brief report

Hematopoietic stem cell transplant versus chemotherapy plus tyrosine kinase inhibitor in the treatment of pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL)

Khadra Salami [a], Khaldoun Alkayed [a], Hadeel Halalsheh [a], Ayad Ahmed Hussein [b], Maha Riziq [a], Faris Madanat [a,*]

[a] Department of Pediatrics, King Hussein Cancer Center, Amman, Jordan, [b] Bone Marrow and Stem Cell Transplantation Program, King Hussein Cancer Center, Amman, Jordan · FMADANAT@KHCC.JO · Accepted for publication 9 March 2013

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BACKGROUND: Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) remained until recently the molecular genetic abnormality associated with the worst outcome. Hematopoietic stem cell transplant (HSCT) was considered the treatment of choice, however, recent data have indicated that chemotherapy plus tyrosine kinase inhibitor (TKI) maybe an alternative effective therapy.

METHODS: We conducted a retrospective analysis of children (<18 years) with Ph+ ALL who were treated at King Hussein Cancer Center (KHCC) from January 2003 till December 2011.

RESULTS: Over a 9 year period, 411 children were diagnosed and treated for ALL at KHCC. Twenty three (6.6%) had Ph+ ALL; 16 males and 7 females. Median age at diagnosis was 9.5 years (range 1.67–17). The median white blood cell count was $58.6 \times 10^3/\mu L$ (range 1.6–459). Twelve patients underwent HSCT from a full matched related donor; and 10 were treated with intensive chemotherapy plus TKI (imatinib). Those who underwent HSCT were significantly older ($P = 0.004$) and had a higher leukocyte count at diagnosis ($P = 0.53$). After a median follow up of 42.2 months (range 12.7–107), the estimated 5 year event free survival (EFS) and overall survival (OS) were 75% and 91.6%, respectively, for those who underwent HSCT as primary therapy and 49.3% and 83.3%, respectively, for those treated with chemotherapy plus imatinib. There was no significant difference in EFS ($P = 0.98$) or OS ($P = 1$) between the two treatment modalities.

CONCLUSIONS: Our results indicate that chemotherapy plus TKI may be a reasonable treatment option for some children with Ph+ ALL.

The probability of curing children with acute lymphoblastic leukemia (ALL) with current treatment regimens has exceeded 80%.[1–6] Although some adverse prognostic features have lost their clinical significance with improvement in therapy using a risk-adapted approach; others remain associated with poor outcome. The translocation t(9;22) Philadelphia chromosome remained until recently the molecular genetic abnormality that is associated with the worst outcome.[7–9] While Philadelphia chromosome (Ph) is present in about 40% of adult ALL, it only represents 3–5% of childhood ALL.[1,7] Intensive chemotherapy cures less than 30%, while hematopoietic stem cell transplant (HSCT) from a matched related donor has raised the cure rate to about 60%.[8] Findings of studies suggest that matched unrelated donor or cord blood transplantation produce results that are comparable to those obtained with matched related donor transplantation.[9] The development of the tyrosine kinase inhibitor (TKI) imatinib mesylate that target the BCR–ABL fusion protein produced by the Ph chromosome has revolutionized the treatment

of chronic myelogenous leukemia (CML).[6] Imatinib monotherapy has produced a high response rate in Ph+ ALL but the responses were transient with recurrences within months.[10] Subsequent trials in adults with Ph positive ALL using imatinib as front line treatment combined with chemotherapy either concurrently or sequentially has improved outcome significantly.[11,12] Transplant candidates had a better chance of receiving allogeneic transplantation with imatinib-combined regimen.[12,13] In a children's oncology group (COG) study, continuous imatinib in addition to intensive chemotherapy has produced in a cohort of 50 patients 3-year event free survival (EFS) of 80%, similar to those who underwent matched-sibling donor transplantation.[3]

At the King Hussein Cancer Center (KHCC), children with Ph+ ALL are offered HSCT from an HLA-matched donor in first remission. Those with no available donor or who decline HSCT are treated with continuous imatinib combined with intensive chemotherapy. In this report, we present their treatment results.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of children below 18 years of age diagnosed with Ph+ ALL and treated at KHCC from January 2003 through December 2011.

Diagnosis of Ph+ ALL was based on fluorescence in situ hybridization (FISH) and cytogenetic analysis done on the bone marrow obtained at the time of diagnosis. All children were treated according to the KHCC ALL-1102 protocol, a locally adapted ALL therapy based on St. Jude Children Research Hospital protocols (a hybrid of total XIII and total XV protocols).[14] According to our protocol, patients with Ph+ ALL were treated on the high risk arm.[15]

Chemotherapy

Treatment included three phases: Five week remission induction phase with a seven drug regimen [prednisolone, vincristine, daunorubicin, cytarabine, 6-mercaptopurine (6MP), cyclophosphamide, and L-asparaginase], (Figure 1). Consolidation phase [four cycles of high-dose methotrexate (MTX) at a dose of 4 g/m^2, given as a 24-h infusion with leucovorin rescue, 2 weeks apart, and daily oral 6MP (50 mg/m^2)] (Figure 2). The last phase was a maintenance phase which consisted of extended weekly L-asparginase administration followed by rotating pairs of drugs (cyclophosphamide–cytarabine, etoposide–cytarabine, vincristine–dexamethasone, and 6MP–MTX). The 6MP dose was 50 mg/m^2/day in the first 20 weeks of maintenance therapy increased to 75 mg/m^2/day; the MTX dose was 20 mg/m^2 PO weekly. The target absolute neutrophil count was between 300 and $1500 \times 10^3/\mu L$.

Two courses of 3-week re-induction were given on weeks 7 and 17 of maintenance therapy. Induction I consisted of vincristine, doxorubicin, dexamethasone, and L-asparaginase. High-dose cytarabine was administered in induction II. Dexamethasone was administered in weeks one and three to minimize osteonecrosis.

All children with Ph+ ALL and have fully matched related donor were referred to HSCT after

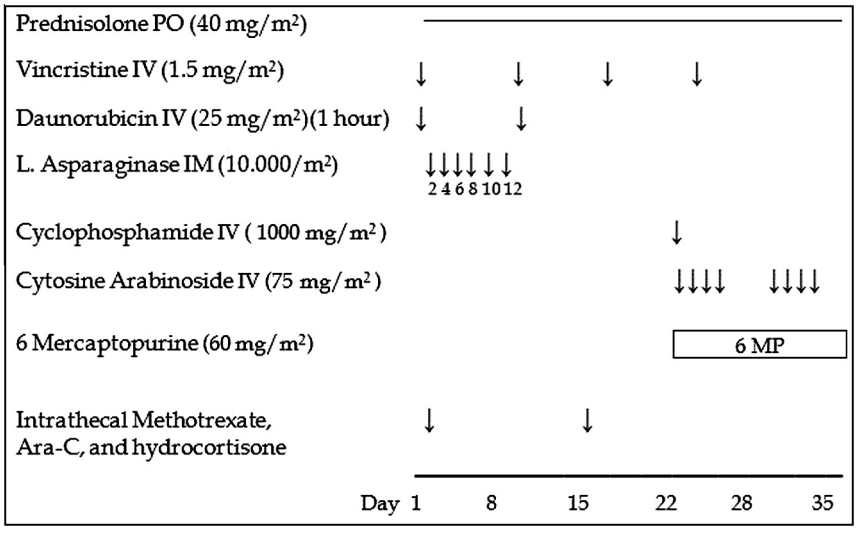

Figure 1. ALL-1102 – induction.

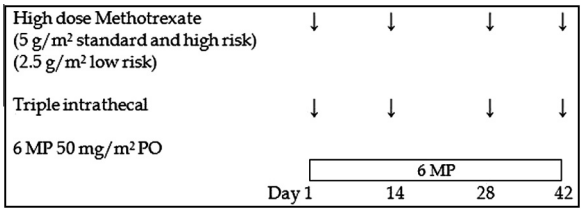

Figure 2. ALL-1102, consolidation.

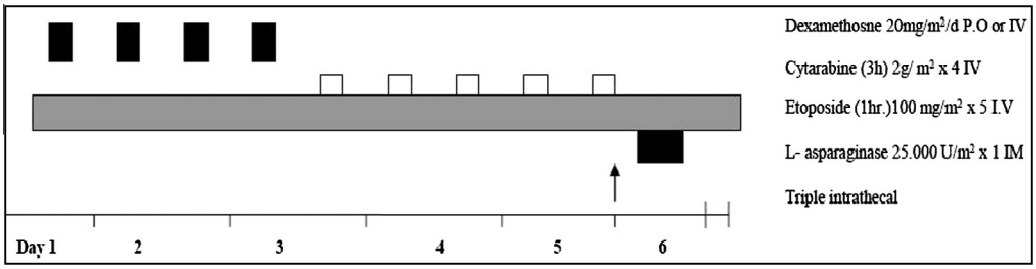

Figure 3. Intensification chemotherapy.

consolidation and intensification courses; otherwise, they were continued on chemotherapy.

The intensification course consisted of high dose cytarabine, etoposide, dexamethasone, and L-asparaginase (Figure 3).

Bone marrow examination, FISH, and PCR (polymerase chain reaction) evaluation for Ph chromosome and BCR/ABL gene product were performed on all children before HSCT.

Central nervous system (CNS) prophylaxis consisted of triple intrathecal therapy (methotrexate, cytarabine, and hydrocortisone) irrespective of the CNS status; the total doses administered were 25 and no radiation. Imatinib mesylate was started on day 15 of remission induction at a dose of 340 mg/m^2/day orally and it was continued until the end of therapy or until the time of HSCT. The total duration of treatment was 2.5 years for females and 3 years for males.

Stem cell transplantation

Supportive care: All patients were hospitalized for their transplant in the bone marrow transplant unit at high-efficiency particulate air (HEPA) filtered rooms. They all received antimicrobial prophylaxis against *Pneumocystis carinii*, Herpes virus, and fungal infections with trimethoprim–sulfamethoxazole, acyclovir, and fluconazole, respectively. Cytomegalovirus (CMV) reactivation was monitored by the pp65 antigenemia test weekly starting from the time of neutrophil engraftment till 100 days post transplantation. Treatment with gancyclovir was initiated when two consecutive positive antigenemia of more than two cells/250 white blood cells documented, until a minimum of two negative tests was obtained.

Conditioning regimen and graft versus host disease (GVHD) prophylaxis: All patients received myeloablative conditioning that included fractionated total body irradiation of 12 Gy delivered in six fractions over 3 days followed by cyclophosphamide 60 mg/kg infused over 1 h daily for 2 days. All patients received GVHD prophylaxis consisted of a short course of MTX (15 mg/m^2 at days +1, 3 and 6) and intravenous cyclosporine starting from day-3. Patients were switched to oral cyclosporine whenever they were able to tolerate oral medications. Cyclosporine was gradually tapered off starting at day 100 post transplant and then stopped completely at day 180 post transplant if there was no GVHD.

Response criteria

Minimal residual disease (MRD) evaluation: A MRD panel was selected according to the patient's previously determined immunophenotype. The following monoclonal antibody combinations CD10/CD19/CD45/CD34 and CD20/CD45/CD19 were performed on each patient's marrow sample and CD33/CD13/CD45/CD19 was performed if the patient's leukemic cells previously expressed a myeloid marker. CD45 and side-scatter were used for the gating strategy. The result was reported as $<0.01\%$ for the negative results and as a percentage for the positive ones. MRD evaluation was performed on day 15 of induction and was repeated on day 22 only if

day 15 showed 5% or more leukemic blasts, otherwise, it was performed at the end of induction.

Day 15 induction bone marrow evaluation: Bone marrow (BM) remission status was evaluated on day 15 of remission induction and was defined as the presence of leukemic blasts by morphology (before July 2005) and minimal residual disease (MRD) (after July 2005) of less than 5%.

End of induction BM evaluation: Complete remission at the end of induction was defined as no leukemic blasts by morphology and an MRD of less than 1%.

Statistical methods

Demographic parameters were summarized as means and ranges for continuous variables, or frequency and percentages for categorical variables. Comparisons between categorical variables were carried out using the Chi-square test and Fisher's exact test as appropriate. Survival and event-free-survival curves were presented using the Kaplan–Meier method and compared with standard error (SE). Comparisons in survival and event free-survival were performed using the Log rank test. P value ≤ 0.05 was considered statistically significant. All analyses were carried out using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Over a 9 year period, 411 children were diagnosed and treated for ALL at KHCC, out of these 23 had Ph+ ALL (6.6%). The median age at diagnosis was 9.5 years (range 1.67–17). There were 16 males and 7 females, with a male to female ratio of 2.3:1. The initial leukocyte count (WBC) at diagnosis ranged from 1.6 to $459 \times 10^3/\mu L$ with a median count of $58.6 \times 10^3/\mu L$. The majority of patients (91.3%) had pre-B cell immunophenotype; two had T-cell phenotype. Twenty children had CNS I status, one had CNS II, and two had CNS III status (7th nerve palsy) (Table 1).

Of the 23 children, one died early in induction due to sepsis. Twelve patients underwent allogeneic HSCT from a full matched related donor; the remaining 10 had no full matched donor ($n = 9$) or declined transplant ($n = 1$) and were treated with intensive chemotherapy plus imatinib mesylate (Table 2).

For the 12 children who underwent HSCT, there were 9 males and 3 females; the median age at diagnosis was 12.5 years (range 4.2–17), and the median initial WBC was $84.8 \times 10^3/\mu L$ (range 1.6–459). Evaluation on day 15 showed remission by morphology (M1) in 11 (91.7%); one failed to achieve remission (M2). All patients were in remission (M1) at the end of induction (Table 3). Bone marrow examination prior to HSCT was in M1 and FISH and BCR/ABL were negative in all patients.

A total of four patients (33%) developed grade II–IV acute GVHD, one of them died with severe skin, gut, and liver acute GVHD. Chronic GVHD developed in three patients (27%), one limited and two extensive; all were controlled and resolved with first line treatment. At the last follow up, all surviving patients are off immune suppression.

Of the 10 children who were treated with intensive chemotherapy plus imatinib mesylate, 6 were males and 4 were females; the median age was 4.4 years (range 1.7–11.9) and the median initial WBC was $23.6 \times 10^3/\mu L$ (range 3.5–340). BM evaluation at day 15 of induction showed complete remission by morphology (M1) in seven patients, two failed to achieve remission (M2), and one had no available BM evaluation. All patients achieved complete remission at the end of induction by bone marrow morphology (M1) (Table 3).

After a median follow up of 42.2 months, the estimated 5-year overall survival rate (OS) for the whole group was 83 ± 9.5%. Based on treatment modality, the estimates of event-free survival (±SE) five years after diagnosis was 75 ± 12.5% for patients who underwent HSCT and 49.3 ± 22.8% for those treated with chemotherapy only ($P = 0.9$) (Figure 4A). The 5-year OS rate for patients who underwent HSCT in first remission (CR1) was 91.6 ± 7.9%, while patients who were treated with chemotherapy only had an 83.3 ± 15.2% OS ($P = 1$) (Figure 4B).

Relapses and deaths

Of the 23 patients, five relapsed. Two patients relapsed after HSCT from a fully matched related donor 10 and 11 months post transplant; both are in clinical and molecular remission 25 and 53 months, respectively, after treatment with TKI (dasatinib in one, and imatinib in the other). Three patients relapsed after treatment with intensive chemotherapy and imatinib mesylate; the first developed asymptomatic isolated CNS relapse at the end of therapy evaluation. He was subsequently treated with additional intensive chemotherapy, cranial radiation, and dasatinib; but experienced a second relapse (BM) 18 months after his first relapse. The second developed isolated bone marrow relapse one year after finishing treatment; he underwent HSCT from his father (one antigen mismatch), and remained in remission 10 months after HSCT. The third patient

Table 1. Patients' characteristics.

Gender	
Male	16 (69.6%)
Female	7 (30.4%)
Age (years)	
Median	9.5
Range	1.67–17
WBC × 10^3/μL	
Median	58.6
Range	1.6–459
Follow up (months)	
Median	42.2
Range	12.7–107
Immunophenotype	
Pre B cell	21 (91.3%)
T cell	2 (8.7%)
CNS	
I	20 (87%)
II	1(4.3%)
III	2 (8.7%)
Treatment	
Bone marrow transplantation	12 (54.5%)
Chemotherapy	10 (45.5%)

WBC: White blood count, CNS: central nervous system.

developed bone marrow relapse at 22 months of chemotherapy; he underwent HSCT from a related cord blood but experienced a second bone marrow relapse and died of disease. One child died of severe GVHD 96 days post HSCT.

DISCUSSION

In this report we reviewed children treated for Ph+ ALL at KHCC over a 9 year period. In our cohort of patients, improved survival of children with Ph+ ALL was evident compared to the old published data.[3,6,9,12] Advances in HSCT techniques, better selection of donors, and the introduction of TKI have contributed to the overall improvement in the outcome of this difficult subset of patients.

Patients younger than 10 years with initial leukocyte count of less than 50×10^3/μL at the time of diagnosis had better long term disease free survival.[7] In our study, the median age of patients was 9.5 years and the median initial WBC count was 58.6×10^3/μL, possibly contributing to our good overall results. There was no significant difference in the EFS and OS between the patients who underwent HSCT compared to those treated with chemotherapy only. However, those who underwent HSCT were older and had a higher leukocyte count at diagnosis. This observation may have impacted the outcome and confirms the need for more randomized controlled studies to identify patients who would benefit from allogeneic HSCT as the primary therapy versus those who would be adequately treated using TKI plus chemotherapy only.[8]

One of the reasons for the poor outcome for patients with Ph+ ALL was the higher rate of induction remission failure. In a retrospective study by Arico et al, the rate was reported to be 18% in comparison to 2–3% failure rate in a series of unselected patients with childhood ALL.[9] In the era of using TKI like imatinib, the rate of remission induction in Ph+ ALL patients has improved dramatically.[13,16] All our patients achieved complete remission at the end of induction; this is in agreement with the new reported results from the European studies.[17]

Another cause of treatment failure in Ph+ ALL patients was the high rate of relapse.[12] Historically the relapse rate was highest early in the course of treatment. In our study, five children had relapsed; two were treated primarily with HSCT and relapsed during the first year post transplant; three were treated with imatinib plus chemotherapy and relapsed during the third and fourth years (BM in 2, CNS in 1). Use of Imatinib could be a factor in the occurrence of relapses late in the course of the disease.

The addition of imatinib to the intensive chemotherapy was found to be well tolerated.[9–13] Imatinib was started at day 15 of induction at a dose of 340 mg/m^2 and continued till the end of therapy. Major toxicities were limited; one child developed excessive GI toxicity and imatinib was replaced by dasatinib; a second child, a member of a twin, experienced a significant delay in growth. No dose reduction was necessary.

The impact of using TKI after HSCT is controversial with conflicting data.[18–20] The COG study showed no difference in EFS for 6 months of TKI

Table 2. Patient characteristic, response and outcome.

Patient No.	Sex	Age (years)	Immunotype	WBC × 10^9	CNS	D15	D35	Treatment	Duration of remission (months)	Status (follow up) (months)
1	M	14	Pre B	7.9	III	CR	CR	BMT	_	NED (89)
2	M	17	Pre B	110.9	I	CR	CR	BMT	_	NED (82)
3	M	4	Pre B	244	I	CR	CR	CTX	Relapse/BM(22)	DOD (44)
4	M	14	T cell	376	III	NA	NA	NA	_	Died (0.42)
5	F	11	Pre B	10.4	I	NA	CR	CTX	_	NED (99)
6	M	17	Pre B	1.6	I	CR	CR	BMT	_	NED (103)
7	M	2	Pre B	3.5	I	Non	CR	CTX	Relapse/BM(47)	NED (60)
8	F	3.5	Pre B	339.7	I	CR	CR	CTX	_	NED (59)
9	M	7	Pre B	86.5	I	Non	CR	CTX	_	NED (43)
10	M	12	Pre B	4.7	I	CR	CR	CTX	_	NED (35)
11	F	15	Pre B	139	I	CR	CR	BMT	_	NED (33)
12	M	14	Pre B	4.1	I	CR	CR	BMT	_	NED (53)
13	M	4.5	Pre B	21.1	I	CR	CR	CTX	Relapse/CNS(36)	NED (52)
14	M	4	Pre B	23.9	I	CR	CR	BMT	Relapse/BM(11)	NED (53)
15	F	10	T cell	459	I	CR	CR	BMT	_	NED (35)
16	M	6	Pre B	26	I	CR	CR	CTX	_	NED (32)
17	F	1.5	Pre B	7.8	I	CR	CR	CTX	_	NED (32)
18	M	16.5	Pre B	2.2	I	CR	CR	BMT	Relapse/BM(10)	NED (25)
19	M	5.5	Pre B	58.6	I	CR	CR	BMT	_	NED (13)
20	M	9.5	Pre B	132	I	Non	CR	BMT	_	NED (12)
21	F	3	Pre B	229	I	CR	CR	CTX	_	NED (9)
22	M	8.5	Pre B	348	I	CR	CR	BMT	_	NED (16)
23	F	11	Pre B	338	II	CR	CR	BMT	_	Died (11)

Age: Age at diagnosis, CNS: central nervous system, D15: bone marrow evaluation by morphology at day 15 induction, D35: bone marrow evaluation at day 35, NED: no evidence of disease, BMT: bone marrow transplant, CTX: chemotherapy, DOD: died of disease.

maintenance following HSCT compared with historical transplant outcome.[3] In our patients, we did not use TKI following HSCT. It is of interest that two of the children who relapsed after HSCT responded to TKI and are still in continuous remission.

Additional studies are needed to find out if the use of second generation TKI (like dasatinib and nilotinib) will improve the outcome further. Both agents are more potent inhibitors of BCR–ABL kinase activity,[6] and dasatinib may have the added advantage of better CNS penetration.[21]

Our study has some limitations; the number of patients is small and the follow up period is relatively short. Log Rank test may fail to detect the differences in survival time due to small sample size. The low incidence of Ph+ ALL and the shortage of large prospective studies make the optimal treatment strategy for this high risk group unclear.

In conclusion, outcome of children with Ph+ ALL has improved significantly. The best treatment option is still not clear. A subset of patients may benefit from treatment with chemotherapy plus TKI. This creates an opportunity for our regional cancer institutions to initiate a multicenter study.

Acknowledgment

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Table 3. Comparison between patient's characteristics, response, and outcome according to treatment modalities.

Characteristic	Stem cell transplant	Chemotherapy	*P* value
Gender, n (%)			
Male	9 (75%)	6 (60%)	0.65
Female	3 (25%)	4 (40%)	
Age (years)			
Median (range)	12.5 (4.2–17.0)	4.4 (1.7–11.9)	0.0041
WBC ($\times 10^3/\mu l$)			
Median (range)	84.8 (1.6–459)	23.6 (3.5–340)	0.53
D15-morphology			
CR	11 (91.7%)	7 (70%)	0.36
Non remission	1 (8.3%)	2 (20%)	
NA		1 (10%)	
D35-morphology			
CR	12 (100%)	10 (100%)	NA
5-Year EFS	75%	49.3%	0.98
5-Year OS	91.6%	83.3%	1.0

CR: Complete remission, NA: not available, EFS: events free survival, OS: overall survival.

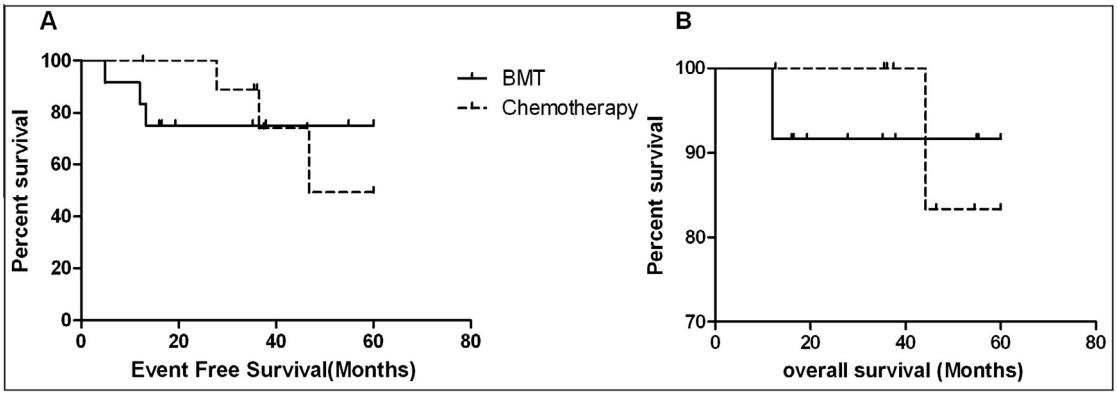

Figure 4. 5-year event free survival and overall survival according to treatment modality.

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