

Bone marrow transplantation and acute myeloid leukemia: Brazilian guidelines

Lucia Mariano da Rocha Silla¹
 Frederico Dulley²
 Rosaura Saboya²
 Eduardo Paton³
 Fabio Kerbauy⁴
 Adriano de Moraes Arantes⁵
 Nelson Hamerschlag⁶

¹Hospital de Clínicas de Porto Alegre – HCPA, Porto Alegre, RS, Brazil

²Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo - USP, São Paulo, SP, Brazil

³Hospital de Câncer de Barretos, Barretos, SP, Brazil

⁴Universidade Federal de São Paulo – UNIFESP, São Paulo, SP, Brazil

⁵Hospital Araújo Jorge – HAJ, Goiânia, GO, Brazil

⁶Hospital Israelita Albert Einstein - HIAE, São Paulo, SP, Brazil

Conflict-of-interest disclosure:

The authors declare no competing financial interest

Submitted: 11/21/2012

Accepted: 12/11/2012

Corresponding author:

Nelson Hamerschlag
 Hospital Israelita Albert Einstein
 Av Albert Einstein 627 sala 1203 Morumbi
 05651-901 – São Paulo, SP, Brazil
 Phone 55 11 3747-3203
 hamer@einstein.br

www.rbhh.org or www.scielo.br/rbhh

DOI: 10.5581/1516-8484.20130016

Introduction

This report aims to define guidelines for the indication of hematopoietic stem cell transplantation in the treatment of acute myeloid leukemia in Brazil. This report on the role of hematopoietic stem cell transplantation in the treatment of acute myeloid leukemia was presented to and ratified by the Brazilian Bone Marrow Transplantation Society at the meeting on the Brazilian Guidelines for hematopoietic stem cell transplantation. This consensus is based on a review of the international literature and on the Brazilian experience in hematopoietic stem cell transplantation. The optimal treatment for acute myeloid leukemia in first complete remission is not yet defined. There is a consensus on the indication of allogeneic transplantation with myeloablative conditioning for patients presenting cytogenetic changes considered high risk. Allogeneic transplantation is not indicated in first complete remission for patients with low cytogenetic risk, and it appears that allogeneic transplantation, autologous transplantation, and consolidation chemotherapy are equivalent for patients with intermediate risk. In advanced disease and secondary leukemia, allogeneic transplant is the main therapeutic tool. New medications and therapeutic regimens have enabled the adoption of transplant in older individuals.

Prevalence and mortality rates of acute myeloid leukemia

Acute myeloid leukemia (AML) accounts for 90% of all cases of acute leukemia in adults, with an average age at diagnosis of 63 years⁽¹⁾. In the United States, 18,000 new cases of leukemia are diagnosed each year; 12,000 of which are acute^(2,3). In the state of Rio Grande do Sul, Brazil, a hundred new cases of relapsed AML are diagnosed annually in patients of all ages, with an incidence of 0.5-1:100,000 people and an average age at diagnosis of 42 years. Seventy-nine per cent of cases of relapsed AML occur in adults (> 18 years). After five years, only 90 patients (17%) of the 532 patients diagnosed between 1996 and 2000 were still alive⁽⁴⁾. These data are in accordance with the data in the literature, and suggest that outside clinical trials, and despite the advancement of knowledge in this field, AML is still a fatal disease in the vast majority of the cases. Estimates of the Brazilian Instituto Nacional do Câncer (Inca) indicate that the number of new cases of leukemia in Brazil in 2012 will be 4570 in males and 3940 in females, with a risk of five new cases per 100,000 men and four per 100,000 women⁽⁵⁾. But in Brazil, just as there is a lack of specific data on each type of leukemia worldwide⁽³⁾, the database of the National Health Service, DATASUS, only gathers information on the incidence and mortality for 'leukemia' in general, and does not specifically differentiate acute myeloid leukemia. For leukemia in general, the mortality rate in 2010 ranged from 1.20 (Amapá) to 4.08 (Rio Grande do Sul) per 100,000 female patients with leukemia and from 0.81 (Acre) to 5.28 (Rio Grande do Sul) per 100,000 male patients⁽⁶⁾. Meanwhile, DATASUS recorded 5935 deaths from leukemia in Brazil in 2010⁽⁷⁾. It is likely that the Brazilian data are underestimated.

Hematopoietic stem cell transplantation and acute myeloid leukemia

AML is currently the most common indication for hematopoietic stem cell transplantation (HSCT) worldwide⁽⁸⁾. The rationale for the indication of HSCT is based on the fact that this disease is the result of the accumulation of cells produced by extremely rare malignant stem cells, which are capable of self-renewing⁽⁹⁾ and resistant to the cytotoxic effects of chemotherapy⁽¹⁰⁾, resulting in disease relapse. Due to the resistance to chemotherapy, the malignant stem cell can undergo additional mutations⁽¹¹⁾ and is destroyed in a small number of patients, even in those who undergo doses of myeloablative chemotherapy or radiation administered for HSCT. The benefits of allogeneic HSCT derive from the destruction of these stem cells by the donor's immune system [T and natural killer (NK) lymphocytes], the graft-versus-leukemia effect^(12,13).

Issues related to the disease and the patient greatly influence the endpoints of HSCT for AML. It has recently been systematically shown that the presence of comorbidities greatly compromises the results of HSCT, as a result of which this therapeutic option is not

recommended for patients with high comorbidity burdens⁽¹⁴⁾. Therefore, for the elderly, as described below, in patients with low comorbidity burdens or no comorbidities at all, the results of HSCT may be similar to those observed in young patients who receive this therapeutic option.

Results of hematopoietic stem cell transplantation for acute myeloid leukemia - international report

Allogeneic HSCT, a treatment for AML but which is accompanied by considerable morbimortality, is available to few patients due to age, lack of donors or unavailable hospital beds. Data from the Center of International Blood and Marrow Transplant Research (CIBMTR) show that until 2009, around 20,234 cases of AML were transplanted according to all hospitals that reported this data. Of these, around 52% underwent allogeneic HSCT from related donors and 48% from unrelated donors⁽¹⁵⁾. According to Appelbaun⁽¹⁶⁾, of the 13,000 new cases of AML annually reported in the United States, considering transplant hospitals that are not members of the CIBMTR, no more than 2000 patients have the chance of undergoing HSCT. However, the availability for unrelated donors has increased with the use of allogeneic transplantation, especially in patients between the ages of 40 to 65 years. In the literature, half of the donors for transplantation in first complete remission (CR1) are unrelated and in later stages of the disease, unrelated donors are more frequently used⁽³⁾.

The results of related allogeneic HSCT with a myeloablative regimen for AML depend, above all, on the stage of the disease, early (CR1), intermediate (≥ second CR) or advanced (relapsed or refractory), with survival rates of around 53%, 44% and 20% in 5 years, respectively; while for myeloablative HSCT from unrelated donors, survival is around 40% in the early and intermediate stages, and 18% in the advanced stage, over the same period of time⁽¹⁵⁾. The data on HSCT for AML reported by Brazilian hospitals to the CIBMTR are, overall, very similar to those published. However, it is important to point out that not all cases of AML in CR1 are indicated for HSCT (see below).

Risk factors

In addition to risk factors related to the stage of the disease and the presence of comorbidities, the classification of risk according to cytogenetic changes as proposed by the South West Oncology Group (SWOG)⁽¹⁷⁾ and the Medical Research Council (MRC) AML 10 Trial⁽¹⁸⁾ (Table 1) is essential to define treatment for the different sub-types of AML. A series of molecular changes has been associated with AML and trials have been carried out to better define their prognostic role (Table 2)^(12,19-22).

Indication of allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia in first complete remission

A recently published meta-analysis, which included 6700 patients enrolled in prospective trials on HSCT for AML in CR1, showed that the results for related allogeneic HSCT with high doses of chemotherapy are higher than for autologous HSCT in high- and intermediate-risk patients. Allogeneic HSCT is not indicated for low risk patients⁽²³⁾. Low-risk patients (Table 1), with core binding factor (CBF) leukemia, CBF-AML [(8;21), inv(16) or t(16;16)] or acute progranulocytic leukemia [t(15-17)] have a moderate risk of relapse and around 50% of survival in 5 years when they undergo only chemotherapy⁽²⁴⁾.

Indications of autologous hematopoietic stem cell transplantation for acute myeloid leukemia in first complete remission

Although successive meta-analyses have demonstrated the non-superiority of autologous HSCT over high dose chemotherapy⁽²⁵⁻²⁷⁾, experience in Brazil in the treatment of AML seems to suggest a role for autologous HSCT⁽²⁸⁾. Between 1996 and 2000, the five-year survival rate for the 532 patients with AML was 17%⁽⁴⁾. However, it is important to point out that in this study, the

Table 1 - Criteria for risk classification in acute myeloid leukemia		
	South West Oncology Group ⁽¹⁷⁾ Criteria	Medical Research Council ⁽¹⁸⁾ Criteria identical to South West Oncology Group except
Favorable	t(15;17) + any other abnormality inv(16)/t(16;16)/del(16q) + any other abnormality t(8;21) without del(9q) or complex karyotype	t(8;21) + any other abnormality
Intermediate	+8, -Y, +6, del(12p) normal karyotype	abnormal 11q23 del(9q), del(7q) – without other abnormalities complex karyotype (≥ 3 abnormalities but < 5 abnormalities) all significant abnormalities unknown prognosis
Unfavorable	-5/del(5q), -7/del(7q) t(8;21) with del(9q) inv(3q), abnormal 11q23, 20q. 21q, del(9q), t(6;9) T(9;22), abnormal 17p complex karyotypes (≥ 3 abnormalities)	complex karyotypes (≥ 5 abnormalities)
Unknown	All other clonal anomalies with < 3 abnormalities	

Table 2 - Acute myeloid leukemia molecular abnormalities⁽¹²⁾

Gene	Clinical and biological characteristics
Nucleophosmin 1 (<i>NPM1</i>)	Protein with pleomorphic functions associated with the female gender, number of blasts (CD33 ⁺ and 34 ⁺ or below) and high HDL, 25% to 35% of AML predominantly with NK (45-62%) associated with FLT3-ITD and mutation of the TKD genotype <i>NPM1mut/FLT3-ITDneg</i> associated with good prognosis and appears to not benefit from myeloablative allogeneic HSCT. Where present, it is indicative of good prognosis, regardless of the FLT3-ITD status ⁽¹⁹⁾
<i>FLT3</i>	From the family of tyrosine-kinase receptors class III, it is associated with poor prognostic FLT3-ITDpos ITDpos; FLT3-TKDpos and has an uncertain prognosis
ITD	28% to 34% of NK-AML is associated with unfavorable prognosis; the determination of ITD seems important
TKD	Mutation of around 11% to 14% of the NK-AML associated with improved OS; high levels of this molecule are associated with improved OS
CCAAT enhancer binding protein alpha (<i>CEBPA</i>)	Important transcription factor in the differentiation of neutrophils particularly associated with NK-AML and del(9q) associated with higher CR rate, improved RFS and OS
myeloid/lymphoid gene (<i>MLL</i>)	It is partial tandem duplication; 5% to 11% of NK-AML associated with shorter duration of CR or with reduced RFS or EFS; autologous HSCT appears to have a favorable role in the endpoints
<i>RAS</i>	<i>NRAS</i> mutation found in ~ 9% of the NK-AML without prognostic significance
Wilms' tumor suppressor gene (<i>WT1</i>)	Mutation found in ~ 10% of the NK-AML, this mutation does not appear to have an impact on the endpoints, but is associated with the <i>WT1mut/FLT3-ITDpos</i> genotype - increases the risk of failure during induction ⁽²⁰⁾
<i>DNMT3A</i>	Mutation recently described in ~ 20% of NK-AML Independently associated with poor prognosis ⁽²¹⁾

ITD: internal tandem duplication; TKD: mutation in the tyrosine-kinase domain; NK: normal karyotype; CR: complete remission; OS: overall survival; RFS: relapse-free survival; EFS: event-free survival

surviving patients and those in CR after 5 years included, though few in number, patients who had undergone allogeneic HSCT and patients in palliative care or untreated. However, in a retrospective study on the results of allogeneic and autologous HSCT for AML in Brazil⁽²⁹⁾, there were no differences for overall survival (OS) between these two types of transplantations. Therefore, in Brazil, autologous HSCT is an accepted procedure of consolidation therapy for AML, after two rounds of induction and at least one round of consolidation therapy, for intermediate-risk patients without any HLA-compatible donor. In low-risk patients [without the c-KIT mutation and in the presence of Nucleophosmin 1 (*NPM1*)], chemotherapy is only recommended at high doses and allogeneic or autologous HSCT is not indicated. In cases of unfavorable cytogenetics, allogeneic HSCT is preferable and should be indicated whenever possible. For AML-M3 in molecular second complete remission (CR2), autologous HSCT is acceptable⁽³⁰⁾.

Consolidation therapy and hematopoietic stem cell transplantation

The number of consolidation therapies prior to an allogeneic HSCT has never been investigated prospectively. A CIBMTR retrospective study involving 431 patients suggests that additional chemotherapy after CR is not beneficial and allogeneic HSCT should be performed as soon as possible⁽³¹⁾. For autologous HSCT, as mentioned above, in Brazil, at least one round of consolidation therapy is recommended prior to transplantation⁽²⁸⁾.

Bone marrow or peripheral blood transplant

In a meta-analysis of nine randomized studies that included 1111 patients, it was demonstrated that peripheral blood (PB) HSCT is superior to bone marrow (BM) HSCT as it results in a

reduced relapse rate, improved OS and improved disease-free survival (DFS)⁽³²⁾. However, it is important to highlight that PB HSCT is associated with a significant risk of extensive graft-versus-host disease (GVHD), particularly in unrelated HSCT⁽³³⁾ and should be reserved for patients with advanced disease (\geq CR2)⁽³⁴⁾.

Therapeutic regimens

The comparison between busulfan (Bu) + cyclophosphamide (CY) and Bu + total body irradiation (TBI) administered to 581 patients (381 administered with Bu-CY and 200 with Bu-TBI) showed that, although Bu-TBI seems to be related to reduced relapse, significant differences were not observed for transplanted-related mortality (TRM), DFS and OS⁽³⁵⁾. More recently, the fludarabine (Flu) + Bu association has been used and seems to be associated with less toxicity and efficacy similar to Bu-CY in a retrospective comparison⁽³⁶⁾. Although promising and similar results to this therapeutic regimen were observed in Brazil by Conexão Caipira collaborative group⁽³⁷⁾, it is important to emphasize that the original protocol was designed for the use of intravenous Bu (Flu 30 mg/m², Bu 1 mg/kg x 16 doses orally, target Bu). Based on this evidence, it is acceptable in Brazil⁽²⁸⁾ to use three therapeutic options, Bu-CY/Bu-melphalan (Mel), Flu-Bu and Bu-TBI, depending on the treatment center's experience in each option and availability.

Unrelated allogeneic hematopoietic stem cell transplantation

With the exception of one trial that involved a small number of patients⁽³⁸⁾, there have been no prospective studies comparing unrelated and related allogeneic HSCT. The results of retrospective analysis suggest that unrelated allogeneic HSCT is an option for patients who do not have HLA-compatible related

donors. With more sensitive molecular techniques for HLA typing, the results for unrelated HSCT seem to be similar to those of related HSCT in high-risk AML patients⁽³⁹⁾.

In a retrospective study reported by the CIBMTR involving 2223 patients who underwent related and unrelated HSCT, although a higher incidence of acute Grade II-IV GVHD was observed in the unrelated transplanted patients, transplant-related mortality (TRM) and OS were similar between the two identical HLA groups (8:8)⁽⁴⁰⁾. As for the origin of the cells, the results seem to be similar between unrelated BM and umbilical cord blood donors⁽⁴¹⁾.

Hematopoietic stem cell transplantation in relapsed or refractory acute myeloid leukemia

Allogeneic HSCT is accepted in the treatment of refractory AML⁽⁴²⁾. In one publication, the three-year survival rate for 1673 transplanted patients with relapsed or refractory AML was 19%⁽⁴³⁾. Nevertheless, in the late relapsed sub-group, without blasts in the peripheral blood, with performance status > 90%, and favorable cytogenetics and who received grafts from related HLA-compatible donors, the three-year survival rate was 43%. Approximately 30% of patients who were prematurely transplanted during relapse (i.e., < 30% of blasts in the BM) had disease-free survival similar to patients transplanted in CR2⁽⁴⁴⁾. Although the difference between relapsed or refractory AML is not clear in the literature, HSCT can be an option for this group of patients.

Hematopoietic stem cell transplantation in the elderly

The median age of patients with AML/myelodysplastic syndrome (MDS) is 65 years⁽⁴⁵⁾. The number of patients with long-term survival is very low, regardless of the choice of chemotherapeutic regimen used for remission induction or consolidation^(46,47). Historically, myeloablative transplant in the elderly has been performed little and this is associated with an extremely high mortality rate associated with the therapeutic regimen⁽⁴⁸⁾. It has become clear that age *per se* is not an obstacle for HSCT⁽⁴⁹⁾, since comorbidities and performance status exceed age in the determination of the risk of transplant-related mortality. A two-year survival of 68% was observed in a study by MD Anderson involving patients treated at the Hospital Israelita Albert Einstein (HIAE) in Brazil⁽⁵⁰⁾. Based on the comparative study between intravenous Bu and Flu, and Bu and Cy, which demonstrated improved OS, leukemia-free survival and reduced toxicity in patients with AML in the Bu-Flu group, 79 patients aged between 60 and 80 years with AML and MDS were investigated. These data confirm that provided that patients have a good performance status, the use of therapy with Bu-Flu - using Bu intravenously - can be beneficial. HSCT with reduced therapy or reduced toxicity is today a well-established treatment for elderly patients with AML⁽⁵¹⁾.

Final recommendations

To improve the results and corroborate with the various types of HSCT for the treatment of AML in Brazil, a national effort should be made for quality karyotyping, and for the development

of molecular techniques to be used as tools in the classification of risk and to categorize the ideal treatment for AML.

To summarize, the consensus and the respective quality determinations of evidence and strength of recommendation were:

- Allogeneic HSCT is recommended for high-risk AML (A1).
- Allogeneic HSCT is recommended for intermediate-risk AML (B2).
- Allogeneic HSCT is recommended for relapsed/refractory AML (C2).
- Autologous HSCT is recommended for AML after consolidation therapy (B2).
- Autologous HSCT is recommended for AML in CR1; this is preferable to chemotherapy in the Brazilian experience (C2).
- Autologous HSCT is accepted for AML-M3 in molecular CR2 (C2).
- PB stem cells are a more common source than BM in advanced disease (B1).
- The recommended therapeutic regimens include: Bu-Cy/Bu-Mel, Flu-Bu and TBI-Cy, TBI-Cy. For umbilical cord cases, antithymocyte globulin (ATG) regimens should be considered (B1).
- Allogeneic HSCT for the treatment of AML can be used in patients aged between 60 and 80 years with good performance status and absence of significant comorbidities.

References

1. Jemal A, Thomas A, Murray T, Thun M: Cancer statistics, 2002. *CA Cancer J Clin.* 2002;52(1):23-47. Erratum in: *CA Cancer J Clin.* 2002;52(3):181-2; *CA Cancer J Clin.* 2002;52(2):119. Comment in: *CA Cancer J Clin.* 2002;52(1):6-7.
2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin.* 2007;57(1):43-66.
3. Juliusson G, Lazarevic V, Hörstedt AS, Hagberg O, Höglund M; Swedish Acute Leukemia Registry Group. Acute myeloid leukemia in the real world: why population-based registries are needed. *Blood.* 2012;119(17):3890-9.
4. Capra M, Vilella L, Pereira WV, Coser VM, Fernandes MS, Schilling MA, et al. Estimated number of cases, regional distribution and survival of patients diagnosed with acute myeloid leukemia between 1996 and 2000 in Rio Grande do Sul, Brazil. *Leuk Lymphoma.* 2007;48(12):2381-6.
5. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2012: incidência de câncer no Brasil [Internet]. Rio de Janeiro: Inca; 2011. [cited 2012 Sep 27]. Available from: <http://www.inca.gov.br/estimativa/2012/estimativa20122111.pdf>
6. Brasil. Instituto Nacional do Câncer. Atlas de mortalidade por câncer. Taxas de mortalidade por câncer, brutas e ajustadas por idade, pelas populações mundial e brasileira, por 100.000, segundo sexo, localidade e por período selecionado [Internet]. Rio de Janeiro: Inca; 2013. [cited 2012 Jun 24]. Available from: <http://mortalidade.inca.gov.br/Mortalidade/prepararModelo04.action>.
7. Brasil. Ministério da Saúde. DATADUS: Tecnologia da informação a serviço do SUS. Informações de Saúde. Notas técnicas. Mortalidade-Brasil [Internet]. Brasília: Ministério da Saúde. [cited 2012 Sep 27]. Available from: <http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sim/cnv/obt10uf.def>

8. Baldomero H, Gratwohl M, Gratwohl A, Tichelli A, Niederwieser D, Madrigal A, Frauendorfer K; European Group for Blood and Marrow Transplantation EBMT. The EBMT activity survey 2009: trends over the past 5 years. *Bone Marrow Transplant.* 2011;46(4):485-501.
9. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, et al. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. *Nature.* 1994;367(6464):645-8.
10. Dean M, Fojo T, Bates S. Tumour stem cells and drug resistance. *Nat Rev Cancer.* 2005;5(4):275-84.
11. Ding L, Ley TJ, Larson DE, Miller CA, Kodoldt DC, Welch JS, et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. *Nature.* 2012;481(7382):506-10.
12. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood.* 1990;75(3):555-62.
13. Velardi A, Ruggeri L, Mancusi A. Killer-cell immunoglobulin-like receptors reactivity and outcome of stem cell transplant. *Curr Opin Hematol.* 2012;19(4):319-23.
14. Sorror ML, Giralt S, Sandmaier BM, De Lima M, Shahjahan M, Maloney DG, et al. Hematopoietic cell transplantation specific comorbidity index as an outcome predictor for patients with acute myeloid leukemia in first remission: combined FHCRC and MDACC experiences. *Blood.* 2007;110(13):4606-13.
15. Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: Summary Slides [Internet]. Center for International Blood & Marrow Transplant Research; 2011. [cited 2012 Sep 6]. Available from: <http://www.cibmtr.org/slides>
16. Appelbaum FR. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia when a matched related donor is not available. *Hematology Am Soc Hematol Educ Program.* 2008:412-7.
17. Slovak ML, Kopecky KJ, Cassileth PA, Harrington DH, Theil KS, Mohamed A, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood.* 2000;96(13):4075-83.
18. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. *Blood.* 1998;92(7):2322-33. Comment in: *Blood.* 2000;96(5):2002.
19. Schneider F, Hoster E, Unterhalt M, Schneider S, Dufour A, Benthaus T, et al. NPM1 but not FLT3-ITD mutations predict early blast cell clearance and CR rate in patients with normal karyotype. AML(NK-AML) or high-risk myelodysplastic syndrome (MDS). *Blood.* 2009;113(21):5250-3.
20. Gaidzik VI, Schlenk RF, Moschny S, Becker A, Bullinger L, Corbacioglu A, Krauter J, Schlegelberger B, Ganser A, Döhner H, Döhner K; German-Austrian AML Study Group. Prognostic impact of WT1 mutations in cytogenetically normal acute myeloid leukemia: a study of the German-Austrian AML Study Group. *Blood.* 2009;113(19):4505-11.
21. Ostronoff F, Othus M, Ho PA, Kutny M, Geraghty DE, Petersdorf SH, et al. Mutations in the DNMT3A exon 23 independently predict poor outcome in older patients with acute myeloid leukemia: a SWOG report. *Leukemia.* 2013;27(1):238-41.
22. Döhner H. Implication of the molecular characterization of acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program.* 2007:412-9.
23. Koreth J, Schlenk R, Kopecky KJ, Honda S, Sierra J, Djulbegovic BJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA.* 2009;301(22):2349-61. Comment in: *JAMA.* 2009;302(15):1647; author reply 1647-8.
24. Marcucci G, Mrózek K, Ruppert AS, Maharry K, Kolitz JE, Moore JO, et al. Prognostic factors and outcome of core binding factor acute myeloid leukemia patients with t(8;21) differ from those of patients with inv(16): a Cancer and Leukemia Group B study. *J Clin Oncol.* 2005;23(24):5705-17.
25. Nathan PC, Sung L, Crump M, Beyene J. Consolidation therapy with autologous bone marrow transplantation in adults with acute myeloid leukemia: a meta-analysis. *J Natl Cancer Inst.* 2004;96(1):38-45.
26. Levi I, Grotto I, Yerushalmi R, Ben-Bassat I, Shpilberg O. Meta-analysis of autologous bone marrow transplantation versus chemotherapy in adult patients with acute myeloid leukemia in first remission. *Leuk Res.* 2004;6(6):605-12.
27. Breems DA, Boogaerts MA, Dekker AW, Van Putten WL, Sonneveld P, Huijgens PC, et al. Autologous bone marrow transplantation as consolidation therapy in the treatment of adult patients under 60 years with acute myeloid leukaemia in first complete remission: a prospective randomized Dutch-Belgian Haemato-Oncology Co-operative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) trial. *Br J Haematol.* 2005;128(1):59-65.
28. Silla LMR, Dulley F, Saboya R, Paton E, Kerbauy F, Arantes AM, et al. Transplante de células-tronco hematopoiéticas e leucemia mieloide aguda: diretrizes brasileiras. *Rev Bras Hematol Hemoter.* 2010;32(supl.1):61-5.
29. Hamerschlak N, Barton D, Pasquini R, Sarquis YN, Ferreira E, Moreira FR, et al. Estudo retrospectivo do tratamento de leucemia mieloide aguda com o transplante de medula óssea: a experiência brasileira. *Rev Bras Hematol Hemoter.* 2006;28(1):11-8.
30. Thomas X, Dombret H, Cordonnier C, Pigneux A, Gardin C, Guerci A, et al. Treatment of relapsing acute promyelocytic leukemia by all-trans retinoic acid therapy followed by timed sequential chemotherapy and stem cell transplantation. APL Study Group. *Acute promyelocytic leukemia.* 2000;14(6):1006-13.
31. Tallman MS, Rowlings PA, Milone G, Zhang MJ, Perez WS, Weisdorf D, et al. Effect of postremission chemotherapy before human leukocyte antigen-identical sibling transplantation for acute myelogenous leukemia in first complete remission. *Blood.* 2000;96(4):1254-8.
32. Stem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. *J Clin Oncol.* 2005;23(22):5074-87.
33. Anasetti C, Logan BR, Lee SJ, Waller EK, Weisdorf DJ, Wingard JR, et al. Increased incidence of chronic graft-versus-host disease (GVHD) and no survival advantage with filgrastim-mobilized peripheral blood stem cells (PBSC) compared to bone marrow (BM) transplants from unrelated donors: results of Blood and Marrow Transplant Clinical Trials Network (BMT CTN) protocol 0201, a phase III, prospective, randomized trial [abstract]. *Blood.* 2011;118: abstract 1. Presented at: ASH Annual Meeting Abstracts; aug 11; Washington, CD: American Society of Hematology; 2011. [cited 2012 Sep 6]. Available from: <http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/1?maxtoshow=&hits=10&RESULTFORMAT=&fulltext=Increased+incidence+of+chronic+graft-versus-host+disease+&searchid=1&FIRSTINDEX=0&volume=118&issue=21&resourcetype=HWCIT>
34. Nagler A, Labopin M, Shimoni A, Mufti GJ, Cornelissen JJ, Blaise D, et al. Mobilized peripheral blood stem cells compared with bone marrow from HLA-identical siblings for reduced-intensity conditioning transplantation in acute myeloid leukemia in complete remission: a retrospective analysis from the Acute Leukemia Working Party of EBMT. *Eur J Haematol.* 2012;89(3):206-13.
35. Litzow MR, Pérez WS, Klein JP, Bolwell BJ, Camitta B, Copelan EA, et al. Comparison of outcome following allogeneic bone marrow transplantation with cyclophosphamide-total body irradiation versus busulphan-cyclophosphamide conditioning regimens for acute myelogenous leukaemia in first remission. *Br J Haematol.* 2002;119(4):1115-24.
36. de Lima M, Couriel D, Thall PF, Wang X, Madden T, Jones R, et al. Once-daily intravenous busulfan and fludarabine: clinical and pharmacokinetic results of a myeloablative, reduced-toxicity conditioning regimen for allogeneic stem cell transplantation in AML and MDS. *Blood.* 2004;104(3):857-64.

37. Bornhauser M, Storer B, Slattery JT, Appelbaum FR, Deeg HJ, Hansen J, et al. Conditioning with fludarabine and targeted busulfan for transplantation of allogeneic hematopoietic stem cells. *Blood*. 2003;102(3):820-6.
38. Gupta V, Tallman MS, He W, Logan BR, Copelan E, Gale RP, et al. Comparable survival after HLA-well-matched unrelated or matched sibling donor transplantation for acute myeloid leukemia in first remission with unfavorable cytogenetics at diagnosis. *Blood*. 2010;116(11):1839-48. Comment in: *Blood*. 2010;116(11):1822-3.
39. Portier DA, Sabo RT, Roberts CH, Fletcher DS, Meier J, Clark WB, et al. Anti-thymocyte globulin for conditioning in matched unrelated donor hematopoietic cell transplantation provides comparable outcomes to matched related donor recipients. *Bone Marrow Transplant*. 2012;47(12):1513-9.
40. Saber W, Opie S, Rizzo JD, Zhang MJ, Horowitz MM, Schriber J. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. *Blood*. 2012;119(17):3908-16.
41. Rocha V, Labopin M, Sanz G, Arcese W, Schwerdtfeger R, Bosi A, Jacobsen N, Ruutu T, de Lima M, Finke J, Frassoni F, Gluckman E; Acute Leukemia Working Party of European Blood and Marrow Transplant Group; Eurocord-Netcord Registry. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med*. 2004;351(22):2276-85. Comment in: *N Engl J Med*. 2005;352(9):935-7; author reply 935-7; *N Engl J Med*. 2004;351(22):2255-7; *N Engl J Med*. 2004;351(22):2328-30; *N Engl J Med*. 2005;352(9):935-7; author reply 935-7; author reply 935-7.
42. Fung HC, Stein A, Slovak M, O'donnell MR, Snyder DS, Coehn S, et al. A long-term follow-up report on allogeneic stem cell transplantation for patients with primary refractory acute myelogenous leukemia: impact of cytogenetic characteristics on transplantation outcome. *Biol Blood Marrow Transplant*. 2003;9(12):766-71.
43. Duval M, Klein JP, He W, Cahn JY, Cairo M, Camitta BM, et al. Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. *J Clin Oncol*. 2010;28(23):3730-8.
44. Clift RA, Buckner CD, Appelbaum FR, Schoch G, Petersen FB, Bensinger WI, et al. Allogeneic marrow transplantation during untreated first relapse of acute myeloid leukemia. *J Clin Oncol*. 1992;10(11):1723-9.
45. Champlin R. Reduced-intensity allogeneic hematopoietic transplantation should be considered a standard of care for older patients with acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2011;17(12):1723-4.
46. Farag SS, Maharry K, Zhang MJ, Pérez WS, George SL, Mrózek K, DiPersio J, Bunjes DW, Marcucci G, Baer MR, Cairo M, Copelan E, Cutler CS, Isola L, Lazarus HM, Litzow MR, Marks DI, Ringdén O, Rizzieri DA, Soiffer R, Larson RA, Tallman MS; Bloomfield CD, Weisdorf DJ; Acute Leukemia Committee of the Center for International Blood and Marrow Transplant Research and Cancer and Leukemia Group B. Comparison of reduced-intensity hematopoietic cell transplantation with chemotherapy in patients age 60-70 years with acute myelogenous leukemia in first remission. *Biol Blood Marrow Transplant*. 2011;17(12):1796-803.
47. Burnett AK, Milligan D, Goldstone A, Prentice A, McMullin MF, Dennis M, Sellwood E, Pallis M, Russell N, Hills RK, Wheatley K; United Kingdom National Cancer Research Institute Haematological Oncology Study Group. The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome: the results of the LRF AML14 trial. *Br J Haematol*. 2009;145(3):318-32. Comment in: *Br J Haematol*. 2009;145(3):333.
48. Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz MA, Sierra J, Tallman MS, Löwenberg B, Bloomfield CD; European LeukemiaNet. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115(3):453-74.
49. Appelbaum F. Preparative regimens and ageism. *Biol Blood Marrow Transplant*. 2011;17(10):1419-20.
50. Alatrash G, de Lima M, Hamerschlag N, Pelosini M, Wang X, Xiao L, et al. Myeloablative reduced-toxicity i.v. busulfan-fludarabine and allogeneic hematopoietic stem cell transplant for patients with acute myeloid leukemia or myelodysplastic syndrome in the sixth through eighth decades of life. *Biol Blood Marrow Transplant*. 2011;17(10):1490-6. Comment in: *Biol Blood Marrow Transplant*. 2011;17(12):1878; *Biol Blood Marrow Transplant*. 2011;17(10):1419-20.
51. Champlin R. Reduced-intensity allogeneic hematopoietic transplantation should be considered a standard of care for older patients with acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2011;17(12):1723-4.