Long-Term Outcomes of *de novo* Acute Myeloid Leukemia in Thai Patients

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Background: *Acute myeloid leukemia (AML) is the heterogeneous disease. As per previous reports, there are some differences in clinical features and cytogenetic biomarkers of AML among different ethnic backgrounds. Therefore, we conducted a retrospective study to analyze clinical outcomes and predictive factors of Thai AML patients receiving chemotherapy treatment.*

Material and Method: *The authors performed a retrospective analysis of 106 adults with newly diagnosed* de novo *AML at Ramathibodi Hospital between 2003 and 2007. Of 101 patients with non- M3 subtype, the patients received induction and consolidation chemotherapy with anthracyclin plus cytarabine based regimens (3 + 7). All patients achieving complete remission (CR) were treated with intensive chemotherapy using intermediate dose cytarabine plus anthracyclin based protocol. All patients with M3 subtype, the induction chemotherapy consisted of a combination of all-trans retinoic acid (ATRA) and anthracyclin. All patients achieving complete remission (CR) were treated with three courses of mitoxantrone as consolidation chemotherapy, followed by maintenance chemotherapy with methotrexate, etoposide and ATRA.*

Results: *Of the 106 patients, median age was 43.5 years (15-73 years) and 19 (17.9%) were older than 60 years. Fifty-six patients (52.8%) were female. Common subtypes were M4 (28.3%), M1 (26.4%) and M2 (20.8%). Of the 95 patients who were performed with cytogenetic analysis, 55 (58%) had abnormal karyotype. AML with recurrent cytogenetic translocations, complex chromosome, trisomy 8, polyploidy, del 5q and del 7q were found in 16.8, 6.3, 5.3, 5.3, 2.1 and 3.2%, respectively. Most patients (70.5%) had intermediate-risk cytogenesis. Eighty patients (75.5%) were treated with idarubicin and cytarabine induction regimen. Of the 96 evaluable patients, 60 (62.5%) achieved complete remission (CR), 38 (39.6%) with the first course of chemotherapy. Median time to CR was 54 days (25-168 days). The CR rate was 78.6% for the good-risk cytogenetic group, 67.2% for the intermediate- risk cytogenetic group, and 37.5% for the poor-risk cytogenetic group. Median follow-up time was 10.4 months, 5-year-DFS and 5-year-OS were 41 and 22.2%, respectively. Patients with poor-risk cytogenetic factors had significantly lower CR rate ($p = 0.021$). The CR status significantly predicted OS ($p < 0.001$).*

Conclusion: *The overall complete remission rate of Thai AML patients is in 60%. Only a small proportion of the presented patients have long-term DFS and OS, the significant factor for predicting survival of Thai AML patients is the complete remission status. Poor-risk cytogenetic factors are associated with poor treatment outcomes.*

Keywords: *Acute myeloid leukemia, Treatment outcome, Prognosis*

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Acute myeloid leukemia (AML) is heterogeneous in subtypes, clinical presentation, cytogenesis and molecular patterns, all of which affect the treatment outcomes. Age, karyotype and white blood cell count at diagnosis have the effect on survival and responses to treatment. AML with CD7 expression has been reported to be associated with unfavorable clinical outcomes[1-4]. The younger age at being diagnosed has been shown to have better complete remission (CR) rate. In general, the CR rate of AML patients aged < 40, 40-60 and > 60 years are 75, 68 and 47%, respectively[5]. However, the 3-year disease-free survival (DFS) rate for patients receiving maintenance chemotherapy is not as good[6-11].

There are some differences in clinical features and cytogenetic biomarkers of AML among different ethnic backgrounds. For example, age at presentation is higher in Caucasian patients (65-70 years)[12,13] compared with that of Asian patients (48-50 years)[14,15]. While the most common recurrent cytogenetic translocations in Singaporean patients is t (15;17)[14], the most common recurrent cytogenetic translocations in Japanese and Australian patients is t (8;21)[15]. Although the prognostic factors and clinical outcomes in adult AML patients have been previously reported, it is possible that these parameters in Thai AML patients are different from others. Hence, we conducted a retrospective study to analyze the treatment outcomes and to identify the prognostic factors in adult Thai AML patients who had been treated and followed at Hematology unit of Ramathibodi Hospital. The objectives of the present study were to evaluate the rates of complete remission, relapse, disease- free survival and overall survival (OS) and to determine the predictive parameters for CR, DFS and OS in Thai AML patients.

Material and Method

Patients

Clinical data of 106 patients with newly diagnosed *de novo* AML or biphenotypic leukemias at Ramathibodi Hospital during January 2003-December 2007 were reviewed. All patients were above 15 years of age and were not previously treated with chemotherapy. Patients who refused induction chemotherapy were excluded from the present study. The data which included the clinical features, the clinical outcomes, the results of cytogenetic and immunophenotypic analysis of AML were collected from chart-review.

Acute myeloid leukemia was defined as presence of 20% or more of marrow blasts which are not lymphoblast cells. Subtype of AML was classified by World Health Organization (WHO) classification[16]. Biphenotypic leukemia was diagnosed following the criteria of European Group for the Immunological characterization of Leukemias (EGIL)[17]. Cytogenetic analysis was performed using chromosome G-banding technique. The cytogenetic-risk classification was classified by Cancer and Leukemia Group B (CALGB 8461) and Southwest Oncology Group/Eastern Cooperative Oncology Group study[18,19]. CR was defined as normocellular or hypercellular marrow with less than 5% blasts in the marrow. Evaluation of response was performed 21-35 days after each course of chemotherapy. DFS was defined as the length of time from the date of CR to relapse and OS was defined as the interval between treatment and death.

Chemotherapy

Induction chemotherapy

Of 101 patients with non-M3 subtype, eighty (75.5%) received intravenous (IV) idarubicin 12 mg/m^2/day for 3 consecutive days together with IV cytarabine 100 mg/m^2/day for 7 consecutive days. Seventeen patients (15.1%) were treated with IV mitoxantrone 12 mg/m^2/day for 3 consecutive days together with IV cytarabine 100 mg/m^2/day for 7 consecutive days. Two patients (1.9%) received IV doxorubicin 45 mg/m^2/day for 3 consecutive days together with IV cytarabine 100 mg/m^2/day for 7 consecutive days. The remaining two patients (1.9%) received oral idarubicin 12 mg/m^2/day for 3 days (days 1, 3 and 5) together with oral etoposide 100 mg/m^2/day for 5 consecutive days.

Five patients with M3 subtype were treated with IV idarubicin 12 mg/m^2/day for 3 days (days 1, 3 and 5) together with oral all-trans retinoic acid (ATRA) 45 mg/m^2/day in two divided doses from day 0 and was continued until achieving bone marrow morphological CR.

Consolidation chemotherapy

Except patients with M3 subtype, all received the same chemotherapy regimen as induction phase.

All patients with M3 subtype received three courses of IV mitoxantrone 10 mg/m^2/day for 3 days (days 1, 3 and 5).

Intensive chemotherapy

All patients who received idarubicin combined with cytarabine for induction and consolidation were treated with mitoxantrone and intermediate dose cytarabine regimen. This regimen consisted of

IV cytarabine 3,000 mg/m^2/day in two divided doses for 4 consecutive days (days 1-4) and IV mitoxantrone 12 mg/m^2/day from day 5 for 2 consecutive days. The remaining 19 patients who received induction and consolidation chemotherapy with combination of cytarabine and mitoxantrone or cytarabine and doxorubicin were treated with IV cytarabine 3,000 mg/m^2/day in two divided doses for 4 consecutive days (days 1-4) and IV idarubicin 12 mg/m^2/day from day 5 for 2 consecutive days. A number of our patients refused the second or the third course of intensive chemotherapy, therefore, only 11 patients had completed three courses of intensive chemotherapy.

Patients with M3 subtype were treated with oral ATRA 45 mg/m^2/day in two divided doses for 15 consecutive days and were repeated every three months. Oral etoposide 50 mg/m^2/day and oral methotrexate 15 mg/ m^2/week were continued for two years.

Supportive care

G-CSF 5 mg/kg/day was given for all patients diagnosed with febrile neutropenia following induction chemotherapy until being out of febrile neutropenia and was given for all patients who received the consolidation or maintenance chemotherapy as prophylaxis until absolute neutrophil count (ANC) $\geq$ 1,500/ mm^3.

Statistical analysis

The parameters which included age, fever, white blood cell count, karyotypic data, expression of CD7 were compared between patients with and without CR by using Chi-square. Cox's proportional hazards model was used to analyze for independent prognostic factors. OS and DFS were calculated using the kaplan-Meier method. Difference between group was calculated using the log-rank test for univariate analysis. All calculations were performed using the statistical package of social sciences software, SPSS version 16. $P < 0.05$ was considered significant.

Results

Patients' characteristics

Of 106 patients, fifty-six (52.8%) were female. Median age was 43.5 years (range; 15-73 years), nineteen (17.9%) were older than 60 years. M4, M1, M2 and M5 subtypes were observed in 28.3, 26.4, 20.8 and 14.2%, respectively. Only five patients (4.7%) had M3 subtype. Nineteen patients (17.9%) had WBC count >100,000/mm^3, median hemoglobin (Hb) level was 8.4 g/dl (range; 4.1-13.5 g/dl) and median platelet count was 54,000/mm^3 (range; 8,000-427,000/mm^3). Of 95 patients who had undergone immunophenotypic and cytogenetic analysis, 21 (22.1%) were positive for CD7 expression and 55 (58%) had abnormal karyotype. The cytogenetic abnormalities were recurrent cytogenetic translocations (16.84%), complex chromosome (6.31%), trisomy 8 (5.26%), polyploidy (5.26%), del 7q (2.1%) and del 5q (3.16%). Sixty-seven patients (70.5%) had intermediate-risk cytogenetic karyotype, sixteen (16.84%) had good-risk cytogenetic karyotype and the remaining twelve (12.63%) had poor-risk cytogenetic karyotype. Only 10 patients (9.4%) underwent HLA identical allogeneic hematopoietic stem cell transplantation (HSCT) after achieving CR with induction chemotherapy. Other patients' characteristics are shown in Table 1.

Of 106 patients, 10 died early (< 21 days) from infection during treatment with first induction chemotherapy and were excluded from analysis. Of the 96 remaining patients, 60 (62.5%) achieved CR, 38 (39.6%) with the first course of chemotherapy. Median time to CR was 54 days (25-168 days). CR rate in patients aged > 60 and $\leq$ 60 years were not significantly different (50% vs 64.6%), respectively. Of the 55 patients with abnormal karyotype, 29 (52.7%) achieved complete cytogenetic remission, good risk cytogenetic pattern in 11, intermediate risk cytogenetic pattern in 15 and poor risk cytogenetic pattern in 3 patients. In patients who were not M3 subtype, CR rate was not significantly different whether induction chemotherapy was mitoxantrone/cytarabine (75%), or idarubicin/cytarabine (58.33%) or doxorubicin cytarabine (50%). Patients who had good-risk cytogenetic pattern achieved significantly higher CR rate than those of intermediate-risk and poor-risk cytogenetic patterns (85.7 vs. 67.2 vs. 37.5%) ($p = 0.001$). Disease relapse was evidenced in 24 patients (40%), the median time to relapse was 11.2 months (range; 1.5-62 months). Relapse rate was significantly greater in poor-risk cytogenetic group (3/3) than those of the intermediate-risk (13/41 or 31.7%) and good-risk cytogenetic groups (6/12 or 50%) ($p = 0.045$). In the good risk cytogenetic group, five out of nine (55.6%) CR patients who had t (8;21) with other additional chromosome abnormalities had disease relapse while only one out of three with t (15;17) did. With a median follow-up of 10.4 months, 1-year and 5-year-OS were 46 and 22.2% whereas 1-year and 5-year-DFS were 64 and 41%, respectively (Fig. 1). Seventy-six patients (71.7%) expired. Most common cause of death was

Table1. Patients' characteristics of acute myeloid leukemia (n = 106)

Characteristic	Number of patients (%)
Presence of hyperleucocytic syndrome	2 (1.89)
Presence of central nervous system involvement	2 (1.89)
Febrile at presentation	51 (48.1)
Hb < 8 g/dL	45 (42.5)
WBC ≥ 50,000/ mm^3	40 (37.7)
Platelets < 20,000/ mm^3	16 (15.1)
Presence of pancytopenia	28 (26.4)
Serum albumin < 30 g/L	11 (10.4)
Abnormal cytogenetic pattern	55 (58)
Good risk cytogenetic pattern	16 (29.2)
t (15;17) (n = 55)	5 (9.1)
t (8;21) (n = 55)	3 (5.5)
t (8;21)/-X (n = 55)	4 (7.3)
t (8;21)/-Y (n = 55)	3 (5.5)
t (8;21), der 21 (n = 55)	1 (1.8)
inv (16) or t (16;16)	0
Intermediate risk cytogenetic pattern	26 (47.2)
+8	5 (9.1)
+21	4 (7.3)
Del 5q/del 7q	2 (3.6)/ 3 (5.5)
Polyploidy	5 (9.1)
der 9	2 (3.6)
Abnormal chromosome 11/+4	2 (3.6)/ 2 (3.6)
Other	1 (1.8)
Poor risk cytogenetic pattern	13 (23.6)
Complex chromosome	9 (16.4)
-7	1 (1.8)
der 3	1 (1.8)
Other	2 (3.6)

infection (40/76 or 52.6%), the other causes of death were disease progression (23/76 or 30.3%) and intracerebral bleeding (5/76 or 6.6%). No definite cause of death was found in 8 patients (11.8%).

As shown in Table 2, in the univariate analysis, afebrile at diagnosis (p = 0.023), platelet count < 20,000/mm^3 (p = 0.002), good or intermediate-risk cytogenetic group (p = 0.001) and absence of pancytopenia at presentation (p = 0.026) were significantly associated with CR. Pancytopenia at presentation (p = 0.035) and status of not in CR following chemotherapy (p < 0.001) including status of not in CR after receiving first induction course of chemotherapy (p = 0.001) were significant parameters adversely affecting OS (Fig. 2).

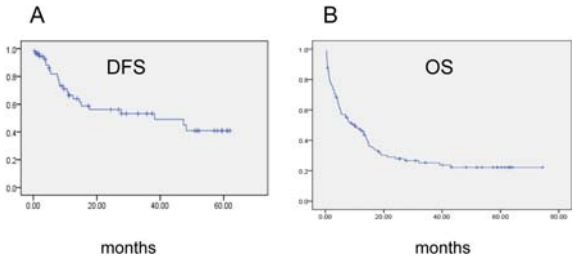

Fig. 1 (A) Disease- free survival in AML patients
(B) Overall survival in AML patients

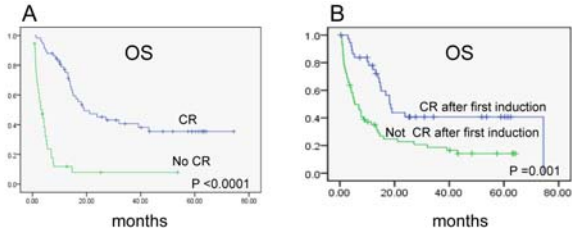

Fig. 2 (A) Overall survival in AML patients according to the status of CR
(B) Overall survival in AML patients according to the status of CR after first induction

None of the parameters had an effect on DFS. However, by using multivariate analysis, only status of no CR was an independent risk factor for OS. (p < 0.001), There was no independent prognostic factor for CR.

Discussion

It has been previously reported that age at diagnosis of AML in the Asian population is lower than that of Caucasian population which is commonly found in elderly patients aged > 60 years. The present study supports this notion. Recurrent cytogenetic translocations were found in 16.84% and the t (8;21) was the most common type. Prevalence of t (8;21) in M2 subtype was found in 27.27%, which is similar to the previous reports in Japanese patients but is higher than that reported in Australian patients (15.3%)[15]. None of our patients had inv (16) or t (16;16). It is possible that ethnic background or different environment has some effects on molecular pathology in AML.

The present study supports other studies that AML patients with poor-risk cytogenetic group have significantly lower CR and has a higher relapse rate. However, those latter outcomes may be distorted

Table 2. Prognostic factors for complete remission, disease free survival and overall survival

Factors	Complete remission			Disease free survival			Overall survival		
	Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value
Age > 60 years	0.547	0.175-1.713	0.296	1.499	0.445-5.052	0.514	1.054	0.556-1.999	0.871
Febrile at diagnosis	0.377	0.160-0.885	0.023	1.910	0.791-4.613	0.150	0.859	0.547-1.349	0.509
Pancytopenia at diagnosis	0.353	0.138-0.900	0.026	0.506	0.197-1.298	0.156	0.591	0.362-0.964	0.035
Hb < 8 g/dL	1.375	0.593-3.186	0.457	0.935	0.416-2.101	0.870	1.396	0.881-2.214	0.156
Wbc > 100,000 (mm^3)	0.882	0.286-2.724	0.828	1.187	0.353-3.986	0.782	0.695	0.400-1.206	0.196
Platelet < 20,000 (mm^3)	0.162	0.047-0.560	0.002	1.949	0.260-14.596	0.516	0.673	0.370-1.226	0.196
Serum albumin < 30 g/L	0.443	0.111-1.771	0.240	21.479	0.000-54.50	0.629	0.528	0.248-1.126	0.098
CD7 expression	0.993	0.348-2.836	0.990	1.871	0.439-7.979	0.397	0.931	0.506-1.713	0.819
Poor cytogenetic risk group	8.314	1.980-34.913	0.001	2.992	0.875-10.234	0.081	1.854	0.935-3.674	0.077
CR	-	-	-	-	-	-	7.473	4.305-12.972	<0.001
CR after first induction chemotherapy	-	-	-	0.892	0.390-2.042	0.786	2.479	1.461-4.207	0.001
Treatment with BMT	-	-	-	1.038	0.354-3.041	0.946	2.211	0.891-5.486	0.087
Disease relapse	-	-	-	-	-	-	0.515	0.260-1.021	0.057

by the small number of CR in patients who had poor-risk cytogenetic karyotype. Most patients who had t (8;21) with other additional cytogenetic abnormalities had relapse. This finding is similar to the data of Marcucci et al; they demonstrated that in non white patients who had t (8;21) with non del 9 cytogenetic abnormalities had shorter DFS[20]. However, since the number of AML cases with t (8;21) in the present study was very small, the rate of disease relapse in this group of patients should be further explored in a future study. DFS and OS were also not different from others.

Poorer overall survival rates in the present study may be partly caused by the serious infection which occurred during the febrile neutropenia period. Because of the limitation of isolation rooms, the presented patients were treated with conventional chemotherapy in general medicine wards that could increase the risk of serious infection. Therefore, a better supportive care system might improve long-term survival in our AML patients.

Although a superiority of mitoxantrone over idarubicin or doxorubicin in terms of CR rate and OS has been observed but it can not be concluded that mitoxantrone induces highest CR since the present study was not the randomized controlled trial and most of the patients were treated with idarubicin. The other limitation of the present study is that only a small number of patients (10.38%) had completed treatment with five courses of chemotherapy following the standard treatment protocol.

In conclusion, the overall complete remission rate of Thai AML patients is 60%. Only a small proportion of the presented patients have long-term DFS and OS, the significant factor for predicting survival of Thai AML patients is complete remission status. Poor- risk cytogenetic group is associated with poor treatment outcomes.

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ผลการรักษาระยะยาวในผู้ป่วยไทยที่ได้รับการวินิจฉัยมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดไมอิลอยด์

พิมพ์ใจ นิภารักษ์, สุภร จันทร์จารุณี, อาทิตย์ อังกานนท์, อุมาพร อุดมทรัพยากุล, พันธ์เทพ อังชัยสุขศิริ, บุษบา ฤกษ์อำนวยโชค, แสงสุรีย์ จูฑา, วิชัย อติชาตการ

ภูมิหลัง: *โรคมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดไมอิลอยด์ เป็นโรคที่มีการแสดงออกได้หลากหลายในด้านของชนิดและรูปร่างของเซลล์มะเร็ง ลักษณะทางคลินิก ความผิดปกติของโครโมโซมและความผิดปกติในระดับโมเลกุล ดังนั้น คณะผู้จัดทำจึงได้จัดทำการศึกษานี้ขึ้นเพื่อทำการศึกษาถึงผลการรักษาและปัจจัยที่มีผลต่อการพยากรณ์โรคของผู้ป่วยไทยที่เป็นโรคมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดไมอิลอยด์*

วัสดุและวิธีการ: *ทางคณะได้ทำการศึกษาย้อนหลังผู้ป่วยไทยทั้งหมด 106 คน ที่ได้รับการวินิจฉัยโรคมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดไมอิลอยด์ที่โรงพยาบาลรามาธิบดีในช่วงปี 2546-2550*

ผลการศึกษา: *จำนวนผู้ป่วยทั้งหมด 106 คน ค่ามัธยฐานของอายุเท่ากับ 43.5 ปี โดยมีอายุตั้งแต่ 15-73 ปี ผู้ป่วยที่มีอายุมากกว่า 60 ปี มีจำนวน 19 คน คิดเป็นร้อยละ 17.9 และมีผู้ป่วยหญิงทั้งหมด 56 คน คิดเป็นร้อยละ 52.8 ชนิดของมะเร็งเม็ดเลือดขาวเฉียบพลันไมอิลอยด์ที่พบบ่อยคือ AML (M4) คิดเป็นร้อยละ 28.3 ชนิดที่พบบ่อยรองลงมาคือ AML (M1) และ AML(M2) คิดเป็นร้อยละ 26.4 และ 20.8 ตามลำดับ พบผู้ป่วยจำนวน 55 คน มีความผิดปกติที่โครโมโซมจากผู้ป่วยทั้งหมด 95 คน ที่ได้รับการตรวจหาความผิดปกติของโครโมโซม โดยผู้ป่วยร้อยละ 70.5 มีความผิดปกติทางโครโมโซม ที่จัดอยู่ในกลุ่มของ intermediate-risk cytogenesis ผู้ป่วยส่วนใหญ่คิดเป็นร้อยละ 75.5 ได้รับการรักษาด้วยยาเคมีบำบัด idarubicin ร่วมกับ cytarabine จากจำนวนผู้ป่วยทั้งหมด 96 คน ที่สามารถประเมินการตอบสนองต่อการรักษาด้วยยาเคมีบำบัดได้ พบว่ามีจำนวนผู้ป่วย 60 คน คิดเป็นร้อยละ 62.5 ที่มีการตอบสนองต่อยาเคมีบำบัดชนิด complete remission สำหรับค่ามัธยฐานของระยะเวลาที่ผู้ป่วยมีการตอบสนองต่อการรักษาชนิด complete remission คือ 54 วัน โดยมีระยะเวลาตั้งแต่ 25-168 วัน ผู้ป่วยที่มีการตอบสนองต่อยาเคมีบำบัดชนิด complete remission จัดเป็นผู้ป่วยที่อยู่ในกลุ่ม good-risk, intermediate- risk และ poor-risk cytogenesis คิดเป็นร้อยละ 78.6, 67.2 และ 37.5 เรียงตามลำดับ ค่ามัธยฐานของระยะเวลาในการตรวจติดตามการรักษาคือ 10.4 เดือน โดยพบอัตราการอยู่รอดโดยปราศจากตัวโรค และอัตราการมีชีวิตรอดที่ 5 ปี คิดเป็นร้อยละ 41 และ 22.2 ตามลำดับ ผู้ป่วยที่จัดอยู่ในกลุ่ม poor-risk cytogenesis มีอัตราการตอบสนองชนิด complete remission ต่ำที่สุดเมื่อเปรียบเทียบกับผู้ป่วยที่จัดอยู่ในกลุ่ม good-risk และ intermediate-risk cytogenesis อย่างมีนัยสำคัญทางสถิติ และพบว่าผู้ป่วยที่มีการตอบสนองต่อยาเคมีบำบัดชนิด complete remission จะมีอัตราการมีชีวิตอยู่ยาวนานกว่าผู้ป่วยที่ไม่ได้ complete remission อย่างมีนัยสำคัญ*

สรุป: *จากการศึกษานี้พบว่าผู้ป่วยที่มีการตอบสนองต่อยาเคมีบำบัดชนิด complete remission ในผู้ป่วยไทยที่ได้รับการวินิจฉัยมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดไมอิลอยด์ คิดเป็นร้อยละ 60 โดยมีผู้ป่วยจำนวนน้อยที่มีอัตราการอยู่รอด โดยปราศจากตัวโรคและมีอัตราการรอดชีวิตที่ยาวนาน การตอบสนองต่อยาเคมีบำบัดชนิด complete remission เป็นปัจจัยที่บ่งบอกถึงการพยากรณ์โรคในส่วนของการมีชีวิตที่ยาวนาน และผู้ป่วยที่จัดอยู่ในกลุ่ม poor-risk cytogenesis จัดเป็นกลุ่มผู้ป่วยที่มีพยากรณ์โรคที่ไม่ดี*