Published in final edited form as:

Pediatr Blood Cancer. 2012 April ; 58(4): 519–524. doi:10.1002/pbc.23201.

Superior Outcome of Pediatric Acute Myeloid Leukemia Patients with Orbital and CNS Myeloid Sarcoma: A Report from the Children's Oncology Group

Donna L. Johnston, MD¹, Todd A. Alonzo, PhD², Robert B. Gerbing, MSc³, Beverly J. Lange, MD⁴, and William G. Woods, MD⁵

¹ Division of Hematology/Oncology, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

² Department of Preventive Medicine, University of Southern California, Los Angeles, CA

³ Children's Oncology Group, Arcadia, CA

⁴ Pediatric Oncology, Children's Hospital of Philadelphia, Philadelphia, PA

⁵ Aflac Cancer Center and Blood Disorders Service Children's Healthcare of Atlanta, Emory University, Atlanta, GA

Abstract

Background—Extramedullary leukemia (EML) is common in pediatric acute myeloid leukemia (AML) and occurs as leukemia cells within the cerebrospinal fluid (CSF) or as a solid tumor (myeloid sarcoma-MS). The effect of MS on survival is unknown.

Methods—Patients on CCG protocols 2861, 2891, 2941 and 2961 being treated for AML with intensive-timing chemotherapy were classified for the presence of EML (CSF leukemia, CNS-MS, orbital-MS, or non-CNS MS). CSF leukemia was classified as CNS 3 (> 5 wbc in the CSF with blasts) and non-CSF leukemia as CNS1/2 (<5 wbc in the CSF with or without blasts). Characteristics and outcomes of these patients were compared.

Results—Of the 1459 total patients, 1206(82%) had no EML, 154(11%) had CSF leukemia, 19(1%) had CNS-MS, 23(2%) had orbital-MS, and 57(4%) had non-CNS MS. The CR rate was significantly higher in patients with orbital-MS and CNS-MS than in those with non-MS and non-CNS MS (96% and 95% vs 78% and 78%, $p=0.034$). Patients with orbital-MS and CNS-MS had significantly higher overall survival than patients with non-CNS MS (92% and 73% vs 38%, $p<0.001$), CNS3 patients (92% and 73% vs 51%, $p<0.001$), and CNS1/2 patients (92% and 73% vs 50%, $p<0.001$). Patients with orbital-MS had a significantly lower relapse rate.

Conclusion—Patients with myeloid sarcoma involving orbital and CNS sites had a significantly better survival than patients with non-CNS MS, with CSF leukemia, or with no extramedullary leukemia.

Keywords

Myeloid Sarcoma; Acute Myeloid Leukemia; Chloroma

Corresponding Author: Dr. Donna Johnston, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario, K1H 8L1, Canada, Telephone: (613) 737-7600 ext 2370, Fax: (613) 738-4828, djohnston@cheo.on.ca.

Presented at the American Society of Hematology Meeting, San Francisco, CA, December 6, 2008

Conflict of Interest

The authors have no conflict of interest to declare.

Introduction

Extramedullary leukemia (EML) is a common finding in pediatric acute myeloid leukemia (AML) and can occur as both a myeloid sarcoma (MS) or as leukemia cells in the cerebrospinal fluid (CSF). Myeloid sarcoma, formally known as extramedullary leukemia or chloroma, is an extramedullary proliferation of myeloid blasts that disrupt the normal architecture of the tissue it is found in (1). MS is often seen within the central nervous system (CNS) and these are often treated in a similar fashion as leukemia cells within the CSF. In a recent review of EML in children with newly diagnosed AML, Dusenbery et al (2), found that compared to patients with no MS, those with non-skin MS had a better survival than patients with MS involving the skin. They did not examine the influence of leukemia in the CSF or CNS MS on survival. A previous study by Abbott et al (3), and a recent COG study (4) have shown that CSF leukemia at diagnosis in pediatric AML does not affect overall survival, however, neither examined MS.

In this study, we sought to determine the clinical features and outcomes of patients with CNS MS, orbital MS, CSF leukemia, non-CNS MS, and no MS. Children included in this study were those with *de novo* AML treated on Children's Cancer Group (CCG) protocols 2861, 2891 (intensive timing arm), 2941 and 2961. These patients were all treated in a similar fashion with intensive timing induction therapy followed by high-dose cytarabine-based chemotherapy or stem cell transplantation. This analysis represents the largest cohort, among pediatric and adult patients, with MS at diagnosis and describes the outcome for these patients.

Methods

Patients and Therapy

Information regarding the presence of MS and CNS disease at diagnosis was obtained from the data submitted by institutions for patients enrolled on protocol. Eligibility included patients with *de novo* AML, and patients with myelodysplastic syndrome, Down syndrome, FAB M3 APL, t(15;17), and secondary AML were excluded. Only patients on CCG 2891 who received intensive timing treatment were included to ensure fairly uniform therapy for all patients analyzed. As a result, a total 1459 eligible patients on CCG 2861, CCG 2891, CCG 2941 and CCG 2961 were used for these analyses.

Patients were classified into 3 groups: 1) CNS1, CSF white blood cell count <5 without blasts on the cytospin; 2) CNS2, white blood cell count in the CSF <5 with blasts; and 3) CNS3, white blood cell count in CSF ≥ 5 with blasts. A group of patients were not classified due to either missing data or white cell count in the CSF ≥ 5 with no blasts. As a result, there were a total of 1113 patients in the CNS1 category, 192 in the CNS2 category, 154 in the CNS3 category, and 148 patients that were not classified, thus not eligible for this study. Since we have previously shown that there is no difference in survival between CNS1 and CNS2 patients, these groups have been combined in this study (4). Patients with MS were identified and classified as CNS MS (eg brain, spinal cord), orbital MS, non-CNS MS (eg skin) or unknown. As a result there were 19 patients with CNS MS (of whom 4 also had CNS3 status), 23 patients with orbital MS, and 57 patients with non-CNS MS. Of the 57 patients with non-CNS MS, 48 of them had skin only MS. There were only 2 patients with isolated MS and no marrow involvement. Fifty-eight patients were classified as having MS but no location was specified, and these patients were not included in this analysis.

Patients enrolled on CCG protocols 2861 and 2891 (intensive timing arm), were treated as previously reported (5,6). A summary of their treatment is as follows: induction

chemotherapy consisted of five drugs (dexamethasone, cytarabine, 6-thioguanine, etoposide, and daunomycin (DCTER)) given at diagnosis and then repeated after a 6-day rest. Patients received intrathecal cytarabine at the start of each DCTER cycle during induction and received a total of 4 doses. Central nervous system involvement with leukemia was diagnosed if the patient had CNS3 status and these patients received additional twice weekly intrathecal cytarabine for a total of 6 doses, and if this failed to clear the leukemia cells they then received twice weekly triple intrathecal therapy for a total of 6 doses. All patients randomized to chemotherapy also received intrathecal chemotherapy with each post consolidation cycle, except Capizzi, for another 3 doses. Radiation therapy was supposed to be given to patients who had MS (dose 2000 cGy) or who had CNS leukemia that did not clear after 6 doses of intrathecal chemotherapy (dose 2400 cGy). In a previous analysis, 12/44 (27%) patients with skin MS and 30/74 (41%) patients with non-skin/non-CNS MS received radiation therapy on this protocol (2). Postremission patients with a matched related donor were allocated to an allogeneic bone marrow transplant (BMT). The remaining patients received autologous BMT on 2861, and on 2891 were randomized to intensification with autologous BMT versus intensive timing high dose cytarabine.

Patients enrolled on CCG protocols 2941 and 2961 were treated as previously reported (7,8). Briefly, on protocol 2941 treatment was as follows: induction chemotherapy consisted of a 4 day cycle of 5 drugs (dexamethasone, cytarabine, 6-thioguanine, etoposide, and either daunomycin or idarubicin) which was then repeated 6 days later. This was repeated and following this, patients with a matched related donor received a BMT, while the remaining patients received Capizzi II intensification followed by interleukin-2 (IL-2) therapy. On protocol 2961 treatment was similar to this with induction therapy consisting of a 4 day cycle of 5 drugs (dexamethasone, cytarabine, 6-thioguanine, etoposide, and idarubicin) followed by a similar cycle 6 days later using daunomycin instead of idarubicin. Patients were then randomized to a second 2 cycles of chemotherapy the same as the first 2 cycles or a course of fludarabine, cytarabine and idarubicin. Following this, patients with a matched related donor received a BMT, while the others received Capizzi II intensification and were then randomized to IL-2 therapy. CNS prophylaxis consisted of 8 doses of intrathecal cytarabine, given days 0 and 14 in induction, days 0,10 and 35 in consolidation, and days 0,7 and 14 in course 2 intensification. Patients with CNS leukemia at diagnosis received additional intrathecal cytarabine on days 5 and 7, and if this failed to clear the leukemia cells they then received twice weekly triple intrathecal therapy beginning day 10 until the CSF was clear of leukemia cells (for a maximum of 6 doses), and if this failed to clear the leukemia cells they were removed from protocol. Patients who presented with MS whether or not they were symptomatic were supposed to receive 2000 cGy of radiation even if the MS resolved with chemotherapy.

Statistical Methods

This report analyzes data collected on CCG 2861 through September 21, 2001, on CCG 2891 through January 14, 2004, on CCG 2941 through April 14, 2005, and on CCG 2961 through October 30, 2006. The significance of observed differences in proportions was tested using the Chi-squared test and Fishers exact test when data were sparse. The Mann-Whitney test was used to determine the significance between differences in medians. The Kaplan-Meier method was used to calculate estimates of OS, EFS, and DFS. Cox proportional hazard models were also used to estimate hazard ratios for univariate and multivariate analyses. Overall survival is defined as time from study entry to death. Event free survival is defined as time from study entry to failure at course 1 or course 2, relapse or death. Disease free survival is defined as time from end of course 2 for patients in remission or who have residual leukemia to relapse or death. Differences between groups of patients were tested for significance using the log-rank statistic for OS, EFS and DFS analyses.

Confidence intervals were calculated using Greenwood's estimate of the standard error. Relapse risk was defined as the cumulative incidence of relapse and was estimated by considering deaths due to non-progressive disease as competing events. Isolated bone marrow or CNS relapse were defined as relapse in the marrow or CNS respectively with no evidence of disease relapse elsewhere within 30 days of the relapse. Concurrent relapse was defined as a relapse of both the bone marrow and CNS at the same time, or within 30 days of the first relapse. The cumulative incidence of isolated bone marrow relapse was estimated by considering concurrent bone marrow and CNS relapses, isolated CNS relapses and first event deaths as competing events. The cumulative incidence of isolated CNS relapse was estimated by considering concurrent bone marrow and CNS relapses, isolated bone marrow relapses and first event deaths as competing events. Significant differences in cumulative incidence were determined by Gray's test. Children lost to follow-up were censored at their date of last known contact or at a cutoff 6 months prior to September 2001, January 2004, April 2005, and October 2006 for CCG 2861, CCG 2891, CCG 2941 and CCG 2961, respectively.

Results

Patient Characteristics

A total of 1459 patients treated with intensive timing chemotherapy were analyzed in this study. At diagnosis, 76% were CNS1, 13% were CNS2, and 11% were CNS3. At diagnosis, 1% had CNS MS, 2% had orbital MS, 4% had non-CNS MS and only 4 patients (0.3%) with CNS MS had CNS3 status. The characteristics of the patients with MS and CNS3 status are presented in Table I. More patients with orbital MS and CNS MS were in the 3–10 year age range compared to the non-CNS MS and CNS3 patients. Also, patients with orbital MS had a significantly lower incidence of hepatosplenomegaly. Patients with CNS leukemia (CNS3) had a significantly higher white blood cell count at presentation compared to the other EML patients. There were significantly more patients with orbital MS and CNS MS with M2 morphology compared to non-CNS MS and CNS3 patients, and significantly more patients with M4 morphology in patients with CNS leukemia compared to the other EML patients. Finally, significantly more patients with both orbital MS and CNS MS had t(8;21) cytogenetics compared to non-CNS MS and CNS3 patients, and significantly more patients with CNS MS had +21 cytogenetics compared to other EML patients.

A total of 163 patients were identified as having myeloid sarcoma (Table II) including 23% at a site in the CNS and 36% with an unknown site. Only 17% of CNS-MS patients had CNS3 status.

A total of 24% of patients received bone marrow transplant on these studies (65% of these were allogeneic transplants and 35% autologous transplants). The percentage of patients in each MS group who received transplants is shown in Table III. There were no significant differences in the patients from each group who received a transplant.

Outcome

The complete remission rate by the end of course 2 was significantly higher in the orbital MS patients and CNS MS patients compared to the non-CNS MS and non MS patients (96% and 95% vs 78% and 78 % respectively, $p=0.034$). The patients with orbital MS, followed by CNS MS had significantly higher overall survival compared to non-CNS MS and non MS patients (92% and 73% vs 38% and 50% respectively, $p<0.001$) (Table III, Figures 1 and 2). They also had a higher event free survival (76% and 52% vs 34% and 40% respectively, $p=0.004$). There was no significant difference in bone marrow relapse, isolated CNS relapse or relapse risk among the orbital MS, CNS MS, non-CNS MS and non MS

patients, however the orbital MS patients had a significantly lower relapse risk (23%) compared to the CNS MS, CNS3 and MS/CNS3 patients (38%, 51%, and 75% respectively, $p=0.010$). Comparing orbital MS patients, CNS MS patients and CNS3 patients, the patients with orbital MS had significantly higher overall survival (91%) and event free survival (78%) followed by CNS MS patients (84% and 58% respectively) (Table IV). The risk of CNS relapse was higher in the CNS3 patients compared to the orbital MS and CNS MS patients, although not significantly. In comparing the CNS1/2 patients with no MS, CNS3 patients with no MS, orbital MS, CNS MS and non-CNS MS patients, the patients with orbital MS had a significantly higher overall survival and disease free survival both from study entry and from the end of course 2 compared to the other patient groupings (Table V). The higher incidence of $t(8;21)$ in the orbital MS and CNS MS patients does not explain the superior outcome of these patients, as multivariate analyses that adjusted for cytogenetics (low risk vs not low risk), showed the outcome for the orbital MS patients was still significantly better for OS (HR=0.16, 95% CI: 0.04–0.70, $p=0.015$) and EFS (HR=0.29, 95% CI: 0.11–0.80, $p=0.016$) compared to the non-CNS group. Although EFS for CNS MS patients is not significantly different than the non-CNS MS group in multivariate analysis, the HRs are qualitatively similar. The lack of significance may be due to in part to only having 12 CNS MS patients in the multivariate analysis compared with 23 in the univariate analysis.

Of the 9 patients who had non-CNS MS that did not involve the skin, 6 died and 3 are still alive (one following a relapse).

Discussion

Patients with orbital myeloid sarcoma had a better survival than those with CNS MS, non-CNS MS, as well as a better survival than patients with CNS leukemia and patients with neither myeloid sarcoma nor CNS leukemia. We are missing the location of the myeloid sarcoma in approximately one third of cases, but despite this limitation, this study represents the largest analysis of pediatric patients with myeloid sarcoma. In a previous study of extramedullary leukemia in children with newly diagnosed AML (2), patients with non-skin extramedullary leukemia (including the CSF) had a better survival than patients with extramedullary leukemia involving the skin. We reinforced this finding since in this study, 48 of the 57 patients with non-CNS MS had skin disease, representing the majority of the non-CNS MS patients. This should provide reassurance to clinicians caring for patients with myeloid sarcoma involving CNS or orbital sites.

Our results of improved survival in patients with orbital myeloid sarcoma are in contrast to a Turkish study which found that children with AML and orbital granulocytic sarcoma had a very poor outcome with a mean survival time of 8.7 months (9). Another study though, of children with orbital granulocytic sarcoma had similar results to ours, with all 9 of these patients surviving their disease (10). Thus, this set of results combined with the results of this study are reassuring.

One recent study of extramedullary infiltration (EMI) in children with AML included leukemic infiltration of organs other than the liver, spleen and lymph nodes, and also included CNS leukemia in their EMI definition (11). They found that this occurred in 56(23%) of their 240 cases and the patients with extramedullary infiltration had a higher white cell count, higher proportion of M4/M5, and a higher incidence of $inv16$ and $11q23$ abnormalities. The EMI was isolated as skin involvement in 13(23%) of their cases. Other studies also have shown that MS is often associated with $t(8;21)$ and M2 subtype (12–14). A small study also found a high incidence of abnormalities of chromosomes 8 and 21 in patients with granulocytic sarcomas (10). Nine of their 15 patients with granulocytic

sarcoma had these chromosomal findings and all 9 of these patients had periorbital involvement of the granulocytic sarcoma, thus orbital MS. We found that there was a higher incidence of t(8;21) in patients with orbital and CNS MS, and these 2 groups of patients had a higher incidence of M2 morphology.

The significantly higher incidence of t(8;21) in the orbital MS and CNS MS patients in our study compared to the non-CNS MS, the CNS3 and the CNS 1/2 without MS patients is not the explanation for the superior outcome of these patients, based on the Cox regression analyses done. This correlates with data on the presence of t(8;21) in two small studies: A Turkish study did not find that the presence of t(8;21) had a favorable effect on prognosis of children with orbital MS (9). As well, a small Argentinean study examined children with t(8;21) and found the survival in these patients was 70% if they had no MS, and 58% if they had a MS (15). The 8 patients with MS in this study had an orbital MS in 5 cases and a CNS MS in 3 cases (including 1 with orbital and CNS MS). Their orbital MS and CNS MS survival was significantly lower than in our study, perhaps due to the small number of patients in their study.

The incidence of MS (orbital, CNS and non-CNS) and CNS3 in our study was 243 of 1459 (16.7%) which is slightly lower than the Kobayashi study (11) of only 240 cases. As well, in our larger study, we found that patients with all types of MS had relatively low median white counts ($8.4\text{--}13.1 \times 10^3/\mu\text{L}$), while patients with CNS3 had a significantly higher median white blood cell count ($71.1 \times 10^3/\mu\text{L}$).

Kobayashi et al found that overall survival did not differ between patients with or without extramedullary infiltration (11). They also found that EFS was significantly lower in children with CNS leukemia compared to those without EMI or with “myeloblastoma.” We found that patients with orbital MS, followed by CNS MS had a better overall survival and even free survival than the non-CNS MS patients and patients with CNS3 status, and patients with no EML (CNS1/2 patients with no MS).

In comparing this group of patients, to the entire cohort of patients treated on trials CCG 2891 and CCG 2961, the overall survival on these protocols was 51% and 52% respectively (6,8). Thus, the overall survival of 92% for patients with orbital MS and 73% for patients with CNS MS is significantly better than the cohort treated on these protocols. In fact, in comparing orbital and CNS MS patients to patients with no EML (CNS1/2 and no MS), the overall survival was significantly higher (92% and 73% respectively vs 50%).

Patients on these protocols who had MS were supposed to be treated with radiation therapy at a dose of 2000 cGy but we know that of patients on protocols 2861 and 2891, only 36% of patients with MS are known to have received radiation therapy (2). As well, on protocol 2961 radiation therapy was prescribed to be given to all patients with myeloid sarcoma, but data was not collected documenting the administration of radiation therapy and so we cannot comment on its role in the therapy of MS. In a recent small study of pediatric granulocytic sarcoma, none of the 15 patients received local radiation therapy and these patients had an improved DFS compared to patients with AML and no granulocytic sarcoma (10). The recent COG de novo AML protocol AAML0531 did not recommend the use of radiation therapy to treat patients with MS unless the mass was causing a significant deficit, as clinicians are trying to avoid the long term complications of radiation therapy. It will be important to capture the data on radiation therapy for patients with MS to definitively determine if the difference seen in the CNS MS patients compared to the non-CNS MS patients is related to utilization of radiation therapy.

This study represents the largest cohort by far of pediatric patients with AML examined for the presence of myeloid sarcoma at diagnosis. Patients with MS involving orbital and CNS

sites had a better survival than patients with non-CNS MS as well as those with leukemia in the CSF and those with neither myeloid sarcoma nor CNS leukemia. The reason for this improved survival is not due to the presence of t(8;21), and further investigation into this group of patients is warranted.

Acknowledgments

Funding for CCG 2861, 2891, 2941 and 2961 was provided by Chair's Grant U10 CA98543 and U10 CA98413

References

1. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009; 114:937–951. [PubMed: 19357394]
2. Dusenbery KE, Howells WB, Arthur DC, et al. Extramedullary leukemia in children with newly diagnosed acute myeloid leukemia. *J Pediatr Hematol Oncol*. 2003; 25:760–768. [PubMed: 14528097]
3. Abbott BL, Rubnitz JE, Tong X, et al. Clinical significance of central nervous system involvement at diagnosis of pediatric acute myeloid leukemia: a single institution's experience. *Leukemia*. 2003; 17:2090–2096. [PubMed: 14523477]
4. Johnston DL, Alonzo TA, Gerbing RB, et al. The Presence of Central Nervous System Disease at Diagnosis in Pediatric Acute Myeloid Leukemia Does Not Affect Overall Survival: A Children's Oncology Group Study. *Pediatr Blood Cancer*. 2010; 55:414–420. [PubMed: 20658610]
5. Woods WG, Kobrinsky N, Buckley J, et al. Intensively timed induction therapy followed by autologous or allogeneic bone marrow transplantation for children with acute myeloid leukemia or myelodysplastic syndrome: A Children's Cancer Group pilot study. *J Clin Oncol*. 1993; 11:1448–1457. [PubMed: 8336184]
6. Woods WG, Kobrinsky N, Buckley J, et al. Timed-sequential induction therapy improves postremission outcome in acute myeloid leukemia: a report from the Children's Cancer Group. *Blood*. 1996; 87:4979–4989. [PubMed: 8652810]
7. Lange BJ, Dinndorf P, Smith FO, et al. Pilot study of idarubicin-based intensive-timing induction therapy for children with previously untreated acute myeloid leukemia: Children's Cancer Group study 2941. *J Clin Oncol*. 2004; 22:150–156. [PubMed: 14701777]
8. Lange BJ, Smith FO, Feusner J, et al. Outcomes in CCG-2961, a Children's Oncology Group phase 3 trial for untreated pediatric acute myeloid leukemia: a report from the Children's Oncology Group. *Blood*. 2008; 111:1044–1053. [PubMed: 18000167]
9. Gozdasoglu S, Yavuz G, Unal E, et al. Orbital granulocytic sarcoma and AML with poor prognosis in Turkish children. *Leukemia*. 2002; 16:962. [PubMed: 11986967]
10. Schwyzer R, Sherman GG, Cohn RJ, et al. Granulocytic sarcoma in children with acute myeloblastic leukemia and t(8;21). *Med Pediatr Oncol*. 1998; 31:144–149. [PubMed: 9722895]
11. Kobayashi R, Tawa A, Hanada R, et al. Extramedullary infiltration at diagnosis and prognosis in children with acute myelogenous leukemia. *Pediatr Blood Cancer*. 2007; 48:393–398. [PubMed: 16550530]
12. Reinhardt D, Creutzig U. Isolated myelosarcoma in children – Update and review. *Leuk Lymphoma*. 2002; 43:565–574. [PubMed: 12002760]
13. Tallman MS, Hakimian D, Shaw JM, et al. Granulocytic sarcoma is associated with the 8;21 translocation in acute myeloid leukemia. *J Clin Oncol*. 1993; 11:690–697. [PubMed: 8478662]
14. Chang H, Brandwein J, Yi QL, et al. Extramedullary infiltrates of AML are associated with CD56 expression, 11q23 abnormalities and inferior clinical outcome. *Leuk Res*. 2004; 28:1007–1011. [PubMed: 15289011]
15. Felice MS, Zubizarreta PA, Alfaro EM, et al. Good outcome of children with acute myeloid leukemia and t(8;21)(q22;q22), even when associated with granulocytic sarcoma. *Cancer*. 2000; 88:1939–1944. [PubMed: 10760772]

Figure 1. Kaplan Meier curve for Event Free Survival of Orbital MS, CNS MS, CNS 1/2 and no MS, CNS3 and no MS and Non-CNS MS patients. The p value represents the comparison between all groups for event-free survival.

Figure 2. Kaplan Meier curve for Overall Survival of Orbital MS, CNS MS, CNS 1/2 and no MS, CNS3 and no MS, and Non-CNS MS patients. The p value represents the comparison between all groups for overall survival.

Table 1

Patient Characteristics CNS MS, Orbital MS, Non CNS MS, CNS3 and CNS3 with CNS MS patients.

	A: CNS MS (n=19)		B: Orbital MS (n=23)		C: Non-CNS MS without CNS3 (n=47) ²		D: CNS3 ¹ (n=150)		E: CNS3 with MS (n=4)		A vs. B vs. C vs. D
	N	%	N	%	N	%	N	%	N	%	
Study											p-value
CCG-2861	1	5%	1	4%	3	6%	10	7%	0	0%	0.975
CCG-2891 INT	4	21%	3	13%	6	13%	52	35%	0	0%	0.008
CCG-2941	1	5%	1	4%	4	9%	10	7%	0	0%	0.916
CCG-2961	13	68%	18	78%	34	72%	78	52%	4	100%	0.013
Gender											
Male	11	58%	14	61%	24	51%	83	55%	2	50%	0.878
Female	8	42%	9	39%	23	49%	67	45%	2	50%	
Age (yrs)											
Median (range)	2.5	(0.71 – 16.4)	4.7	(0.65 – 15.2)	8.7	(0.01 – 18.4)	4.5	(0.04 – 19.4)	1.3	(0.48 – 5.5)	0.815
0–2 y	10	53%	9	39%	19	40%	67	45%	3	75%	0.785
3–10 y	6	32%	11	48%	9	19%	35	23%	1	25%	0.051
11–21 y	3	16%	3	13%	19	40%	48	32%	0	0%	0.055
Race											
White	11	58%	17	74%	30	64%	99	67%	3	75%	0.718
Black	2	11%	1	4%	2	4%	10	7%	0	0%	0.776
Hispanic	4	21%	2	9%	8	17%	22	15%	1	25%	0.707
Asian	1	5%	1	4%	2	4%	5	3%	0	0%	0.973
Other	1	5%	2	9%	5	11%	12	8%	0	0%	0.904
Unknown	0		0		0		2		0		
Enlarged liver											
Normal	11	58%	17	74%	29	62%	63	42%	2	50%	0.007
Enlarged	8	42%	6	26%	18	38%	87	58%	2	50%	
Unknown	0		0		0		0		0		
Enlarged spleen											

	A: CNS MS (n=19)		B: Orbital MS (n=23)		C: Non-CNS MS without CNS3 (n=47) ²		D: CNS3 ¹ (n=150)		E: CNS3 with MS (n=4)		A vs. B vs. C vs. D
	13	68%	20	87%	34	72%	69	46%	2	50%	
Normal	13	68%	20	87%	34	72%	69	46%	2	50%	<0.001
Enlarged	6	32%	3	13%	13	28%	81	54%	2	50%	
Unknown	0		0		0		0		0		
FAB Classification											
M0	0	0%	0	0%	0	0%	4	3%	0	0%	0.518
M1	2	12%	0	0%	8	19%	22	16%	0	0%	0.246
M2	7	41%	11	58%	13	31%	22	16%	0	0%	<0.001
M4	4	24%	2	11%	9	21%	61	44%	2	50%	0.003
M5	2	12%	6	32%	12	29%	25	18%	2	50%	0.214
M6	0	0%	0	0%	0	0%	2	1%	0	0%	0.771
M7	2	12%	0	0%	0	0%	4	3%	0	0%	0.075
Other/no data	2		4		5		10		0		
Cytogenetics											
Normal	1	10%	0	0%	5	22%	19	23%	0	0%	0.125
t(8;21)	4	40%	10	56%	4	17%	2	2%	0	0%	<0.001
Abnormal 16	0	0%	1	6%	4	17%	17	20%	0	0%	0.210
Abnormal 11 ³	2	20%	5	28%	7	30%	19	23%	2	100%	0.858
t(6;9)(p23;q34)	0	0%	0	0%	0	0%	1	1%	0	0%	0.892
-7/7q-	0	0%	0	0%	2	9%	2	2%	0	0%	0.315
-5/5q-	0	0%	0	0%	0	0%	1	1%	0	0%	0.892
+8	0	0%	0	0%	0	0%	3	4%	0	0%	0.596
+21	2	20%	0	0%	0	0%	0	0%	0	0%	<0.001
No data	9		5		24		67		2		
WBC ($\times 10^3/\mu\text{L}$) - median (range)	8.4	(3 – 155)	13.1	(3.6 – 55)	11.8	(1.2 – 309)	71.1	(0.9 – 575)	6.6	(6.3 – 74.3)	<0.001
Platelets ($\times 10^3/\mu\text{L}$) - median (range)	54	(8 – 325)	90	(7 – 484)	100	(6 – 686)	48	(2 – 411)	203	(31 – 282)	0.011

¹ 2 patients with Orbital MS and CNS3 are included.

² Excludes 10 patients who were non-CNS MS but were also CNS3.

Any abnormality of chromosome 11 was included (including but not limited to 11q23).

3

Table II

CSF characteristics for patients with myeloid sarcoma.

	CNS1/2 N (%)	CNS3 N (%)	Not Classified N (%)	Total N (%of total MS patients)
CNS MS	17 (74)	4 (17)	2 (9)	23 (14)
Orbital MS	21 (84)	2 (8)	2 (8)	25 (15)
Non-CNS MS	40 (70)	10 (18)	7 (12)	57 (35)
Unknown MS	43 (74)	8 (14)	7 (12)	58 (36)
Total	121 (74)	24 (15)	18 (11)	163

Table III

Outcomes for Non MS, CNS MS, Orbital MS and non-CNS MS patients.

	Non MS		CNS MS		Orbital MS		Non-CNS MS		p-value
	N	5 yr% $\pm 2SE\%$	N	5 yr% $\pm 2SE\%$	N	5 yr% $\pm 2SE\%$	N	5 yr% $\pm 2SE\%$	
OS from study entry	1314	50 $\pm$ 3%	23	73 $\pm$ 19%	25	92 $\pm$ 11%	57	38 $\pm$ 13%	<0.001
EFS from study entry	1314	40 $\pm$ 3%	23	52 $\pm$ 21%	25	76 $\pm$ 17%	57	34 $\pm$ 13%	0.004
OS from end course 2	954	61 $\pm$ 3%	20	74 $\pm$ 20%	23	91 $\pm$ 12%	43	48 $\pm$ 16%	0.014
DFS from end course 2	954	51 $\pm$ 3%	20	55 $\pm$ 22%	23	78 $\pm$ 17%	43	45 $\pm$ 15%	0.068
RR from end course 2	954	42 $\pm$ 3%	20	45 $\pm$ 22%	23	22 $\pm$ 17%	43	48 $\pm$ 16%	0.164
BM relapse from end course 2	954	35 $\pm$ 3%	20	20 $\pm$ 18%	23	17 $\pm$ 16%	43	26 $\pm$ 14%	0.227
Isolated CNS relapse from end course 2	954	2 $\pm$ 1%	20	5 $\pm$ 9%	23	0 $\pm$ 0%	43	7 $\pm$ 8%	0.090
Concurrent BM and CNS relapse from end of course 2	954	3 $\pm$ 1%	20	0 $\pm$ 0%	23	4 $\pm$ 8%	43	2 $\pm$ 5%	0.899
CR rate by end of course 2 (95% Confidence Interval)		78% (75%–80%)		95% (76%–100%)		96% (78%–100%)		78% (65%–88%)	0.034

Table IV

Outcomes for CNS MS (not CNS3), Orbital MS, CNS3, and MS and CNS3 patients.

	CNS MS		Orbital MS		CNS3 ¹		MS and CNS3		p-value
	N	5 yr% ±2SE%	N	5 yr% ±2SE%	N	5 yr% ±2SE%	N	5 yr% ±2SE%	
OS from study entry	19	84±17%	23	91±12%	150	51±8%	4	25±43%	<0.001
EFS from study entry	19	58±23%	23	78±17%	150	35±8%	4	25±43%	0.001
OS from end course 2	16	87±18%	22	91±12%	116	59±9%	4	25±43%	0.001
DFS from end course 2	16	63±24%	22	77±18%	116	44±9%	4	25±43%	0.007
RR from end course 2	16	38±24%	22	23±18%	116	51±9%	4	75±43%	0.010
BM relapse from end course 2	16	19±19%	22	18±16%	116	35±9%	4	25±28%	0.138
Isolated CNS relapse from end course 2	16	0±0%	22	0±0%	116	7±5%	4	25±25%	0.077
Concurrent BM and CNS relapse from end of course 2	16	0±0%	22	5±9%	116	5±4%	4	0±0%	0.755

¹ 2 patients with Orbital MS and CNS3 are included in CNS3 column and excluded from orbital MS column.

Table V

Overall survival and disease free survival of CNS1/2 and no MS, CNS3 and no MS, CNS MS, Orbital MS and non-CNS MS patients.

	CNS 1/2, no MS		CNS 3, no MS		CNS MS		Orbital MS		Non-CNS MS		p-value
	N	5 yr% $\pm$ 2SE%	N	5 yr% $\pm$ 2SE%	N	5 yr% $\pm$ 2SE%	N	5 yr% $\pm$ 2SE%	N	5 yr% $\pm$ 2SE%	
OS from study entry	1184	50 $\pm$ 3%	130	52 $\pm$ 9%	23	73 $\pm$ 19%	25	92 $\pm$ 11%	57	38 $\pm$ 13%	<0.001
EFS from study entry	1184	41 $\pm$ 3%	130	34 $\pm$ 9%	23	52 $\pm$ 21%	25	76 $\pm$ 17%	57	34 $\pm$ 13%	0.005
OS from end of course 2	854	61 $\pm$ 3%	100	61 $\pm$ 10%	20	74 $\pm$ 20%	23	91 $\pm$ 12%	43	48 $\pm$ 16%	0.030
DFS from end of course 2	854	52 $\pm$ 4%	100	42 $\pm$ 10%	20	55 $\pm$ 22%	23	78 $\pm$ 17%	43	45 $\pm$ 15%	0.024