Published in final edited form as:

Leuk Res. 2016 January ; 40: 33–37. doi:10.1016/j.leukres.2015.11.010.

Stem Cell Transplantation in Adults with Acute Myelogenous Leukemia, Normal Cytogenetics, and the FLT3-ITD Mutation

Ellin Berman, MD¹, Molly Maloy, MA², Sean Devlin, PhD³, Suresh Jhanwar, PhD⁴,
Esperanza Papadopoulos, MD², and Ann Jakubowski, MD PhD²

¹Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, 1275 York Avenue, New York, New York 10065

²Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, 1275 York Avenue, New York, New York 10065

³Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, 1275 York Avenue, New York, New York 10065

⁴Department of Pathology, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, 1275 York Avenue, New York, New York 10065

Abstract

Following chemotherapy, patients with acute myelogenous leukemia (AML), normal cytogenetics, and the FLT3-ITD mutation have shorter survival compared to wild type (WT) patients. To determine the role of stem cell transplantation (SCT), we performed a retrospective review of adult patients with AML who underwent SCT at our center between January 1, 2007 and December 31, 2011. Of the 200 patients transplanted, 79 patients (40%) had normal cytogenetics; of these, 17 (22%) had the FLT3-ITD mutation, 35 were WT (44%), and 27 (34%) did not have FLT3 testing performed. Clinical characteristics were similar in each group. At four years, overall survival (OS) between FLT3 positive and WT groups was similar: 0.54 (95% CI 0.29–0.75) versus 0.73 (95% CI 0.53–0.99), $p=0.18$. Relapse rates were also similar, 0.09 (95% CI 0.02–0.21) versus 0.12 (95% CI: 0.02–0.32); $p=0.67$. We conclude that SCT can abrogate the poor prognosis in FLT3-ITD positive patients.

Keywords

stem cell transplantation; FLT3 + AML

Address inquiries to: Ellin Berman MD, Memorial Sloan Kettering Cancer Center, H-708, 1275 York Avenue, New York, New York 10065, Tel: 212-639-7762, Fax: 212-794-4338, bermane@mskcc.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest: None of the authors have a conflict of interest.

INTRODUCTION

Cytogenetic and molecular abnormalities in patients at the time of diagnosis are among the most important prognostic factors in patients with acute myelogenous leukemia (AML)^{1–8}. However, approximately 50% of patients have normal cytogenetics; within this group, somatic mutations such as those in FLT-3, TET2, NPM1, ASXL1, IDH1, IDH2, and DNMT3A have been shown to further refine clinical outcomes.^{4,5} FLT3-ITD is of particular interest as this is one of the most common molecular abnormalities, occurring in approximately 25–30% of patients with normal cytogenetics.^{4–8} While the incidence of complete remission (CR) in these patients has been shown to be similar to patients who have wild-type FLT3 (WT), remission duration is shorter and overall survival (OS) following chemotherapy is shorter compared to WT patients, especially in patients who are NPM1 positive.^{4–8} Stem cell transplantation (SCT) is often recommended for patients in first CR (CR1)^{9–11} but not all studies have shown a conclusive advantage.¹²

In order to better understand the role of SCT, including the use of T cell depletion (TCD) methodologies, we retrospectively reviewed all patients at Memorial Sloan Kettering Cancer Center (MSKCC) who underwent a SCT for FLT3-ITD positive AML and compared this group to patients without this mutation who also underwent a SCT during the same time period. We chose 2007 as the start date as that was the year that FLT3-ITD testing began on a routine basis; the last patient was entered in 2011 which permitted a median follow up of almost four years in each group.

PATIENTS AND METHODS

Analysis of patients who had FLT3-ITD testing performed

The Institutional Review Board at MSKCC approved a waiver to perform this study. We first reviewed all patients with AML who underwent SCT at this center between January 1, 2007, and December 31, 2011, to determine whether cytogenetic analysis had been performed at diagnosis. Patients who had normal cytogenetics were identified and those were then screened for results of FLT3-ITD testing. The group included patients in remission (CR1 and CR2) and patients with relapsed or primary refractory disease. No patient had received a FLT3-ITD inhibitor prior to transplant.

Conditioning regimens for patients undergoing TCD grafts

Patients received one of two conditioning regimens, either a high dose chemotherapy program (regimen A) or a full dose hyperfractionated total body irradiation (HFTBI) in combination with chemotherapy (regimen B). Patients over the age of 60 or younger patients with multiple co-morbidities generally received regimen A and younger, otherwise healthy patients, received regimen B. Regimen A consisted of busulphan, melphalan and fludarabine as previously described.¹³ Pharmacokinetics were performed using high-performance liquid chromatography–mass spectrometry following the first dose of busulphan, and subsequent dosing was adjusted to achieve a steady-state level of 600–900 ng/mL. Antithymocyte globulin (ATG), usually rabbit (2.5 mg/kg) and in a few cases equine (30 mg/kg), was administered in 2–3 doses pre-transplant. Regimen (B) consisted of HFTBI followed by

thiotepa, cyclophosphamide, and ATG.¹⁴ All patients had protective lung shielding after an initial 800cGy, and overlying ribs received an additional 600 cGy boost. Male patients received a 400 cGy testicular boost in a single fraction.¹⁵

Conditioning regimens for patients undergoing conventional grafts

The majority of patients who received conventional transplants were treated with a regimen consisting of intravenous busulfan and melphalan.¹⁶ First-dose pharmacokinetics were performed as described above. Equine ATG (15 mg/kg/day, days -4 and -3) was given to patients receiving unrelated donor transplants. A small number of patients also received a variety of other conditioning regimens as listed in Table 1.

Condition regimens for patients undergoing cord blood (CB) transplants

Five of the 7 patients who received CB transplants were conditioned with a regimen of TBI (400 cGy) plus cyclophosphamide, thiotepa and fludarabine as previously reported.¹⁷ For the two remaining patients who received CB grafts, one received a regimen of TBI (1320) plus cyclophosphamide and fludarabine, and the other the clofarabine-containing regimen.¹⁸

Donors

Donors included matched siblings or matched/mismatched unrelated adult donors were recruited via the National Marrow Donor Program (NMDP). Two umbilical CB grafts were used for a small proportion of the patients (Table 1). Mobilization of peripheral blood stem cells (PBSC) from donors was performed by administration of granulocyte colony stimulating factor (G-CSF) followed by apheresis on the 5th and, if needed the 6th, day post-injection. Selection of CD34⁺ stem cells was accomplished using the Isolex 300i Magnetic Cell Separator system followed by sheep red blood cell (sRBC)-rosette depletion of T cells or, beginning in 2010, the Miltenyi CliniMACS Cell Separator. These methods achieved an approximate 5 log₁₀ depletion of CD3⁺ cells.¹⁹ If bone marrow (BM) was used, a decision often based on donor preference, T cells were removed by sequential soybean agglutination and sheep RBC-rosette depletion.²⁰ Fresh BM or PBSC grafts were infused through a central venous catheter 24–48 hours after completion of conditioning. TCD was the only GVHD prophylaxis. CB units were selected on the basis of 4–6/6 HLA-A, -B antigen, -DRB1 allele match to the recipient; a cryopreserved total nucleated cell (TNC) dose of at least 1.5×10^7 /kg/unit; and the bank of origin as previously described.¹⁸ Unit–unit HLA match was not considered in CB unit selection. High-resolution HLA-A, -B, -C, -DRB1 and DQ allele typing of CB units was performed routinely but usually did not influence unit selection. Units were thawed using albumin-dextran dilution¹⁹ or thawed with wash.

GVHD prophylaxis

For patients undergoing a TCD SCT, no GVHD prophylaxis was given. For patients undergoing an unmodified graft, GVHD prophylaxis consisted of 4 doses of intravenous methotrexate (15 mg/m² on day +1, 10 mg/m² on days +3, +6, and +11) and continuous-infusion intravenous tacrolimus (0.03 mg/kg/24 hours) starting on day -1. Folinic acid rescue every 6 hours for 4–6 doses began 24 hours after each methotrexate dose.

Patients who received CB transplants received cyclosporin (CSA) and mycophenolate mofetil (MMF) for GVHD prophylaxis starting day -3, and none received ATG. In the absence of GVHD, MMF was tapered after day 45, and the CSA was tapered after day 100.

Supportive care

Patients were managed clinically according to MSKCC standard guidelines as previously described.¹⁵ First line treatment for GVHD, when it occurred, was topical steroids followed by budesonide or systemic steroids.

Statistical Methods

Kaplan -Meier methodology and the logrank test were used to compare overall and disease-free survival by mutational status and transplant type. The incidence of relapse was estimated using cumulative incidence functions, treating death without relapse as a competing event. All analyses were conducted using the R statistical package.

RESULTS

A total of 200 adult patients with AML were transplanted during the study period and 191 (96%) had initial cytogenetic analysis performed at diagnosis. One hundred and twelve patients had abnormal cytogenetics (59%) and the remaining 79 patients (41%) had a normal karyotype. Thirty-five of the 79 patients were WT (44%), 17 were FLT3-ITD positive (22%), and 27 patients (34%) did not have FLT3-ITD testing performed.

Patient characteristics are shown in Table 1. The WT group was similar to the FLT3-ITD group with respect to median age (55 versus 56 years), number of patients age 60 (34% versus 29%), number of patients in CR1 (63% versus 76%), type of donor (matched related, matched unrelated, and mismatched unrelated), and stem cell source (bone marrow, peripheral blood, cord blood).

Twenty five of the 35 WT patients (71%) received a TCD transplant (8 with a TBI conditioning regimen and 17 with a busulfan- based regimen) while 11 of the 17 FLT3-ITD patients (65%) received a TCD transplant (6 patients with a TBI conditioning and 5 patients with a busulfan- based regimen). In both groups, the majority of patients who underwent a TCD transplant were in CR1: 18 of 25 patients (72%) in the WT group and 10 of 11 patients (91%) in the FLT3-ITD group. None of the patients in the FLT3-ITD group received any FLT-3 related medication such as sorafenib, sunitinib, azacitidine, or any investigational drug post-transplant. Median follow up was similar in both groups, 3.2 years in the WT group and 3.6 years in the FLT3-ITD group. The cumulative incidence of relapse was similar in both groups: 0.09 (95% CI: 0.02–0.21 in the WT group and 0.12 (95% CI: 0.02–0.32), in the FLT3 ITD group, $p=0.67$ (Table 1). OS was 0.54 (95% CI: 39–75) in the WT group and 0.73 (95% CI: 53–99) in the FLT3-ITD group $p=0.18$ at 4 years, respectively (Figure 1). Disease free survival was the same as OS, since all 5 patients who relapsed died. If only CR1 patients are considered, the OS was 0.71 (95% CI: 54–94) in the WT group and 0.79 (95% CI: 65–99) in the FLT3-ITD group. Causes of death are shown in Table 2. Fifteen patients died in the WT group (43%) and 4 died in the FLT3-ITD (24%). Eight of the 17 FLT3-ITD positive group developed GVHD (47%) as did 16 of the 35 patients in the WT

group 16 (46%). . The majority of patients in each group had acute GVHD: 1 patient in the FLT3-ITD positive group and 8 patients in the WT group developed chronic GVHD. The incidence of GVHD did not appear to influence the relapse rate in either group although numbers are very small: one of the two relapsed patients in the FLT3-ITD group had prior GVHD as did one of the four patients who relapsed in the WT group.

Ten of the 17 FLT3-ITD patients were tested concomitantly for NPM1. Six patients were positive, and of these, five are alive.

DISCUSSION

Most previously reported studies that have examined the impact of the FLT3-ITD mutation in patients with AML have done so in patients with normal cytogenetics, although this mutation has also been demonstrated in patients with abnormal karyotypes, albeit at a much lower frequency.⁸ Patients in the current study, all of whom had normal cytogenetics, were identified through our institutional transplant data base, and had received treatment for their AML at MSKCC or had been referred after treatment elsewhere. The FLT3-ITD group was similar to the WT group with regards to patients > age 60, patients in CR1, patients who received a TCD graft, source of donor stem cells, and incidence of GVHD (Table 1). Our results show that at 4 years, FLT3-ITD positive patients have relapse and OS rates comparable to those of WT patients.

Comparison of our results with previous studies is difficult given the small number of patients in some groups, short follow up times in others, and the use of different comparator groups as summarized in Table 3.⁹⁻¹² The Brunet study is of particular interest as this represents the largest study reported to date.⁹ Using the European Group for Blood and Marrow Transplantation data base between 2000 and 2008, the authors followed 206 patients who had FLT3 testing performed; of these, 120 (58%) were FLT3-ITD positive, a result much higher than other studies.⁴⁻⁸ Compared to the 86 WT patients, patients who were FLT3-ITD positive had a higher incidence of relapse post transplant (30% vs 16%, $p=.006$) and had a shorter leukemia free survival (58% versus 71%, $p=.04$). Of note, the median follow up of both groups was short: 19 months for the FLT3-ITD group and only 12 months for the WT group. This unusually low relapse rate and high leukemia free survival of the WT group, 16% and 71% respectively, is not typical of most AML studies, although as noted, follow up was relatively short in both arms.^{21, 22} The Gale study¹² used both allografts and autografts; in the former group, the donor source was not provided. When both transplant groups were combined, there was no difference in the relapse rate between FLT positive and negative patients (31% and 25%, respectively).

In contrast to other studies, our series included patients who received transplants from both related and unrelated matched donors, as well as mismatched unrelated donors, a feature common now to most large transplant series as alternative transplants are increasingly represented. Mismatched unrelated donors comprised almost 30% of patients in both the WT and FLT3-ITD positive groups and DFS and OS for the patients in this study were similar to those of other published studies.^{23,24}

More recently, OS has been shown to be related to variability in ITD length, allele burden, ITD insertion site,^{25,26} allelic ratio,²⁷ and quantitative FLT3-ITD mRNA levels.²⁸ We were unable to address these important variables within our FLT3-ITD positive population; hence, it is possible that our results might be explained by one or more of these factors. In our small group of patients who were also positive for NPM1, survival did not appear compromised as five of the six patients are still alive.

In summary, acknowledging the relatively small number of patients in our study and the lack of FLT3-ITD characteristics, the favorable results with SCT in FLT3-ITD patients support the OS benefit of SCT in this subgroup of AML patients. The impact of TCD could not be accurately ascertained as only 11 of 25 patients in the FLT-3 ITD positive group received a TCD graft, however, there was no obvious negative impact.

Acknowledgments

The authors thanks the patients, their families, and the nursing and support staff of the Adult Bone Marrow Transplant Unit, Memorial Sloan Kettering Cancer Center

Bibliography

1. Keating MJ, Smith TL, Kantarjian H, et al. Cytogenetic pattern in acute myelogenous leukemia: a major reproducible determinant of outcome. *Leukemia*. 1988; 2:403–412. [PubMed: 3164797]
2. Lowenberg B, Downing JR, Burnett A. Acute myeloid leukemia. *N Engl J of Medicine*. 1999; 341:1051–1062.
3. Byrd JC, Mrozek K, Dodge RK, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). *Blood*. 2002; 100:4325–4236. [PubMed: 12393746]
4. Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J of Med*. 2012; 366:1079–1089. [PubMed: 22417203]
5. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J of Med*. 2008; 358:1909–1919. [PubMed: 18450602]
6. Kayser S, Schlenk RF, Londono MC, et al. Insertion of FLT3 internal tandem duplication in the tyrosine kinase domain-1 is associated with resistance to chemotherapy and inferior outcome. *Blood*. 2009; 114:2386–2392. [PubMed: 19602710]
7. Fröhling S, Schlenk RF, Breitnick J, et al. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. *Blood*. 2002; 100:4372–4380. [PubMed: 12393388]
8. Thiede C, Steudel C, Mohr B, et al. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. *Blood*. 2002; 99:4326–4335. [PubMed: 12036858]
9. Brunet S, Labopin M, Esteve J, et al. Impact of FLT3 internal tandem duplication on the outcome of related and unrelated hematopoietic transplantation for adult acute myeloid leukemia in first remission: a retrospective analysis. *J Clin Oncology*. 2012; 30:735–741.
10. Lin PH, Lin CC, Yang HI, et al. Prognostic impact of allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia patients with internal tandem duplication of FLT3. *Leuk Res*. 2012; 37:287–292. [PubMed: 23276395]
11. DeZern AE, Sung A, Kim S, et al. Role of allogeneic transplantation for FLT3/ITD acute myeloid leukemia: outcomes from 133 consecutive newly diagnosed patients from a single institution. *Biol Blood Marrow Transplant*. 2011; 17:1404–1409. [PubMed: 21324374]
12. Gale RE, Hills R, Kottaridis PD, et al. No evidence that FLT3 status should be considered as an indicator for transplantation in acute myeloid leukemia (AML): an analysis of 1135 patients,

- excluding acute promyelocytic leukemia, from the UK MRC AML 10 and 12 Trials. *Blood*. 2005; 106:3658–3665. [PubMed: 16076872]
13. Boulad F, Jakubowski A, Papadopoulos E, et al. Phase II trial of a chemotherapy-only regimen of busulfan, melphalan, fludarabine and R-ATG followed by allogeneic T-cell depleted (TCD) hematopoietic stem cell transplants (HSCT) for the treatment of myeloid malignancies. *Blood*. 2007; 110:2991. [PubMed: 17625066]
 14. Devine SM, Carter S, Soiffer RJ, et al. Low risk of chronic graft-versus-host disease and relapse associated with T cell-depleted peripheral blood stem cell transplantation for acute myelogenous leukemia in first remission: results of the blood and marrow transplant clinical trials network protocol 0303. *Biol Blood Marrow Transplant*. 2011; 17:1343–1351. [PubMed: 21320619]
 15. Jakubowski AA, Small TN, Young JW, et al. T cell depleted stem-cell transplantation for adults with hematologic malignancies: sustained engraftment of HLA-matched related donor grafts without the use of antithymocyte globulin. *Blood*. 2007; 110:4552–4559. [PubMed: 17717135]
 16. Small TN, Young JW, Castro-Malaspina H, et al. Intravenous busulfan and melphalan, tacrolimus, and short-course methotrexate followed by unmodified HLA-matched related or unrelated hematopoietic stem cell transplantation for the treatment of advanced hematologic malignancies. *Biol Blood Marrow Transplant*. 2007; 13:235–244. [PubMed: 17241929]
 17. Ponce DM, Sauter C, Devlin S, et al. A novel reduced-intensity conditioning regimen induces a high incidence of sustained donor-derived neutrophil and platelet engraftment after double-unit cord blood transplantation. *Biol Blood Marrow Transplant*. 2013; 19:799–803. [PubMed: 23416850]
 18. Boulad F, Koehne G, Kernan NA, et al. Clofarabine, melphalan, and thiotepe, followed by allogeneic unmodified bone marrow or peripheral blood stem cell transplant, by unmodified double cord blood transplant, or by CD34+ T-cell depleted stem cell transplant for the treatment of hematologic malignancies. *Blood (ASH Annual Meeting Abstracts)*. 2012; 120:3144.
 19. Fritsch G, Scharner D, Fröschl G, et al. Selection of CD34-positive blood cells for allogeneic transplantation: approaches to optimize D34-Cell recovery, purity, viability, and T-cell depletion. *Onc Res and Treatment*. 2000; 23:449–456.
 20. Collins, NH.; Bleau, SA.; Kernan, NA.; O'Reilly, RJ. T cell depletion of bone marrow by treatment with soybean agglutinin and sheep red blood cell rosetting. In: Areman, HJ.; Deeg, HJ.; Sacher, RA., editors. *Bone marrow and stem cell processing: A manual of current techniques*. Philadelphia, PA: F. A. Davis; 1991. p. 171-180.
 21. Buchner T, Schlenk RF, Schaich M, et al. Acute Myeloid Leukemia (AML): different treatment strategies versus a common standard arm- combined prospective analysis by the German AML Intergroup. *J Clin Oncol*. 2012; 30:3604–3610. [PubMed: 22965967]
 22. Tefferi A, Letendre L. Going beyond 7+3 regimens in the treatment of adult acute myeloid leukemia. *J Clin Oncol*. 2012; 30:2425–2428. [PubMed: 22529263]
 23. Michallet M, Sobh M, Serrier C, et al. Allogeneic hematopoietic stem cell transplant for hematological malignancies from mismatched 9/10 human leukocyte antigen unrelated donors: comparison with transplants from 10/10 unrelated donors and human leukocyte antigen identical siblings. *Leuk Lymph*. 2014; 20:1–5.
 24. Kekre N, Antin JH. Hematopoietic stem cell transplantation donor sources in the 21st century: choosing the ideal donor when a perfect match does not exist. *Blood*. 2014; 17:334–343.
 25. Meshinchi S, Stirewalt DL, Alonzo TA, et al. Structural and numerical variation of FLT3/ITD in pediatric AML. *Blood*. 2008; 111:4930–4933. [PubMed: 18305215]
 26. Stirewalt DL, Kopecky KJ, Meshinchi S, et al. Size of FLT3 internal tandem duplication has prognostic significance in patients with acute myeloid leukemia. *Blood*. 2006; 107:3723–3726.
 27. Schlenk DF, Kayser S, Bullinger L, et al. for the German-Austrian Study Group. Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. *Blood*. 2014; 124:3441–3449. [PubMed: 25270908]
 28. Schneider F, Hoster E, Unterhalt E, et al. The *FLT3*ITD mRNA level has a high prognostic impact in NPM1 mutated, but not in NPM1unmutated AML with a normal karyotype. *Blood*. 2012; 119:4383–4386. [PubMed: 22374696]

Highlights

- Patients with FLT3+ AML have poor prognosis with chemotherapy alone
- We reviewed a single center experience with SCT in FLT3 + patients
- Stem cell transplant can abrogate the poor prognosis in FLT3+ AML patients

Figure 1.
Overall Survival of FLT3-ITD positive patients compared to FLT3-ITD negative patients

Table 1**Patient Characteristics**

	WT (n=35)	FLT3-ITD positive (n=17)
Median age years (range)	55 (27–68)	56.3 (19.6–71)
No pts age 60	12 (34%)	5 (29%)
M/F	22/13	10-Jul
Status:		
CR-1	22 (63%)	13 (76%)
CR-2	5 (14%)	1 (6%)
other	8 (23%)	3 (18%)
Donor:		
Matched related	15 (43%)	6 (35%)
Matched unrelated	11 (31%)	6 (35%)
Mismatched unrelated	9 (26%)	5 (29%)
Source:		
Bone marrow	0	1 (6%)
Peripheral blood	32 (91%)	12 (71%)
Cord blood	3 (9%)	4 (23%)
Stem Cell Source:		
Unmodified	10 (29%)	6 (35%)
T-cell depleted (TCD)	25 (71%)	11 (65%)
Conditioning		
1200 TBI		
TCD	8 (23%)	6 (35%)
Unmodified	1	0
CB	0	1
Busulphan based		
TCD	17 (49%)	5 (29%)
Unmodified	5	2
Other		0
Clofarabine-based		
CB	0	1
400 TBI + chemo		
Unmodified	1	0
CB	3	2
GvHD (any grade)	16 (46%)	8 (47%)
Median f/u mos (range)	38 (2–65)	44 (3–53)
Relapse incidence at 4 years:	0.09 (0.02–0.21)	0.12 (0.02–0.32) (12%)
OS at 4 years:	0.54 (0.39–0.75) ¹	0.73 (0.53–0.99) ²

	WT (n=35)	FLT3-ITD positive (n=17)
DFS at 4 years:	0.54 (0.39–0.75) ¹	0.73 (0.53–0.99) ²

^{1,2}These numbers are the same since the 5 patients who relapsed died within 4 years

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Cause of Death in WT and FLT-3ITD Patients

	WT (n=35)	FLT3-ITD (n=17)
Relapse	3	2
GVHD	5	1
Infection	3	1
Graft failure	2	0
Other	2 (GI bleed, second cancer)	0
Total	15 (43%)	4 (24%)

Table 3
Summary of studies that have evaluated the role of SCT in patients with FLT3-ITD positive AML

Author	Comparator Group	Numbers of pts in each group	Type of SCT	Median follow up	Results
Gale ⁹	FLT3-ITD vs WT pts in CR1	35 pts FLT3 received allo; 37 pts FLT3 received auto	Conventional: Matched related Autograft Donor source: not stated	10 years	Increased relapse rate for FLT3-ITD pts following auto or allo SCT compared to WT pts ($p=.02$) No difference in OS between FLT3-ITD pts who did/did not receive SCT ($p=.4$)
Brunet ²⁰	FLT3-ITD and WT pts < age 60 in CR1; SCT between the two groups	120 pts FLT3-ITD 86 pts WT	Conventional: Matched related MUD Donor source: BM, PB	19 mos in FLT3-ITD group and 12 mos in WT group	Relapse rate was 30% in FLT3-ITD pts and 16% in WT pts ($p=.006$) LFS was 58% in FLT3-ITD pts and 71% in WT group ($p=.04$)
Lin ²¹	FLT3-ITD vs WT pts in CRs 1, 2, 3; no age limit; SCT vs no SCT	10 pts FLT3-ITD 24 pts WT	Conventional: HLA matched sibling MUD Donor source: not stated	Provided as person-years of follow up: 65 years in WT group and 26 years in FLT3-ITD group	SCT pts: Median OS in FLT3-ITD pts: not reached; Median OS in WT pts: 53.4 mos No SCT pts: Median OS in FLT3-ITD pts: 9.8 mos; Median OS in WT pts: 40.7 mos
DeZern ²²	FLT3-ITD vs WT < age 60 in CR1	11 pts FLT3-ITD 17 pts WT	Conventional: HLA matched sibling MUD Haploidentical Syngeneic (n=1) Autologous (n=1) Donor source: not stated	Not provided	SCT pts only: Median OS in FLT3-ITD pts was 54 mos; Median OS in WT pts: >60 mos
Current	-WT vs FLT3-ITD pts who received SCT; no age limit	17 pts FLT3-ITD 35 pts WT	Conventional and TCD: Matched related MUD Mismatched unrelated Donor source: BM, PB, CB	38 mos in FLT3-ITD group and 44 mos in WT group	OS was 73% in FLT3-ITD pts OS was 54% in WT pts ($p=.18$)