IDR group, and 525 to the DNR group. The two groups were well balanced for pretreatment characteristics such as age, initial WBC counts, FAB classification, and cytogenetic prognostic grouping.

Response to Induction Therapy

Overall, of 1,057 evaluable patients, 823 (77.9%) achieved CR. Of 532 patients in the IDR group, 416 (78.2%) achieved CR, and of 525 in the DNR group, 407 (77.5%) obtained it (P = 0.79). Non-inferiority for the primary end point was assessed by determining whether the lower bound of the 95% confidence interval (CI) of the difference between the CR rates for DNR and IDR groups was less than - 10%. The CR rate of the DNR group was non-inferior to that of the IDR group (Table 2). In the IDR group, 341 (64.1%) patients achieved CR after the first course, and in the DNR group, 321 (61.1%) did so (P = 0.39). The average period to achieve CR was 33.8 days (95% CI, 32.9 to 34.6) in the IDR group and 32.4 days (95% CI, 31.6 to 33.2) in the DNR group (P = 0.038). CR rates related to FAB classification, age, and cytogenetics are shown in Table 3. Although they were few in number, patients with FAB M6 responded better to IDR: 78% of 17 patients in the IDR group and 38% of 16 in the DNR group achieved CR (P = 0.037). There were no differences in CR rate between the two groups in other FAB subtypes, cytogenetic risk groups, age, myeloperoxidase (MPO) positivity of blasts, initial WBC count, and performance status (Table 3). Overall, logistic regression analysis revealed that induction regimen was not an independent prognostic factor but that cytogenetic group and percentage of MPO-positive

blasts were significant independent factors for achieving CR (Table 4). Cut-off value of WBC at 20 or 50 x 10^9/L did not change the result.

OS and RFS

At a median follow-up of 48 months, 5-year predicted OS rates were 48% for the IDR group (95% CI, 43% to 53%) and 48% for the DNR group (95% CI, 43% to 53%; P = 0.54) (Fig. 2a), and 5-year predicted RFS rates of CR patients were 41% (95% CI, 36% to 46%) and 41% (95% CI, 35% to 45%), respectively (P = 0.97) (Fig. 2b). Significant unfavorable prognostic features for OS by the Cox proportional hazard model were adverse cytogenetic risk group, age of more than 50 years, WBC more than 20 x 10^9/L, MPO-positive blasts less than 50%, and FAB classification of either M0, M6, or M7, and for RFS, adverse cytogenetic risk group, WBC more than 20 x 10^9/L, MPO-positive blasts less than 50%, LDH of 500 IU/L or more, and age of more than 50 years. Induction regimen was not an independent prognostic factor for either OS or RFS by this multivariate analysis.

Adverse Events

Patients receiving IDR required a slightly but significantly longer time to recover from neutropenia and thrombocytopenia. Median duration with a neutrophil count less than 1.0 x 10^9/L was 28 days for the IDR group and 27 days for the DNR group (P = 0.0011) (Fig. 3a). Median duration with a platelet count less than 100 x 10^9/L was 25 days for the IDR group and 24 days for the DNR group (P = 0.0034) (Fig. 3b). Sepsis occurred more frequently in the IDR group than in the DNR group (8.7% and 4.9%,

respectively, $P = 0.02$). Early death within 60 days occurred more frequently in the IDR group than in the DNR group (4.7% and 2.1%, respectively, $P = 0.03$, Table 5).

Post-remission Therapy

Of the 823 CR patients, 781 patients were randomly assigned to receive either 4 courses of conventional standard-dose consolidation therapy (392 patients) or 3 courses of high-dose Ara-C therapy (389 patients), and 136 patients (16% of CR patients) underwent allogeneic SCT in the first CR. There was no significant difference in OS and RFS by post-remission therapy between IDR and DNR groups (Table 6). In IDR group predicted 5-year OS rates were 57% for the conventional standard-dose consolidation arm (95% CI, 49% to 65%) and 58% for the high-dose Ara-C arm (95% CI, 51% to 66%; P = 0.79, Fig. 4a). In DNR group predicted 5-year OS rates were 56% (95% CI, 48% to 63%) and 58% (95% CI, 50% to 65%; P = 0.71, Fig. 4b), respectively. If two groups were evaluated together, predicted 5-year OS rates were 56% (95% CI, 51% to 62%) and 58% (95% CI, 53% to 62%; P = 0.95), and predicted 5-year RFS rates were 39% (95% CI, 34% to 44%) and 43% (95% CI, 38% to 48%), respectively (P = 0.72). The detailed results of this consolidation phase will be reported in a separate paper (S.M., S.O. and R.O., manuscript submitted to *Blood*).

Discussion

The present randomized study demonstrates that if the dose intensity is appropriately increased, DNR is as effective as a standard dose of IDR for

newly diagnosed adult patients aged less than 65 with AML. Remission induction therapy using 50 mg/m^2 DNR for 5 days resulted in almost the same CR rate and long-term outcome as those using 12 mg/m^2 IDR for 3 days, in combination with 100 mg/m^2 Ara-C for 7 days. Generally, DNR is used at a dose of 45 to 50 mg/m^2 for 3 days in combination with 100 to 200 mg/m^2 Ara-C for 7 days, and 50 to 70% of newly diagnosed adult patients with AML achieve CR. As stated in the introduction section, JALSG used a response-oriented individualized induction therapy in the AML87, AML89, and AML92 studies for AML, which permitted an additional DNR and other anti-leukemia drugs to be administered according to the bone marrow status on day 8 or later.[12-14] The CR rates in these 3 studies ranged from 77 to 80% and the median total dose of DNR was 240 mg/m^2.

On the basis of these experiences and also owing to the regulation of our national medical insurance system, we employed a dose and schedule of DNR of 50 mg/m^2 for 5 days, that is, a total dose of 250 mg/m^2. Additionally we avoided higher daily doses such as 80 mg/m^2 for 3 days, because higher plasma concentration might cause more cardiotoxicity in older patients.[22]

Three randomized studies in the early 1990s[4-6] as well as subsequent studies[23, 24] and meta-analyses[7] reported a superior effect of IDR (12 to 13 mg/m^2 x 3 days) over that of DNR (45 to 50 mg/m^2 x 3 days), in combination with Ara-C, and AML patients receiving IDR obtained 70 to 80% CR without a significant increase in toxic mortality, while those receiving DNR achieved 58 to 65% CR.[4-6] However, because the duration of neutropenia and thrombocytopenia was longer in the IDR groups, it was questioned whether the doses used in these comparisons were equivalent in terms of levels of

toxicity and whether any observed advantage represented an inherent biologic advantage of IDR rather than biologic dose equivalence.[1, 2]

In these randomized studies, Wiernik et al. reported that patients with more than 50 x 10^9/L initial WBC counts obtained only 32% CR by the DNR regimen compared with 68% CR by the IDR regimen, while patients with less than 50 x 10^9/L WBC obtained 65% and 69% CR, respectively[5]. Berman et al. also reported that patients in the IDR group did well regardless of their initial WBC, whereas patients in the DNR group had a decreased response rate as the WBC increased[4]. In the present study, however, a total of 250 mg/m^2 of DNR resulted in almost the same CR rate as a total of 36 mg/m^2 of IDR regardless of initial WBC counts and other prognostic factors such as cytogenetics, age, and FAB classification except M6. Although, among patients with FAB M6, 16 patients in the DNR group had significantly lower CR rate than 17 patients in the IDR group, we have no clear explanation for this observation, because the small number of patients made the further analysis difficult. Thus, the increased total dose of DNR administered in 5 days would be responsible for almost the same satisfactory CR rate and long-term outcome as IDR in 3 days in the present study. As for adverse events, the recovery from neutropenia and thrombocytopenia was slightly but significantly delayed in the IDR group, and sepsis and early mortality occurred more frequently in the IDR group, as shown in Fig. 3 and Table 5.

Before we initiated this AML201 study, there was no evidence that a higher dose of DNR is more effective than its standard dose owing to the lack of a prospective randomized study. In the sequential studies reported by Southwest Oncology Group, however, the CR rate with DNR at a dose of 70

mg/m^2 was better than that with 45 mg/m^2.[25, 26] Very recently, two groups reported that a higher dose of DNR improved the CR rate and OS in prospective randomized studies.[27, 28] The Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON), German AML Study Group (AMLSG) and Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group compared 3-day DNR at 90 mg/m^2 with 3-day DNR at 45 mg/m^2, in combination with 7-day Ara-C, in elderly patients aged 60 to 83 years with AML or high-risk refractory anemia, and reported a higher CR rate for the escalated-treatment group (52% versus 35%, P = 0.002).[27] Although survival end points did not differ significantly overall, among patients aged 60 to 65 years CR rate (73% versus 51%) and OS (38% versus 23%) were significantly higher for the 90 mg/m^2 group. Eastern Cooperative Oncology Group also compared 3-day DNR at 90 mg/m^2 with 3-day DNR at 45 mg/m^2, in combination with 7-day Ara-C, in patients aged 17 to 60 years with AML, and reported higher CR rate (70.6% versus 57.3%, $P < 0.001$) and longer OS (median, 23.7 months versus 15.7 months, P = 0.003) for the high-dose group.[28] With these reports and ours taken together, the optimal total dose of DNR is still to be explored but may rest somewhere between 250 to 270 mg/m^2. Since we used the FAB classification in this study, we did neither include patients with 20 to 30% of blasts in the bone marrow nor those with refractory anemia with excess blasts. Therefore, it is unclear whether our result is applicable to these patients.

IDR is a derivative of DNR and differs from its parent compound by the deletion of a methoxy group at position 4 of the chromophore ring. *In vitro* and preclinical data have shown that IDR is more lipophilic, faster in cellular

uptake, exhibits increased cellular retention, lower in susceptibility to p-glycoprotein-dependent resistance, and less cardiotoxic than DNR. Both IDR and DNR undergo conversion to their respective alcohol metabolites, idarubicinol and daunorubicinol. Unlike the latter, idarubicinol has a prolonged plasma half-life and is thought to have a pharmacological advantage.[29-32]

The pediatric Berlin-Frankfurt-Münster (BFM) group previously compared 12 mg/m^2 IDR for 3 days with 30 mg/m^2 DNR twice daily for 3 days, in combination with Ara-C and etoposide, and reported almost the same CR rates (85% versus 86%, respectively) and predicted 5-year event-free survival (55% versus 49%, respectively, P = 0.29) in newly diagnosed childhood AML.[33] Furthermore, DNR at a dose of 60 mg/m^2 for 3 days as well as IDR at a dose of 12 mg/m^2 for 3 days achieved similar CR rates in the studies by Eastern Cooperative Oncology Group that consisted of a large number of adult patients.[34, 35]

Recently, French Acute Leukemia Association reported a randomized study comparing standard doses of IDA (12 mg/m^2 for 3 days) with high doses of DNR (80 mg/m^2 for 3 days) or IDA (12 mg/m^2 for 4 days) for remission induction in newly diagnosed elderly patients aged 50 to 70 years (median, 60) with AML.[36] CR rates were significantly higher for the standard-dose IDA group (83%) compared with the high-dose DNR group (70%, P = 0.007) but not compared with the high-dose IDR group (78%, P = 0.12). Although OS, relapse incidence, and event-free survival were not different among the 3 arms, DNR (80 mg/m^2 for 3 days) did not improve the CR rate of elderly AML up to the level of the standard-dose IDR.

As for adverse events, recovery from myelosuppression was faster and sepsis was less frequent in the DNR group. Both acute and late-onset cardiotoxicity was only reported in a small number of patients in both groups. Knowing that there was no increase in severe cardiac toxicities in patients receiving high-dose DNR (90 mg/m^2 for 3 days) compared with standard-dose DNR (45 mg/m^2 for 3 days) in the ECOG study (7.9% and 7.2%, respectively) [28], DNR may not necessarily be administered for 5 days as in the present study (50 mg/m^2 for 5 days), although further follow-up observation is needed for late-onset cardiotoxicity.

After the landmark study of Cancer and Leukemia Group B[37], it has been believed that high-dose Ara-C was superior to consolidation therapy that contained intermediate (400 mg/m2 for 5 days) or conventional (100mg/m2 for 5 days) dose of Ara-C. In this study we prospectively compared high-dose Ara-C with consolidation therapy that contained conventional dose of Ara-C and non-cross resistant agents. Our results clearly demonstrated that there was no difference in RFS and OS between the two consolidation arms, even if we used either IDR or DNR as induction chemotherapy.

In conclusion, the intensified dose of DNR in the present setting, that is, 50 mg/m^2 for 5 days, proved to be biologically equivalent in terms of efficacy and not more toxic in terms of myelosuppression compared with the standard dose and schedule of IDR, that is, 12 mg/m^2 for 3 days, for remission induction therapy in newly diagnosed younger patients aged 15 to 64 years (median, 47) with AML.

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Authorship

Contribution: S.O. designed and performed research, collected and interpreted data, and wrote the manuscript; S.M. designed and performed research, analyzed data, and participated in writing the manuscript; H.F., H.K., K.S., N.U., H.O., K.M., C.N., Y.M., A.F., T.N., T.Y., M.T., M.T., F.Y., Y.K., N.A., H.S., and H.H. performed research; S.H. analyzed data; K.O. and T.N. conducted and performed research; and R.O. conducted research, interpreted data, and participated in writing the manuscript.

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References

1. Rowe JM, Tallman MS. Intensifying induction therapy in acute myeloid leukemia: has a new standard of care emerged? *Blood.* 1997;90(6):2121-2126.
2. Löwenberg B, Downing JR, Burnett A. Acute myeloid leukemia. *N Engl J Med.* 1999;341(14):1051-1062.
3. Tallman MS, Gilliland DG, Rowe JM. Drug therapy for acute myeloid leukemia. *Blood.* 2005;106(4):1154-1163.
4. Berman E, Heller G, Santorsa J, et al. Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adult patients with newly diagnosed acute myelogenous leukemia. *Blood.* 1991;77(8):1666-1674.
5. Wiernik PH, Banks PL, Case DC Jr, et al. Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. *Blood.* 1992;79(2):313-319.
6. Vogler WR, Velez-Garcia E, Weiner RS, et al. A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukemia: a Southeastern Cancer Study Group Study. *J Clin Oncol.* 1992;10(7):1103-1111.
7. The AML Collaborative Group. A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. *Br J Haematol.* 1998;103(1):100-109.

8. Berman E, Wiernik P, Vogler R, et al. Long-term follow-up of three randomized trials comparing idarubicin and daunorubicin as induction therapies for patients with untreated acute myeloid leukemia. *Cancer*. 1997;80(11 Suppl):2181-2185.

9. Ohtake S, Miyawaki S, Kiyoi H, et al. Randomized trial of response-oriented individualized versus fixed-schedule induction chemotherapy with idarubicin and cytarabine in adult acute myeloid leukemia: the JALSG AML95 study. *Int J Hematol*. 2010;91(2):276-283

10. Miyawaki S, Sakamaki H, Ohtake S, et al. A randomized, postremission comparison of four courses of standard-dose consolidation therapy without maintenance therapy versus three courses of standard-dose consolidation with maintenance therapy in adults with acute myeloid leukemia: the Japan Adult Leukemia Study Group AML 97 Study. *Cancer*. 2005;104(12):2726-2734.

11. Sakamaki H, Miyawaki S, Ohtake S, et al. Allogeneic stem cell transplantation versus chemotherapy as post-remission therapy for intermediate or poor risk adult acute myeloid leukemia: results of the JALSG AML97 study. *Int J Hematol*. 2010;91(2):284-292.

12. Ohno R, Kobayashi T, Tanimoto M, et al. Randomized study of individualized induction therapy with or without vincristine, and of maintenanceintensification therapy between 4 or 12 courses in adult acute myeloid leukemia. AML-87 Study of the Japan Adult Leukemia Study Group. *Cancer*. 1993;71(12):3888-3895.

13. Kobayashi T, Miyawaki S, Tanimoto M, et al. Randomized trials between behenoyl cytarabine and cytarabine in combination induction

and consolidation therapy, and with or without ubenimex after maintenance/intensification therapy in adult acute myeloid leukemia. The Japan Leukemia Study Group. *J Clin Oncol*. 1996;14(1):204-213.

14. Miyawaki S, Tanimoto M, Kobayashi T, et al. No beneficial effect from addition of etoposide to daunorubicin, cytarabine, and 6-mercaptopurine in individualized induction therapy of adult acute myeloid leukemia: the JALSG-AML92 study. *Int J Hematol*. 1999;70(2):97-104.
15. Usui N, Dobashi N, Kobayashi T, et al. Role of daunorubicin in the induction therapy for adult acute myeloid leukemia. *J Clin Oncol* 1998;16(6):2086-2092.
16. Grimwade D, Walker H, Oliver F, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. *Blood*. 1998;92(7):2322-2333
17. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003;21(24):4642-4649.
18. Blackwelder WC. "Proving the null hypothesis" in clinical trials. *Control Clin Trials*. 1982;3(4):345-353.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457-481.
20. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc A*. 1972;135(2):185-206.

21. Cox DR. Regression models and life tables. *J R Stat Soc B*. 1972;34:187-220.

22. Speyer J, Wasserheit C. Strategies for reduction of anthracycline cardiac toxicity. *Semin Oncol*. 1998;25(5):525-537

23. Mandelli F, Petti MC, Ardia A, et al. A randomised clinical trial comparing idarubicin and cytarabine to daunorubicin and cytarabine in the treatment of acute non-lymphoid leukaemia. A multicentric study from the Italian Co-operative Group GIMEMA. *Eur J Cancer*. 1991;27(6):750-755.

24. Reiffers J, Huguet F, Stoppa AM, et al. A prospective randomized trial of idarubicin vs daunorubicin in combination chemotherapy for acute myelogenous leukemia of the age group 55 to 75. *Leukemia*. 1996;10(3):389-395.

25. Hewlett J, Kopecky KJ, Head D, et al. A prospective evaluation of the roles of allogeneic marrow transplantation and low-dose monthly maintenance chemotherapy in a treatment for adult acute myelogenous leukemia (AML): a Southwest Oncology Group study. *Leukemia*. 1995;9(4):562-569.

26. Weick JK, Kopecky TJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previosly untreated acute myeloid leukemia: a Southwest Oncology Group study. *Blood*. 1996;88(8):2841-2851.

27. Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1235-1248.

28. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1249-1259.

29. Berman E, McBride M. Comparative cellular pharmacology of daunorubicin and idarubicin in human multidrug-resistant leukemia cells. *Blood*. 1992;79(12):3267-3273.

30. Carella AM, Berman E, Maraone MP, Ganzina F. Idarubicin in the treatment of acute leukemias. An overview of preclinical and clinical studies. *Haematologica*. 1990;75(2):159-169.

31. Kuffel MJ, Ames MM. Comparative resistance of idarubicin, doxorubicin and their C-13 alcohol metabolites in human MDR1 transfected NIH-3T3 cells. *Cancer Chemother Pharmacol*. 1995;36(3):223-226.

32. Hollingshead LM, Faulds D. Idarubicin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the chemotherapy of cancer. *Drugs*. 1991;42(4):690-719.

33. Creutzig U, Ritter J, Zimmermann M,et al. Idarubicin improves blast cell clearance during induction therapy in children with AML: results of study AML-BFM 93. AML-BFM Study Group. *Leukemia*. 2001;15(3):348-354.

34. Cassileth PA, Lynch E, Hines JD, et al. Varying intensitiy of postremission therapy in acute myeloid leukemia. *Blood.* 1992;79(8):1924-1930.

35. Cassileth PA, Harrington DP, Appelbaum FR, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *N Engl J Med.* 1998;339(23):1649-1656.

36. Pautas C, Merabet F, Thomas X, et al. Randomized Study of Intensified Anthracycline Doses for Induction and Recombinant Interleukin-2 for Maintenance in Patients With Acute Myeloid Leukemia Age 50 to 70 Years: results of the ALFA-9801 Study. *J Clin Oncol.* 2010;28(5):808-814.

37. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. *N Engl J Med.* 1994;331(14):896-903.

Table 1. Patient characteristics

	IDR group (n = 532)	DNR group (n = 525)	*P* value
Age (year)*	47 (15 - 64)	47 (15 - 64)	0.781
=< 50	310	306	0.996
> 50	222	219	
WBC ($x10^9$/L)*	13.7 (0.1 - 382)	15.3 (0.1 - 334)	0.769
=< 20	304	297	
20 < =< 50	95	104	0.427
> 50	125	121	
unknown	8	3	
FAB type (no. of patients)			
M0	30	30	
M1	95	94	
M2	232	233	
M4	100	100	0.997
M5	56	51	
M6	17	16	
M7	2	1	
Cytogenetic group (no. of patients)			
good	128	119	
intermediate	335	346	0.561
adverse	49	44	
unknown	20	16	
MPO positive blast (%)			
< 50	169	187	
>= 50	307	292	0.330
unknown	56	46	
Performance status			
0, 1, 2	512	509	0.524
3	20	16	

* : Number indicates the median, and numbers in parentheses the range

Table 2. Results of induction therapy

	IDR group		DNR group	
	no.	%	no.	%
Patients	532		525	
CR	416	78.2	407	77.5
CR by 1 course	341	64.1	321	61.1
CR by 2 courses	75	14.1	86	16.4
95% CI	74.5 - 81.5		73.8 - 80.9	

Table 3. CR rates by induction therapy

	IDR group (n = 532)	DNR group (n = 525)	*P* value
FAB type	(%)	(%)	
M0	43	63	0.195
M1	86	79	0.236
M2	80	82	0.718
M4	81	79	0.86
M5	77	75	0.96
M6	76	38	0.037
M7	50	100	0.999
Cytogenetic Group			
Favorable	91	96	0.134
Intermediate	79	76	0.359
Adverse	51	43	0.534
unknown	50	69	0.257
Age			
=< 50	83	77	0.108
> 50	73	78	0.225
MPO positive blast (%)			
< 50	68	66	0.709
>= 50	87	88	0.699
WBC at diagnosis ($x10^9$/L)			
=< 20	79	76	0.767
20 < =< 50	82	82	0.993
> 50	74	77	0.824
Performance status			
0, 1, 2	79	78	0.762
3	80	75	0.999

Table 4. Factors to predict CR in all evaluable patients by multivariate analysis

variables		odds ratio	*P* value
Cytogenetic Group	Favorable	10.39	< 0.0001
	Intermediate	4.67	< 0.0001
MPO positive blast	>= 50 %	2.64	< 0.0001
Induction therapy	IDR arm	0.97	0.854

Table 5. Adverse events (WHO Grades 3 to 5) after the start of induction therapy

	IDR group		DNR group		
	no. of patients	%	no. of patients	%	*P* value
Sepsis	46	8.7	26	4.9	0.021
Early Death*	25	4.7	11	2.1	0.026
Bleeding	19	3.6	23	4.4	0.532
Febrile neutropenia	416	78.2	406	77.4	0.761
Acute cardiac toxicity	10	1.9	4	0.8	0.112
Late onset cardiac failure	2	0.38	2	0.38	0.998

*: death within 60 days after the start of induction therapy