*Correspondence: Takeshi Kondo, Department of Gastroenterology and Hematology, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan. E-mail: t-kondoh@med.hokudai.ac.jp*

*Key words: acute promyelocytic leukemia, FIP1L1-RARA.*

*Citation: Kondo T, Mori A, Darmanin S, Hashino S, Tanaka J, Asaka M. The seventh pathogenic fusion gene* FIP1L1-RARA *was isolated from a t(4;17)-positive acute promyelocytic leukemia. Haematologica 2008; 93:1414-1416. doi: 10.3324/haematol.12854*

## References

1. Zelent A, Guidez F, Melnick A, Waxman S, Licht JD. Translocations of the RARα gene in acute promyelocytic leukemia. Oncogene 2001;20:7186-203.
2. Catalano A, Dawson MA, Somana K, Opat S, Schwarer A, Campbell LJ, et al. The PRKAR1A gene is fused to RARA in a new variant acute promyelocytic leukemia. Blood 2007;110:4073-6.
3. Kwok C, Zeisig BB, Dong S, So CW. Forced homo-oligomerization of RARα leads to transformation of primary hematopoietic cells. Cancer Cell 2006;9:95-108.
4. Sternsdorf T, Phan VT, Maunakea ML, Ocampo CB, Sohal J, Silletto A, et al. Forced retinoic acid receptor alpha homodimers prime mice for APL-like leukemia. Cancer Cell 2006;9:81-94.
5. Cools J, Stover EH, Wlodarska I, Marynen P, Gilliland DG. The FIP1L1-PDGFRalpha kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia. Curr Opin Hematol 2004;11:51-7.
6. Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med 2003;348:1201-14.
7. Buijs A, Bruin M. Fusion of FIP1L1 and RARA as a result of a novel t(4;17)(q12;q21) in a case of juvenile myelomonocytic leukemia. Leukemia 2007;21:1104-8.
8. Stover EH, Chen J, Folens C, Lee BH, Mentens N, Marynen P, et al. Activation of FIP1L1-PDGFRalpha requires disruption of the juxtamembrane domain of PDGFRα and is FIP1L1-independent. Proc Natl Acad Sci USA 2006;103:8078-83.
9. Cools J, Stover EH, Gilliland DG. Detection of the FIP1L1-PDGFRA fusion in idiopathic hypereosinophilic syndrome and chronic eosinophilic leukemia. Methods Mol Med 2006;125:177-87.
10. Zimonjic DB, Pollock JL, Westervelt P, Popescu NC, Ley TJ. Acquired, nonrandom chromosomal abnormalities associated with the development of acute promyelocytic leukemia in transgenic mice. Proc Natl Acad Sci USA 2000;97:13306-11.
11. Walter MJ, Ries RE, Armstrong JR, Park JS, Mardis ER, Ley TJ. Expression of a bcr-1 isoform of RARα-PML does not affect the penetrance of acute promyelocytic leukemia or the acquisition of an interstitial deletion on mouse chromosome 2. Blood 2007;109:1237-40.

## Early discharge from hospital after consolidation chemotherapy in acute myeloid leukemia in remission: febrile neutropenic episodes and their outcome in a resource poor setting

Treatment of acute myeloid leukemia (AML) involves administration of myelosuppressive chemotherapy administered after admittance to hospital.[1] Admission to intensive nursing care units till bone marrow recovery leads to prolonged hospital stay. Quality of life and health care issues have made many cancer centers change to outpatient care even during high-risk phases of disease.[2-6]

In India most patients belong to poor socioeconomic backgrounds. There is an acute shortage of hospital beds. Early discharge after myelosuppressive therapy would promote better use of hospital resources, but the safety of this approach in these patients has not been established. We present our experience of the feasibility and safety of early discharge of patients with acute myeloid leukemia after consolidation chemotherapy.

All patients were induced with standard '3+7' chemotherapy using a peripherally inserted central venous (PICC) line. After documentation of complete remission (CR) consolidation chemotherapy with 3 cycles of high dose cytarabine was given.

Eighty-three consecutive episodes of neutropenia after consolidation chemotherapy in 28 acute myeloid leukemia patients in remission were included in the study. Patients were divided into 2 groups.

*Group 1. Outpatients.* These consisted of patients discharged after the chemotherapy was completed to their own homes or temporary residential facilities, which did not have any medical, or home visit facilities. Criteria for inclusion were: (a) no fever or infection; (b) location of residence nearby; (c) ability to come to hospital within one hour if fever developed or condition deteriorated. They had telephone access to the study team.

*Group 2. Inpatients.* These were patients who remained in hospital after high dose Ara C (HiDAC) chemotherapy till recovery of neutrophil counts. The criteria of inclusion were: (a) inability to move to a residential place as specified under group 1 or (b) severe infective course during earlier chemotherapy.

All patients were given the following supportive therapy: prophylactic ciprofloxacin 500 mg twice daily and fluconazole 200 mg/day and simple instructions concerning hygiene. Blood counts were monitored twice a week for Outpatients and on alternate days for Inpatients. Outpatients were seen at least once a week in the outpatient department (OPD). Blood and platelet transfusion support was given in the day care center. Patients who developed fever were administered granulocyte colony stimulating factor (G-CSF). Fever was considered present if the temperature measured orally was ≥38° C on two occasions at least four hours apart during a 24-hour period or was ≥38.5°C on a single occasion. Neutropenia was defined as an absolute neutrophil count (ANC) of $<0.5\times10^9$/L.[7]

All Outpatients who developed fever were admitted and administered IV antibiotics. First line antibiotics included piperacillin-tazobactum or cefoperazone-sulbactum, along with amikacin. Second line empirical antibiotics were generally started if fever persisted for 48-72 hours and there was no clinical improvement. These consisted of a carbapenem or aztreonam. Vancomycin/teicoplanin were added at onset or later as per febrile neutropenia guidelines.[7] Amphotericin was added if there was any suspicion of fungal infection based on clinical or X-ray findings, and empirically if fever and neutropenia persisted despite antibiotic therapy for more than five days.

After resolution of fever and if there was no obvious infection, IV antibiotics were changed to oral antibiotics that were continued for at least five days or till ANC recovered. Outpatients were discharged once oral antibiotics (amoxycillin-clauvulanic acid and levofloxacin) were initiated, while Inpatients remained in hospital till recovery of ANC.

The number of febrile neutropenic episodes, use of antibiotics, patterns of infection and mortality after completion of HiDAC were compared in the 2 groups. The SPSS statistical software (Chicago, IL, USA) was used for analysis.

**Table 1.** Characteristics of Outpatient and Inpatient neutropenic episodes.

| | *Total* | *Outpatients* | *Inpatients* | *p value* |
|---|---|---|---|---|
| N. of neutropenia episodes | 83 | 48 | 35 | |
| Male/Female | 53/30 | 34/14 | 19/16 | |
| Median age in yrs (range) | 22 (6-64) | 22 (6-50) | 21 (6-64) | |
| Median duration of neutropenia in days (range) | 12 (5-22) | 11.5 (5-19) | 13 (5-19) | 0.053 |
| N. of febrile episodes (%) | 49 (59%) | 25 (52%) | 24 (68.5%) | 0.13 |
| Mean days (range) of hospitalization## | – | 6 (3-18) | 16 (9-22) | |
| Days spent at home | – | 16 (11-20) | – | |
| Days of neutropenia at home (388)** | – | 8 (0***-17) | – | |
| Median duration of fever in days (range) | 4 (2-23) | 4 (2-7) | 5 (2-23) | 0.036* |
| Median duration of IV antibiotic use in days (range) | 6 (2-30) | 5 (2-30) | 9 (2-25) | 0.029* |
| 2nd Line IV antibiotic use$ | 9 | 3 | 6 | |
| IV vancomycin/teicoplanain use | 4 | 0 | 4 | |
| IV amphotericin use | 9 (18%) | 2 (8%) | 7 (29%) | |
| **Infection Profile** | | | | |
| Blood culture | | *E. coli-1* | *Pseudomonas aeruginosa-2*, MRSA-1, MSSA-2, Acinetobacter-2, *Candida tropicalis-1* | |
| Urine culture | | *E. coli-1* | *E. coli-1* | |
| Other | | Oral ulcer: *Candida krusei*-1, Pleural effusion tubercular-1 | Varicella (chicken pox)-1 | |
| Mortality | 3 | 1 | 2 | |

*IV: intravenous; MRSA: methicillin resistant Staph aureus; MSSA: methicillin sensitive Staph aureus; *using the Mann Whitney test; $cefoperazone-sulbactam+ amikacin or piperacillin-tazobactam + amikacin; $imipenem-cilastatin and/or aztreonam; **also includes those who were never admitted; ***3 pts developed fever at the onset of neutropenia but at home; ##excludes the 5 days of HiDAC for which patients were admitted.*

Patients' characteristics and outcome in the 2 groups is given in Table 1 and Figure 1. The relative risk of developing fever in Inpatients was 1.51 (CI 0.86-2.66, using the $\chi^2$ test). First line antibiotics cured fever in 88% (22/25) Outpatient febrile neutropenic episodes compared to 58% (14/24) Inpatients. Patients who remained hospitalized after chemotherapy had a higher incidence of culture positive fevers as compared to domiciliary neutropenic fever. There were 3 deaths in the study group (Figure 1).

In recent years, several reports have questioned the necessity of keeping patients in hospital after chemotherapy till full neutrophil count recovery.[3-6] There is little published data of the safety of this approach in centers with limited resources.

Domiciliary management of low risk febrile neutropenia with oral antibiotics relies on an efficient health care infrastructure, where patients would be immediately admitted if their condition deteriorates. Lacking these facilities, we decided to admit all Outpatients who developed fever during neutropenia. Although current guidelines do not recommend antibiotic prophylaxis for neutropenia,[7] new evidence shows benefit.[8,9] In our limited resource setting prophylaxis with ciprofloxacin seemed advisable. Fluconazole is recommended for allogeneic bone marrow transplant patients with varying doses.[10,11] We used fluconazole in 200 mg daily due to the low average weight of our patients.

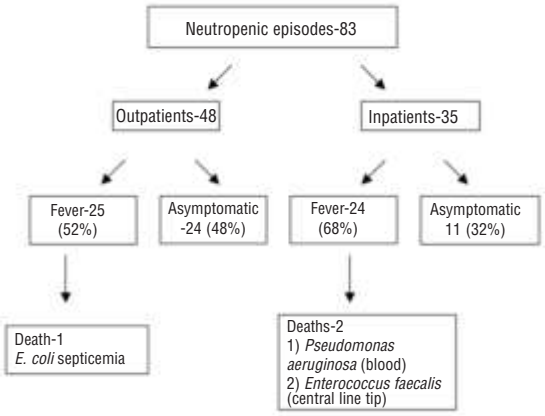


**Figure 1.** Figure showing the outcome of neutropenic episodes.

In a recent editorial, Kern[2] emphasized that improved antimicrobial prophylaxis (fluoroquinolones, aciclovir, fluconazole) together with much more effective supportive care algorithms on one hand, and professional risk assessment and appropriate infrastructure for follow-up on the other, are essential in discussing the successes of early discharge and outpatient management programs.

The one mortality in the Outpatient group was likely due to delayed presentation as the patient reported to hospital 24 hours after onset of fever and died within 18 hours of admission despite intensive resuscitation. It is, therefore, critical to ensure that patients understand the importance of following instructions to report to a medical center immediately on onset of fever or other symptoms suggestive of infection.

Of the 48-neutropenic episodes managed on a domiciliary basis, 23 (48%) did not require admission during their entire nadir. Of the other 25 neutropenic episodes that required re-admission, many hospital days were still saved by the early discharge policy.

The study shows that selected patients can be discharged and given domiciliary treatment safely, even with inadequate home care facilities. However, if the patient cannot reach the hospital immediately in cases of fever, early discharge should be avoided.

*Rahul Naithani, Rajat Kumar, Manoranjan Mahapatra, Neerja Agrawal, Pravas Mishra*

*Department of Hematology, All India Institute of Medical Sciences, New Delhi, India*

*Key words: acute myeloid leukemia, antibiotic prophylaxis, febrile neutropenia, outpatient management.*

*Correspondence: Rahul Naithani, MD, Department of Hematology All India Institute of Medical Sciences New Delhi-110029.*
*Fax: international +91.11.27572869.*
*E-mail: dr_rahul6@hotmail.com*

*Citation: Naithani R, Kumar R, Mahapatra M, Agrawal N, Mishra P. Early discharge from hospital after consolidation chemotherapy in acute myeloid leukemia in remission: febrile neutropenic episodes and their outcome in a resource poor setting. Haematologica 2008; 93:1416-1418.*
*doi: 10.3324/haematol.11696.*

## References

1. Allan DS, Buckstein R, Imrie KR. Outpatient supportive care following chemotherapy for acute myeloblastic leukemia. Leuk Lymphoma 2001;42:339-46.
2. Kern WV. Outpatient management in patients with neutropenia after intensive chemotherapy: is it safe? Ann Oncol 2005;16:179-80.
3. Cherif H, Johansson E, Bjorkholm M, Kalin M. The feasibility of early hospital discharge with oral antimicrobial therapy in low risk patients with febrile neutropenia following chemotherapy for hematologic malignancies. Haematologica 2006;91:215-22.
4. Savoie ML, Nevil TJ, Song KW, Morano SG, Celesti F, Coppola L, et al. Shifting to outpatient management of acute myeloid leukemia: a prospective experience. Ann Oncol 2006;17:763-8.
5. Girmenia C, Alimena G, Latagliata R, Morano SG, Celesti F, Coppola L, et al. Out-patient management of acute myeloid leukemia after consolidation chemotherapy. Role of a hematologic emergency unit. Haematologica 1999;84:814-9.
6. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 2000;18:3038-51.
7. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34:730-51.
8. Leibovici L, Paul M, Cullen M, Bucaneve G, Gafter-Gvili A, Fraser A, et al. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Cancer 2006; 107:1743-51.
9. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 2005;142:979-95.
10. Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. Clin Infect Dis 2001;33:139-44.
11. Trifilio S, Verma A, Mehta J. Antimicrobial prophylaxis in hematopoietic stem cell transplant recipients: heterogeneity of current clinical practice. Bone Marrow Transplant 2004;33:735-9.


## Outcome for children with relapsed acute myeloid leukemia in the Netherlands following initial treatment between 1980 and 1998: survival after chemotherapy only?

We report the outcome of Dutch pediatric relapsed AML patients and focus on patients treated with chemotherapy alone. Median time from first complete remission to relapse was nine months. Second complete remission (CR2) was achieved in 63%. Overall, only 16% of patients were survivors. When only patients who achieved CR2 were analyzed, 50% of the patients treated with allogeneic stem cell transplantation and 24% of the patients treated with chemotherapy alone, were long-term survivors.

The prognosis of children with acute myeloid leukemia (AML) has improved markedly over the last decades with 5-year overall survival rates (5-year pOS) in the most recent treatment protocols as high as 50-60%.[1] In the Netherlands, children with AML are treated according to protocols developed by the Dutch Childhood Oncology Group (DCOG). Since 1980, four protocols for the treatment of childhood AML have been completed, and overall survival has improved from 18% to 42%.[2,3] Relapse remains the most frequent cause of treatment failure, with a cumulative risk of relapse of 30-40% in most pediatric AML studies.[1] In the consecutive Dutch AML protocols, the cumulative risk of relapse was 60, 43, 47 and 26% respectively.[3] Allogeneic stem cell transplantation (alloSCT) is generally recommended as part of treatment of relapsed AML.[4] Formal evidence for this recommendation is lacking, despite evidence of a graft-versus-leukemia effect in AML. At initial diagnosis of high-risk AML, alloSCT seems no better than chemotherapy only.[4] Therefore, the need for alloSCT in relapsed AML may be questioned, at least as a general recommendation.

We studied all Dutch children and adolescents with AML that were initially diagnosed and treated between 1980 and 1998 and relapsed before 1st January 2007. The patients were initially treated according to the Dutch Childhood Oncology Group (DCOG) protocols AML-80, AML-82, AML-87 and AML-92/94.[2,3] We focussed on patients reported to be alive without disease after treatment with chemotherapy only for their relapse and summarized the relevant literature. Since autologous SCT has been reported to provide similar results to intensive chemotherapy, and does not have a graft-versus-leukemia effect, these patients (n=9) were included in the *chemotherapy only* group.[5] Most patients were treated with a reinduction regimen containing cytarabine, most frequently in combination with an anthracycline and etoposide.

A total of 113 relapsed AML cases were identified, with a median time from first complete remission (CR1) to relapse of nine months (range 1-61 months). Ninety of these patients were treated with curative intent and CR2 was achieved in 63%. In univariate analysis, sex, age, WBC, FAB-type and SCT in CR1 were not associated with achievement of CR2. None of the patients who failed to achieve remission on first-line treatment when treated for their initially diagnosed AML (n=11) achieved CR2, compared to 72% of patients who did achieve CR1 on first-line treatment ($\chi^2$ $p<0.0001$). CR1 duration (CR1≤1 year or CR1>1 year) correlated significantly with the probability of achieving CR2 (55 *vs.* 76%, $p=0.04$) and 10-year pOS (13 *vs.* 30%, $p=0.02$) in univariate analysis. The overall 10-year pOS was 16% (standard error (SE) 3%), with 18 disease-free long-term survivors.

AlloSCT was performed in 16 out of the 57 CR2 patients, with 8 (50%) long-term survivors. Ten out of the 41 patients (24%) treated without alloSCT survived. This comparison is biased by the fact that to be able to undergo SCT, it is necessary to have a suitable donor, to maintain CR2 until the SCT and to be in a relatively good condition. In multivariate analysis using Cox-regression, we corrected alloSCT in CR2 for time to transplant. In this analysis of pOS alloSCT was not an independent favorable prognostic factor (HR=0.56, 95% confidence interval (CI) 0.26-1.24, $p=0.15$), as was also the case for CR1 duration (HR=1.5, 95% CI 0.78-2.88, $p=0.23$). This study was limited by its retrospective nature, the diverse treatment schedules used, and the relatively small number of patients, especially when prognostic factors were analyzed. The 10 long-term survivors treated at relapse without alloSCT (7 chemotherapy only, plus 3 auto-SCT) did not have unique or similar clinical or cell biological features and included 6 patients with relapse within 12 months from CR1 (Table 1). Some of these 10 patients had been treated in the 1990s with relatively intensive chemotherapy at initial diagnosis. In 10 out of 18 survivors, late effects of treatment were reported such as