered for neutropenic patients with fever and suspected infections, and meropenem was given for those with abdominal symptoms. Vancomycin and tobramycin were added for gram-positive and gram-negative infections, respectively. Empiric antifungal agents (i.e., voriconazole, liposomal amphotericin B, caspofungin, or micafungin) were recommended for neutropenic patients with persistent fever of unclear etiology for 3 to 5 days.

infection and febrile neutropenia episodes

The National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) was used to define infection episodes, including febrile neutropenia and clinically or microbiologically documented infections, and episodes grade ≥3 were recorded prospectively. Data were discussed in biweekly multidisciplinary meetings to

confirm accuracy. Fever was defined as an oral temperature of 38.0°C for at least 1 h or a single oral temperature of 38.3°C. Neutropenia and profound neutropenia were defined as absolute neutrophil counts (ANCs) of $<0.5\times10^9$/L and $<0.1\times10^9$/L, respectively.[9] The duration of neutropenia was calculated as the percentage of actual neutropenia period (days) in the treatment duration (days). ANC responses were evaluated 1 week after dexamethasone and vincristine pulses. Responses were defined as poor when there was less than a 2-fold increase of ANC from a pre-dexamethasone ANC of $0.5–1.2\times10^9$/L, no increase in ANC from a pre-dexamethasone ANC $>1.2\times10^9$/L, or ANC $<1.0\times10^9$/L for a pre-dexamethasone ANC $<0.5\times10^9$/L. Definitions of the documented infections are given in the supplementary document.

statistical analysis

The treatment period was divided by chemotherapy intensity as follows: remission induction (6 weeks); consolidation (8 weeks); continuation weeks 1–6; reinduction I (weeks 7–9); continuation weeks 10–16; reinduction II (weeks 17–20); and continuation weeks 21–47, 48–71, 72–103, 104–120, and 121–146 (boys only). Incidences (events/100 patient-days) of febrile neutropenia and documented infections were calculated by the number of episodes divided by treatment duration and patient number during the phase.

Associations among clinical factors (age, sex, race, the presence of Down syndrome, white blood cell count at diagnosis, immunophenotype, treatment risk group, CNS status, and body mass index category at diagnosis), ANC, and infection events were evaluated. The Wilcoxon signed-rank test was used to compare the duration of

neutropenia. The Poisson regression model was applied to identify risk factors for infection events. Multivariate regression analysis was performed to identify multiple independent risk factors. Infection events during the 4-week block after dexamethasone and vincristine pulses were analyzed for their association with ANC response by the generalized estimation equation model. Adjustment for multiple hypothesis tests was not applied. All analyses were performed using SAS (r) Proprietary Software Version 9.3.

Results

infection-related complications

Supplementary Table S1 shows patient demographics and clinical characteristics (*n*=409). Supplementary Table S2 lists 2420 episodes of infection-related complications by treatment phase. Febrile neutropenia was the most common infection-related complication (*n*=1107 episodes), followed by documented infections of the upper respiratory tract (*n*=389), ear (*n*=151), bloodstream (*n*=147), and gastrointestinal tract (*n*=145). Incidences of febrile neutropenia and documented infections were higher during induction and the 2 phases of reinduction (Figure 1A). Lip/perioral, gastrointestinal, urinary tract, and fungal infections were also seen in these phases (Figure 1B). Bloodstream infections were mostly seen during induction, followed by reinduction II in which standard- and high-risk patients received high-dose cytarabine therapy. Skin infections were often seen in induction and between week 10 and reinduction II, and pneumonia was frequently seen in reinduction II (Figure 1C). Upper respiratory tract, ear, and catheter infections were seen throughout the treatment course

(Figure 1D), and upper respiratory tract and ear infections tended to increase toward the end of therapy.

Details of blood stream bacterial infections, fungal infections, and respiratory viral isolates are shown in supplementary Tables S3, S4, and S5, respectively.

Of the 409 patients, 4 (0.98%) died of infection: 2 patients died due to *Bacillus cereus* bacteremia during induction therapy on days 12 and 14, respectively, and 2 patients died of presumed septic shock. Postmortem culture in a patient showed *Clostridium* species and *Bacteroides caccae* in the cerebrospinal fluid after the second dose of high-dose methotrexate during consolidation. The other patient with Down syndrome had a presumed infection during continuation week 12, but the causative organism was not identified. The 3-year cumulative incidence of infection-related death was 1.0%±0.9%. No patient died from fungal infection.

absolute neutrophil counts during induction and continuation phases and infection

Because neutropenia is associated with the occurrence of infections, we evaluated the percentage of days with ANC $<0.1\times10^9$/L and ANC $<0.5\times10^9$/L during induction and continuation therapy (Table 1). The median duration of neutropenia (ANC $<0.5\times10^9$/L) was longer during induction (52.0%) than during continuation weeks 1–20 (16.0%) and 21–120 (11.0%). During induction, the longer neutropenia period (for both ANC $<0.1\times10^9$/L and $<0.5\times10^9$/L) was significantly associated with younger age (1–9.9 years) at diagnosis, low-risk subgroup, white race, and B-lineage ALL (all $P\leq0.002$). Female

gender was significantly associated with a longer duration of ANC <0.5x10^9/L (*P*=0.001).

For continuation weeks 1–20, age 1–9.9 years at diagnosis (*P*=0.012) and standard- and high-risk subgroups (*P*=0.007) were significantly associated with longer duration of ANC <0.5×10^9/L (Table 1). For continuation weeks 21–120, age 1–9.9 years at diagnosis was significantly associated with a longer duration of ANC <0.5×10^9/L (*P*=0.010), and white race was significantly associated with longer duration of ANC <0.1×10^9/L (*P*=0.044).

risk factors associated with infections

Table 2 lists the clinical factors significantly associated with infection-related complications. During induction, age 1–9.9 years at diagnosis was significantly associated with frequent febrile neutropenia (*P*=0.002) and white race was significantly associated with documented infection (*P*=0.034). Female gender was associated with higher frequencies of bloodstream infections (*P*=0.041). During continuation weeks 1–20, standard- and high-risk subgroups were associated with a higher incidences of febrile neutropenia (*P*<0.001) and documented infections (*P*=0.043) than the low-risk subgroup. For continuation weeks 21–120, age 1–9.9 years at diagnosis was associated with febrile neutropenia (*P*<0.001), documented infection (*P*<0.001), and upper respiratory infection (*P*=0.006). B-ALL (*P*=0.033) and underweight category (*P*=0.037) were also associated with febrile neutropenia.

Longer duration of ANC <0.5×10^9/L was associated with documented infections during induction (*P*<0.001), weeks 1–20 (*P*=0.009), and weeks 21–120 (*P*=0.050) as

well as bloodstream (*P*=0.003) and upper respiratory (*P*=0.022) infections during induction.

absolute neutrophil counts after dexamethasone and vincristine pulses and infection

Between continuation weeks 24 and 103, patients received dexamethasone and vincristine pulses every 4 weeks. ANC was significantly higher 1 week after the start of pulses (median 1.9×10^9/L, range 0–30.2 $\times10^9$/L) compared to the pre-treatment value (median 1.5×10^9/L, range 0–13.5 $\times10^9$/L) (*P*<0.001). Among the 6990 total treatment periods, patients had poor ANC responses in 3694 (52.8%) and good responses in 3296 periods (Table 3). Poor ANC response was significantly associated with a high frequency of infection. Among 984 infection episodes during this time period, 702 (71.3%) occurred in patients with poor ANC responses as compared to 282 (28.7%) in patients with good ANC responses (*P*<0.001), with an odds ratio of 2.47 (95% confidence interval: 2.12–2.88). Febrile neutropenia, upper respiratory tract infections, and ear infections were common (supplementary Table S6). When ANC responses were individually evaluated within each 4-week block between pulses, patients with poor responses had significantly higher risk of infections than those with good responses in 14 of 20 of the 4-week blocks (*P*<0.05) (supplementary Table S7).

Discussion

This is the first detailed report of all infection-related complications occurring throughout the entire treatment course of a uniformly treated cohort of patients with ALL. As

expected, febrile neutropenia and documented infections were common during the intensified chemotherapy phases (remission induction and reinduction phases). Intensive chemotherapy increases the frequency and duration of neutropenia, which is a major risk factor for infections.[2, 3] Bloodstream, lip/perioral, gastrointestinal, urinary tract, and fungal infections occurred during these phases of treatment, but upper respiratory tract and ear infections, presumably of viral origin because bacterial pathogens were rarely isolated, occurred throughout the treatment course and increased toward the end of therapy. Febrile neutropenia and documented infections, especially severe bacterial and invasive fungal infections, interfere with the uninterrupted administration of chemotherapy; therefore, reducing these events could further improve outcomes of leukemia treatment.

Compared with low-risk patients, standard- and high-risk patients received more intensive chemotherapy with asparaginase, anthracycline, and high-dose dexamethasone, in addition to 2 intensified reinduction phases during continuation weeks 1–20. Thus, they had significantly longer neutropenia periods and a higher frequency of infection episodes. Interestingly, age 1–9.9 years at diagnosis, compared to age ≥ 10 years at diagnosis, was associated with a significantly longer duration of neutropenia in all phases of treatment and with higher incidences of infections during induction and continuation weeks 21–120 when the chemotherapy intensity was not remarkably different between low-risk and standard- or high-risk patients. ALL therapy might induce a more profound immunocompromised status in younger patients, who not only have lower neutrophil counts but also impaired immunoglobulin production and less immunologic memory. White and female patients had a longer duration of neutropenia

during induction and a higher frequency of documented infections and bloodstream infections, respectively. It is possible that because of pseudo-neutropenia due to a minor reduction in hematopoietic myeloid progenitors at steady state,[10] African-American patients received less intensity of chemotherapy. ALL groups in the United Kingdom and Nordic countries reported increased treatment-related mortality in females.[3, 4] The Nordic group speculated gender differences in immunologic response to infections or in toxicity after cytotoxic chemotherapy,[4] which might explain the longer duration of neutropenia during induction therapy in our study. Underweight patients had a higher incidence of febrile neutropenia in later continuation. Their immune responses can be impaired because of decreased production of complement, cytokines, and immunoglobulins due to malnutrition.[11] Whether a reduction of chemotherapy intensity with or without novel molecular targeting agents or immunotherapy leads to a decrease in infection-related complications without compromising overall treatment outcome merits further study.[1]

The cumulative risk of infection-related mortality in our study (1.0%) is lower than that in other trials (1.7%–2.4%), although different treatment regimens make direct comparison difficult. Patients were instructed to call our medical staff first if a febrile episode occurred, and IV antibiotics were available immediately upon arrival. However, there were 2 cases of fatal *B. cereus* bacteremia during induction therapy, which can cause fatal fulminant infection with a short interval between onset and irreversible injury.[12] Induction chemotherapy, presence of neutropenia, administration of glucocorticoids or third-generation cephalosporins, lumbar puncture with intrathecal chemotherapy, and tea consumption are risk factors associated with this severe

infection-related complication.[12] It is unlikely that third- and fourth-generation cephalosporin monotherapy (e.g., ceftazidime and cefepime), which is commonly used as empiric therapy for patients with febrile neutropenia, can eliminate *B. cereus* bacteremia; vancomycin and/or meropenem need to be given.[12] We also instruct patients not to consume tea made from a ball or bag, but allow bottled pasteurized tea. One of our patients with Down syndrome also had a fatal infection-related episode. Increased risk for infection-related complications in patients with Down syndrome is well recognized, and they require special attention.[3] We did not observe fungal infection–related mortality, although it has accounted for as many as 20% of cases of infection-related mortality in some studies.[3] We also captured all possible invasive fungal infection episodes, not limited to the revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG), and identified these in 31 of 409 (7.6%) patients (supplementary Table S4). This rate is much lower than that from another study reporting proven or probable invasive fungal infection in 30 of 125 (24.0%) patients by using EORTC/MSG criteria.[13] This difference might be due to close monitoring of patients especially during induction and reinduction phases, use of particle filtration masks, early initiation of empiric broad-spectrum antifungal therapy, or different disease epidemiology in our study. Patients receiving prolonged continuation chemotherapy are likely to have frequent viral infections (upper respiratory tract or ear infections), especially in the winter months, as shown in our patient cohort. ALL therapy also induces profound B-cell lymphopenia with abnormally low IgG and IgM levels

during continuation therapy and impairs seroconversion after influenza virus vaccinations.[14] Patients were also allowed to attend schools and other social activities after week 21 of the continuation phase, which increased their susceptibility to community-acquired pathogens. As previously suggested,[3] antibiotics and antifungal prophylaxis could be considered in patients with prolonged neutropenia during intensive phases of treatment (i.e., induction and reinduction phases) and in those at risk such as those with Down syndrome. Several studies have shown a potential reduction in infection with fluoroquinolone prophylaxis without an increase in the incidence of fungal infections.[15, 16] However, further evaluation is required to assess the efficacy and potential harms of prophylaxis in this population. For patients with hypogammaglobulinemia or frequent infection episodes, intravenous immunoglobulin replacement can be considered.

Our continuation therapy included monthly pulses of dexamethasone and vincristine. Dexamethasone can induce marrow release, reduce egress into tissue, delay apoptosis of polymorphonuclear leukocytes, and promote demargination of granulocytes by downregulating L-selectin expression.[17, 18] Thus, the finding of a significantly increased risk of infection in the absence of a granulocyte surge after the dexamethasone block is likely related to decreased bone marrow reserve. Therefore, in the current Total Therapy study for childhood ALL, we decrease the doses or hold subsequent myelosuppressive chemotherapy if ANCs do not increase after dexamethasone pulses. Prolonged use of dexamethasone during the continuation phase is also associated with an increased risk of severe infection and death.[19] As randomized studies with or without dexamethasone and vincristine pulses during

continuation therapy did not show survival benefit for intermediate-risk ALL patients,[20] it is important to evaluate the effects of pulses on survival and infection in all risk groups of ALL.

In conclusion, infection-related complications are associated with young age, white race, intensive chemotherapy, and lack of neutrophil surge after dexamethasone treatment. These findings can be useful to devise future therapeutic interventions, such as close monitoring of patients, use of prophylactic antibiotics, administration of immunoglobulins, modifications of chemotherapy dosing based on bone marrow reserve, or the rational reduction of intensity of chemotherapy regimen stratified by leukemia risk factors.

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disclosure

The authors declare no competing interests.

references

1. Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Lancet 2013; 381: 1943-1955.
2. Afzal S, Ethier MC, Dupuis LL et al. Risk factors for infection-related outcomes during induction therapy for childhood acute lymphoblastic leukemia. Pediatr Infect Dis J 2009; 28: 1064-1068.
3. O'Connor D, Bate J, Wade R et al. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003. Blood 2014; 124: 1056-1061.
4. Christensen MS, Heyman M, Mottonen M et al. Treatment-related death in childhood acute lymphoblastic leukaemia in the Nordic countries: 1992-2001. Br J Haematol 2005; 131: 50-58.
5. Hurwitz CA, Silverman LB, Schorin MA et al. Substituting dexamethasone for prednisone complicates remission induction in children with acute lymphoblastic leukemia. Cancer 2000; 88: 1964-1969.
6. Sung L, Lange BJ, Gerbing RB et al. Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia. Blood 2007; 110: 3532-3539.
7. Inaba H, Gaur AH, Cao X et al. Feasibility, efficacy, and adverse effects of outpatient antibacterial prophylaxis in children with acute myeloid leukemia. Cancer 2014; 120: 1985-1992.
8. Pui CH, Campana D, Pei D et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med 2009; 360: 2730-2741.
9. Freifeld AG, Bow EJ, Sepkowitz KA et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis 2011; 52: e56-93.
10. Hsieh MM, Tisdale JF, Rodgers GP et al. Neutrophil count in African Americans: lowering the target cutoff to initiate or resume chemotherapy? J Clin Oncol 2010; 28: 1633-1637.
11. Chandra RK. Nutrition and the immune system from birth to old age. Eur J Clin Nutr 2002; 56 Suppl 3: S73-76.
12. Gaur AH, Patrick CC, McCullers JA et al. Bacillus cereus bacteremia and meningitis in immunocompromised children. Clin Infect Dis 2001; 32: 1456-1462.
13. Sahbudak Bal Z, Yilmaz Karapinar D, Karadas N et al. Proven and probable invasive fungal infections in children with acute lymphoblastic leukaemia: results from an university hospital, 2005-2013. Mycoses 2015; 58: 225-232.
14. Caver TE, Slobod KS, Flynn PM et al. Profound abnormality of the B/T lymphocyte ratio during chemotherapy for pediatric acute lymphoblastic leukemia. Leukemia 1998; 12: 619-622.
15. Sulis ML, Blonquist TM, Athale UH et al. Effectiveness of Antibacterial Prophylaxis during Induction Chemotherapy in Children with Acute Lymphoblastic Leukemia. Blood 2015; 126: 249-249.
16. Yeh TC, Liu HC, Hou JY et al. Severe infections in children with acute leukemia undergoing intensive chemotherapy can successfully be prevented by ciprofloxacin, voriconazole, or micafungin prophylaxis. Cancer 2014; 120: 1255-1262.

17. Nakagawa M, Bondy GP, Waisman D et al. The effect of glucocorticoids on the expression of L-selectin on polymorphonuclear leukocyte. Blood 1999; 93: 2730-2737.
18. Weber PS, Toelboell T, Chang LC et al. Mechanisms of glucocorticoid-induced down-regulation of neutrophil L-selectin in cattle: evidence for effects at the gene-expression level and primarily on blood neutrophils. J Leukoc Biol 2004; 75: 815-827.
19. Te Poele EM, de Bont ES, Marike Boezen H et al. Dexamethasone in the maintenance phase of acute lymphoblastic leukaemia treatment: is the risk of lethal infections too high? Eur J Cancer 2007; 43: 2532-2536.
20. Conter V, Valsecchi MG, Silvestri D et al. Pulses of vincristine and dexamethasone in addition to intensive chemotherapy for children with intermediate-risk acute lymphoblastic leukaemia: a multicentre randomised trial. Lancet 2007; 369: 123-131.

figure legend

Figure 1. Incidences of infection-related complications during therapy in children with acute lymphoblastic leukemia. (A) All infections (combined), febrile neutropenia (FN), and documented infections (documented). (B) Lip/perioral, gastrointestinal (GI), urinary tract (UTI), and fungal infections. (C) Bloodstream infections, skin infections, and pneumonia. (D) Upper respiratory (URI), ear, and catheter infections. Incidence (events/100 patient-days) was calculated by the number of episodes divided by treatment duration and patient number during the phase.

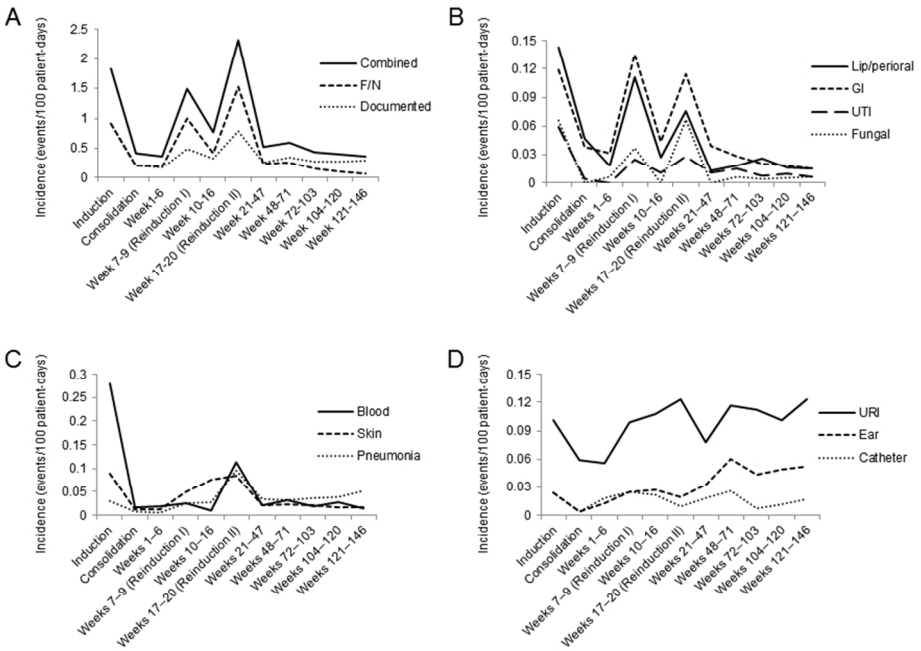

Figure 1

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Table 1. Association of clinical factors with the duration of neutropenia by treatment phase

			*N**	ANC<0.1x10^9/L			ANC<0.5x10^9/L		
				Median (%)	Range (%)	*P*	Median (%)	Range (%)	*P*
Induction									
	All patients		385	8.0	0.0-68.0		52.0	0.0-98.0	
	Age group								
		1–9.9 years	283	10.0	0.0-68.0	<0.001	56.0	0.0-100.0	<0.001
		≥10 years	102	0.0	0.0-60.0		39.5	0.0-96.0	
	Risk group								
		Low risk	187	13.0	0.0-68.0	<0.001	58.0	0.0-100.0	<0.001
		Standard or high risk	198	3.0	0.0-60.0		45.0	0.0-98.0	
	Gender								
		Female	173	8.0	0.0-68.0	0.231	57.0	0.0-116.0	0.001
		Male	212	8.0	0.0-64.0		47.5	0.0-96.0	
	Race								
		White	304	10.0	0.0-68.0	<0.001	55.5	0.0-100.0	<0.001
		Other	81	0.0	0.0-45.0		40.0	0.0-93.0	
	Immunophenotype								
		B-lineage	328	9.5	0.0-68.0	0.002	56.0	0.0-100.0	<0.001
		T-lineage	57	0.0	0.0-50.0		32.0	0.0-93.0	
Continuation weeks 1-20									
	All patients		365	0.0	0.0-32.0		16.0	0.0-72.0	
	Age group								
		1–9.9 years	282	0.0	0.0-25.0	0.068	19.0	0.0-72.0	0.012
		≥10 years	83	0.0	0.0-32.0		11.0	0.0-60.0	
	Risk group								
		Low risk	196	0.0	0.0-24.0	0.299	15.0	0.0-72.0	0.007
		Standard or high risk	169	0.0	0.0-32.0		20.0	0.0-67.0	
	Gender								
		Female	165	0.0	0.0-25.0	0.941	19.0	0.0-72.0	0.091
		Male	200	0.0	0.0-32.0		15.0	0.0-60.0	
	Race								
		White	289	0.0	0.0-32.0	0.318	17.0	0.0-72.0	0.197
		Other	76	0.0	0.0-24.0		15.5	0.0-59.0	
	Immunophenotype								
		B-lineage	314	0.0	0.0-32.0	0.204	16.0	0.0-72.0	0.785
		T-lineage	51	0.0	0.0-26.0		15.0	0.0-56.0	
Continuation weeks 21-120									
	All patients		350	2.0	0.0-10.0		11.0	0.0-41.0	
	Age group								
		1–9.9 years	271	2.0	0.0-10.0	0.127	12.0	0.0-41.0	0.010
		≥10 years	79	0.0	0.0-10.0		9.0	0.0-35.0	
	Risk group								
		Low risk	186	2.0	0.0-10.0	0.595	11.0	0.0-33.0	0.363
		Standard or high risk	164	2.0	0.0-10.0		11.0	0.0-41.0	
	Gender								
		Female	161	2.0	0.0-10.0	0.063	11.0	0.0-41.0	0.757
		Male	189	1.0	0.0-10.0		11.0	0.0-35.0	
	Race								
		White	278	2.0	0.0-10.0	0.044	12.0	0.0-35.0	0.164
		Other	72	0.0	0.0-10.0		10.0	0.0-41.0	
	Immunophenotype								
		B-lineage	303	2.0	0.0-10.0	0.620	11.0	0.0-35.0	0.796
		T-lineage	47	2.0	0.0-8.0		10.0	0.0-41.0	

Abbreviations: ANC, absolute neutrophil count.

*Data for ANCs not available for all patients.

†Duration of neutropenia was calculated as the percentages of actual neutropenia period (days) among treatment duration (days).

#No significant differences were seen among groups based on the presence of Down syndrome, white blood cell count at diagnosis, central nervous system status, or body mass index category at diagnosis.

Table 2. Clinical factors significantly associated with infection-related complications

Infection event	Clinical factors	Poisson regression analysis		Multiple Poisson regression analysis*	
		Estimates	*P*	Estimates	*P*
Induction					
Febrile neutropenia					
	Age 1–9.9 years vs ≥10 years at diagnosis	2.03	0.002	2.04	0.002
	White vs. others	1.61	0.039	1.52	0.071
	Obese vs. healthy weight	1.63	0.027	1.34	0.107
Documented infection					
	White vs. others	1.60	0.034	1.61	0.034
	Obese vs. healthy weight	1.55	0.035	1.27	0.181
	Duration of ANC <0.5x10^9/L	1.02	<0.001		
Bloodstream infection					
	Female vs. male	1.84	0.041		
	Duration of ANC <0.5x10^9/L	1.02	0.003		
Upper respiratory infection					
	Duration of ANC <0.5x10^9/L	1.03	0.022		
Continuation weeks 1 to 20					
Febrile neutropenia					
	Low vs. standard or high risk	0.62	<0.001	0.64	<0.001
	B-lineage vs. T-lineage	0.74	0.021	0.93	0.628
Documented infection					
	Age 1–9.9 years vs ≥10 years at diagnosis	0.73	0.026	0.84	0.268
	Low vs. standard/high risk	0.69	0.006	0.74	0.043
	Duration of ANC <0.5x10^9/L	1.01	0.009		
Continuation weeks 21 to 120					
Febrile neutropenia					
	Age 1–9.9 years vs ≥10 years at diagnosis	1.79	<0.001	1.73	<0.001
	Low vs. standard/high risk	1.25	0.011	0.91	0.370
	White vs. others	1.26	0.048	1.20	0.123
	B- vs. T-lineage	1.65	0.001	1.44	0.033
	Initial WBC count <100x10^9/L vs. ≥100x10^9/L	1.63	0.002	1.33	0.121
	Underweight vs. healthy weight	1.51	0.002	1.29	0.037
Documented infection					
	Age 1–9.9 years vs ≥10 years at diagnosis	1.57	<0.001	1.57	<0.001
	Low vs. standard or high risk	1.15	0.044	0.93	0.416
	Female vs. male	1.18	0.016	1.15	0.056
	B- vs. T-lineage	1.23	0.042	1.05	0.672
	Initial WBC count <100x10^9/L vs. ≥100x10^9/L	1.34	0.010	1.29	0.058
	Underweight vs. healthy weight	1.49	<0.001	1.01	0.882
	Duration of ANC <0.5x10^9/L	1.01	0.050		
Upper respiratory infection					
	Age 1–9.9 years vs ≥10 years at diagnosis	1.59	0.007	1.61	0.006
	Underweight vs. healthy weight	1.51	0.047	0.90	0.507

Abbreviations: ANC, absolute neutrophil count; WBC, white blood cell

*Multiple analysis was performed when there were 2 or more significant clinical presenting factors by univariate analysis. Duration of ANC <0.5x10^9/L was not included in the model. Two-sided *P* values <0.05 are listed.

Table 3. Infection events based on changes in absolute neutrophil counts after dexamethasone and vincristine pulses

ANC response	ANC pre/post pulse	Infection	No infection	Total	*P*	OR (95%CI)
Poor		702	2992	3694	<0.001	2.47 (2.12-2.88)
	(500 to 1200/no doubling)	(234)	(1045)	(1279)		
	(>1200/no increase)	(386)	(1712)	(2098)		
	(<500/<1000)	(82)	(235)	(317)		
Good		282	3014	3296		
Total		**984**	**6006**	**6990**		

Abbreviations: ANC, absolute neutrophil counts; OR, odds radio; CI, confidence interval.