Chapter 7

Current Approach to Allogeneic Hematopoietic Stem Cell Transplantation

Hugo F. Fernandez and Lia Perez

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/53488

1. Introduction

1.1. Aims of chapter

In this Chapter we will discuss the indications for allogeneic hematopoietic stem cell transplantation (HCT). We will focus on the appropriate timing of this procedure for the different hematologic malignancies. We reviewed past approaches using myeloablative conditioning and present some of the newer reduced intensity therapies. Allogeneic transplantation is one of the first known uses of stem cells. Born from the need to rescue damaged bone marrow, it was first used in the setting of aplastic anemia and acute leukemia. Over the years, the technique has changed steadily and support for this procedure has improved immensely. Today this procedure is used to treat multiple malignant blood disorders, bone marrow failure syndromes, immune deficiency syndromes, and hemoglobinopathies. This chapter will focus on the malignant hematopathies. Another aspect of this Chapter will be to review the conditioning regimens used in allogeneic HCT.

2. Indications for transplantation

2.1. Acute myeloid leukemia

Acute myeloid leukemia (AML) Is heterogeneous group of clonal disorders. The disease can present at all ages, but this disorder is most commonly seen in older patients, with a median age at presentation of 67 years. [1] AML can present in a de novo fashion or can progress from antecedent hematological disorders, including myelodysplasia and myeloproliferative neoplasms (secondary AML), or after prior exposure to chemotherapy and/or radiation

therapy (treatment-related AML). Patients who are deemed fit enough to receive therapy can be given various combinations of chemotherapy to induce a remission of the disease. The most common induction therapy is that of cytarabine given as a continuous infusion for 7 days in combination with an anthracycline for 3 days (the 7+3 regimen). This approach has been used for over 40 years with very good results [2-6]. Attempts to improve on this by adding other therapies have not resulted in improved outcomes. More recently, dose intensification of the anthracycline has resulted in improved complete remission (CR) rates and more importantly overall survival (OS) for patients below the age of 65 years [7-10]. Although current induction chemotherapy regimens are successful in obtaining a CR with rates approaching 70-80%; without consolidation chemotherapy, most patients will relapse and die of the disease. Because of the high risk of relapse, AML is the leading indication for allogeneic transplant.

There are several significant prognostic factors that will affect the patient's ability to achieve a CR. The most important is that of age. Other recognized factors are cytogenetic risk profile, molecular mutations, prior exposures to chemotherapy and radiation therapy, and antecedent hematological disorders. [11] These factors also impact on the patient's ability to maintain long-term remission and be cured of the disease. More recently, molecular mutations have come to the forefront in determining overall prognosis. These mutations include nucleophosmin-1 (*NPM1*), fms-like tyrosine kinase-3 (*FLT3), CAAT* enhancer binding protein alpha (*CEBPA*), and c-KIT. Retrospective analyses have shown that, in cytogenetically normal individuals, *NPM-1*and *CEBPA* have improved survival in comparison to those with other mutations [12]. *FLT3-ITD* negatively impacts all cytogenetic and molecular risk groups [12-14]. The European Leukemia Network proposed a new prognostic designation based on both accepted cytogenetic and molecular abnormalities [15]. More recently, newer molecular mutations have been described which in the future may help further delineate the prognostic risk [14]. A recent retrospective study from the Center for International Blood and Marrow Transplantation Research has also reclassified the cytogenetic risk for those patients proceeding to transplantation. [16]

The potential for relapse and the patient's clinical status are factors that determine the consolidation approach. Currently, prognostic factors are used to decide on the most appropriate consolidation therapy for patients with this disease. Multiple studies have demonstrated that patients with the core binding factor AML (*AML/ETO* and *RUNX/RUNX1*] have an excellent response to induction and consolidation chemotherapy. [17] For these patients, allogeneic hematopoietic cell transplantation (HCT) should be reserved for relapse of the disease. Contrary to this, an unfavorable risk profile usually portends a very poor prognosis. Patients with unfavorable cytogenetics (complex cytogenetics, single or multiple monosomal karyotype, *MLL* (11q23) [18]) respond very poorly to induction chemotherapy, and remissions are usually shorter. In patients with cytogenetically normal AML, the presence of *FLT3, MLL, DNMT3A*, and others have also demonstrated shorter disease-free survival (DFS) and OS [12, 19-21].

For more than 15 years, the standard of consolidation therapy for patients with AML in first CR (CR1) has been intensive chemotherapy using high-dose cytarabine. However, this approach is only effective in patients who are below the age of 60 years and have favorable risk cytogenetics [22]. Initially, allogeneic HCT was used as salvage therapy for patients who failed conventional chemotherapy. The sentinel paper was published by Thomas et al., who used allogeneic HCT as

http://dx.doi.org/10.5772/53488

salvage therapy for 100 patients who had relapsed or refractory AML. The 13% OS gave great hope to the use of this modality [23] Subsequent reports from the same group promoted the use of allogeneic HCT as front-line consolidation therapy [24-27]. Randomized trials using genetic randomization demonstrated an improved DFS in patients receiving allogeneic transplantation [28]. Although the US Intergroup trial demonstrated there was no advantage to allogeneic transplantation compared to intensive chemotherapy in patients with de novo AML below the age of 60in CR1[29], more recent studies have demonstrated effectiveness of this approach. The US Intergroup trial had a significant flaw in that a large number of patients allocated to transplantation did not receive the intended therapy. However, retrospective subset analysis did note a significant improvement in patients with unfavorable-risk cytogenetics [30]. A meta-analysis of five trials performed by Yanada et al. (3100 patients) demonstrated an improved OS for patients with unfavorable-risk cytogenetic profiles. Until recently, there was no consensus as to how to treat patients with intermediate risk AML in CR1. Meta-analyses by the HOVON-SAKK group (925 patients) and a systematic review by Koreth et al. (6007 patients) all showed an improved OS for patients with intermediate- and unfavorable-risk cytogenetic profiles. These analyses were limited to related donor transplantations and to younger patients. [31-33] A Markov analysis of 2090 Japanese patients with *de novo* AML in CR1 confirmed the appropriateness of a related or alternative donor HCT over chemotherapy in this setting but not for patients without a matched donor [34]. A recent evaluation of patients with AML with a monosomal karyotype also demonstrated a benefit of allogeneic HCT in this group. [35] The appropriate intensity of the conditioning regimen for patients with myeloid malignancies in first CR is currently being evaluated by the Bone Marrow Transplant Clinical Trials Network (BMT-CTN) in a prospective randomized multi-center trial (0901).

About two-thirds of the patients with AML will not have a matched related donor (MRD). For these patients, matched unrelated donor (MUD) transplantation is an option particularly for those patients with unfavorable-risk profiles. A retrospective study from the CIBMTR reviewed MRD, MUD and partial MUD transplantation in patients with unfavorable-risk cytogenetics. Here the investigators found that MRD and MSD had similar leukemia-free survival and OS. The benefit was not seen in partially MUD or those over the age of 50 years. Other studies have demonstrated the similarities in outcomes compared to sibling transplants. [36-39] The trade-off is an increase in graft versus host disease (GVHD) and its associated mortality for increased disease control (graft versus leukemia effect). The only randomized trial using MUD was a German AML 01/99 trial. Here patients < 60 years of age with high-risk features (non CBF AML and > 5% blasts on the day 15 bone marrow biopsy) who did not have a MRD were randomized to a MUD allogeneic versus autologous HCT. The patients who had a MUD HCT had a superior OS to those treated with an autograft. [36]

Improvements in human leukocyte antigen (HLA) sequencing and selection of donors have reduced the effect of GVHD in this setting. [40] Better treatment options for the conditioning regimen and preventing and treating acute GVHD have provided more confidence in the procedure. [41] Tacrolimus and methotrexate are widely used as GVHD prophylaxis with or without anti-thymocyte globulin (ATG). Newer GVHD prophylaxis combinations such as sirolimus and tacrolimus [42-44], and ATG-Fresenius have reduced the incidence of both acute and chronic GVHD without impacting relapse or OS. [45]

A major challenge which remains is the older patient conventionally described as older than 60 years of age. [46] Interestingly in the case of allogeneic transplantation the threshold for the older patient is closer to 50 years. These patients are affected by worse prognostic factors, comorbidities, and intolerance to therapy. [47] However, multiple reports have demonstrated that transplant is possible with the appropriate conditioning regimen utilizing a non-myeloablative or reduced intensity dosing of therapy. [48]Although no randomized trial between conventional therapy and HCT has been reported to date, results suggest that outcomes are better than conventional chemotherapy for this group of patients. [49, 50] More on this will be discussed later in this chapter.

3. Chronic myeloid leukemia

Translocation between chromosomes 9 and 22 (t(9;22) or Philadelphia chromosome (Ph+) leads to an abnormal fusion protein (BCR-ABL) with dysregulated tyrosine kinase activity resulting in a myeloproliferative disorder characterized by abnormal white cell production known as chronic myeloid leukemia (CML). Without therapy, CML has a predictable progression from a chronic phase (CP) to the more advanced accelerated (AP) and/or blast (BP) phases.Since the introduction of tyrosine kinase inhibitors (TKIs) in October 2001, allogeneic hematopoietic stem cell transplant (HCT) has shifted from a first-line treatment option and to a second-, third-, or even a fourth-line option [51, 52]. The number of allogeneic transplantations in the post-TKI era has significantly decreased in CP CML patients; however, the number of patients transplanted in AP or BP remains the same [53].

Given the excellent results of studies using TKIs as upfront treatment for CP CML, a randomized trial to compare HCT to TKIs has not been performed and has not been justified. The use of TKIs as standard front-line therapy has been supported by few retrospective and/or genetically randomized studies [54, 55]. Imatinib mesylate has activity against progenitors and mature cells but has limited activity against leukemia stem cells [56, 57]. Unfortunately, the majority of patients achieving remission with imatinib mesylate continue to have molecular evidence of persistent disease [58]. Even in those patients who are treated for over 4 years with imatinib mesylate and in remission, BCR-ABL + stem cells are still detected in bone marrow [59].

Allogeneic HCT remains a curative approach with long-term molecular remissions, seen only rarely with TKIs, as the mechanism of the graft versus leukemia effect relies on the presence of antigens on leukemia stem cells [60]. Current indications of transplant are reserved, according to the European leukemia net [61], to the following CML subjects:

- At diagnosis for patients presenting in AP or BP
- Imatinib failure (after second-generation TKI pretreatment) progressing to AP or BP
- Patients with TKI resistant mutations such us T315I
- All patients failing second-generation TKI treatment.

http://dx.doi.org/10.5772/53488

Definitions of imatinib mesylate failure are: 1) a lack to achieve complete hematological remission at 3 months; 2) failure to achieve any cytogenetic response at 6 months; 3) persistence of more than 35% Ph+ metaphases at 12 months; or 4) less than complete cytogenetic response at 18 months. Resistance to imatinib mesylate is defined as loss of complete hematological response or complete cytogenetic response or development during imatinib mesylate treatment of an ABL kinase mutation leading to its resistance.

In summary, the present use of allogeneic HCT is reserved for patients with poor response to TKIs and/or those with advanced disease. Saussele et al. reported an interim analysis from the German CML Study group IV in patients who underwent a 5-arm randomization where 84 patients underwent allogeneic HCT as second-line therapy after imatinib mesylate failure [62].The 3-year survival in CP was 91%, with 59% in AP. The majority of patients (88%) achieved a molecular remission and reported a very low treatment-related mortality (TRM) (8%).The authors at that time concluded that allogeneic HCT could become the preferred second-line option after imatinib mesylate failure for suitable patients with a donor.

Because most patients are treated with TKI before transplant, it is important to understand whether this strategy could potentially jeopardize HCT results. Retrospective comparison of patients treated with imatinib mesylate pre-HCT compared with historical controls showed no effect on OS, progression-free survival, and non-relapse mortality [63]. Based on a Center for International Blood and Marrow Transplant Research (CIBMTR) study reported by Lee et al., imatinib mesylate before HCT in patients with CP CML leads to a better survival but no statistically significant difference in TRM, relapse, and leukemia-free survival and no differences reported in advanced CML. These results are re-assuring for the majority of patients that today are treated with TKIs prior to allogeneic HCT [64]. In summary, imatinib mesylate use before HCT has been shown to not increase toxicity and/or engraftment of subsequent allogeneic HCT [65-68]. Interestingly, risk of chronic GVHD may be decreased with the use of imatinib mesylate pre-HCT [67] and may potentially target GVHD-related fibrotic features if they developed post-HCT[69, 70]. In addition, the use of TKIs before HCT has been shown to improve outcomes if a patient achieves major cytogenetic remission compared to those who do not [67].

Imatinib mesylate as frontline for CP patients leads to a major cytogenetic response rate of 89% and OS of 86% at 7 years. Unfortunately, secondary resistance develops at a rate of 4% per year for CP [71] and 70-90% in AP/BP phases [72-74].With the development of second-generation TKIs (dasatinib and nilotinib) and the compelling results shown of a major cytogenetic response of up to 45% for imatinib mesylate failure patients [75, 76], recommendations for HCT are reserved for patients who have failed not only imatinib but also second-generation TKIs[61]. Front-line therapy with second-generation TKIs for CP CML it is now warranted [77, 78].

The majority of mutations are susceptible to second-generation TKIs, but some are resistant not only to first-generation but also to all second-generation TKIs. Threonine-to-isoleucine substitution at position 315 of Bcr-Abl fusion protein (T315I mutation) is well established to confer resistance to most TKIs [61]. Multiple reports have shown encouraging results with allogeneic HCT in patients for whom allogeneic HCT is recommended earlier in the disease

course [79-82]. The results from efforts to develop third-line TKIs to target resistant mutations are encouraging. On September 4, 2012, the U.S. Food and Drug Administration approved bosutinib tablets (Bosulif®, Pfizer, Inc.) for the treatment of CP, AP, and BP Ph+ CML in adult patients with imatinib-resistant mutants of Abl or intolerance to prior therapy (http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm318203.htm). The pivotal PACE trial data have shown robust anti-leukemic activity of ponatinib in patients with CML at all stages, who are either resistant or intolerant to dasatinib or nilotinib or who have the T315I mutation [83].

For advanced patients, TKIs have facilitated a bridge to the HCT procedure. Long-term outcomes with imatinib mesylate for AP CML are only up to 47 months and 7 months for BP CML[84-86] with a 2-year OS of only 47% and 16% for patients in AP and BP, respectively [87]. The goal for advanced disease patients is to achieve a second CP in order to proceed with allogeneic HCT. Because the rate of mutations is highly increased for these patients, assessment of mutation profile is quite vital to guide TKI selection. Allogeneic HCT represents the best chance for long-term success or even cure in AP/BP CML [88]. Given selection bias, only unfavorable risk CML patients should proceed to allogeneic HCT these days. Reduced intensity conditioning (RIC) regimens have facilitated transplant access to more frail populations; unfortunately a higher relapse risk remains due to aggressive disease and reduced chemotherapy [89-92]. Therefore, there is a need for strategies to improve current leukemia-free survival post-allogeneic HCT.Measurement of minimal residual disease has become particularly important as it has been shown that patients who have increased BCR-ABL expression levels (more than 10^{-4}) experience higher relapses rates [93-95]. Serial BCR-ABL RT-PCR is considered a standard practice and can be used to guide clinical interventions. It is not unusual to decect low level molecular disease; however treatment should be reserved for those patients whose markers increase over time or remain persistently positive. Maintenance therapy with TKIs post-transplant has proven to be tolerable [96]. Carpenter et al. reported that prophylactic use of imatinib mesylate for 1 year in Ph+ acute lymphoblastic leukemia (ALL) and CML lead to a low risk of relapse (18%) [97]. Other groups have also shown that use of TKIs post-HCT can help to minimize relapse risk [98, 99] and/or effectively control relapse post-HCT [100]. Experience of second-generation TKIs in the post-HCT setting are currently being explored in clinical trials (http://clinicaltrials.gov/ct2/show/NCT00702403). An early approach is to consider maintenance with a TKI in those who have shown activity prior to transplant, and BCR-ABL mutation analysis should guide TKI selection. Role of TKIs in the post-HCT setting should also be studied in the context of donor lymphocyte infusions (DLI) as immunotherapy, as it has been shown to be effective for management of early relapse in the pre-TKI era. The synergistic role of TKI with DLI should be further explored [101].

In conclusion, several effective drugs are available today to treat CML upfront during the chronic phase of the disease. Careful monitoring for BCR/ABL and mutation analysis are warranted to determine which patients will be in need of second- or third-line therapies. For patients with advanced-phase disease, HCT remains the option of choice, using a TKI to bridge to allogeneic HCT.

http://dx.doi.org/10.5772/53488

4. Myelodysplastic syndrome

Myelodysplastic syndrome (MDS) is a clonal stem cell disorder that results in a heterogeneous group of disorders characterized by excessive apoptosis of bone marrow cells. It is characterized by low peripheral counts, marrow dysplasia, proliferation and loss of differentiation of hematopoietic progenitors with a median age of 60-70 years at presentation. Mortality is related to bone marrow failure and evolution to secondary AML [102]. Despite development of novel therapeutic agents over the past decades, allogeneic HCT remains the only curative option in this disease. To date, HCT indications, timing, and incorporation of novel drugs before and/or after HCT remains a challenge. Additionally, whether novel treatment agents for elderly MDS patients should be pursued instead of allogeneic HCT remains unanswered. A recent retrospective cohort analysis suggested a survival advantage for allogeneic HCT (39%) compared with azacytidine (23%) therapy in medically fit patients with high-risk MDS of 60-70 years of age [103]. The German MDS study group is testing 5-azacytidine compared to allogeneic HCT in a prospective study for patients with International Prognostic Scoring System (IPSS) intermediate II or high-risk up to age 70 years (NCT01404741).

The IPSS system is based on peripheral blood cytopenias, cytogenetics, and marrow myeloblast percentages and is generally used to identify HCT candidates [104]. A limitation of the IPSS score is that it does not take into account patient age; therefore, development of other scoring system has been proposed. The World Health Organization classification and the World Health Organization classification–based Prognostic Scoring System have both shown relevant prognostic values in post-HCT MDS outcome for OS and relapse [105, 106]. In a recent analysis of 1915 patients with MDS, only 26% had primary MDS without prior therapy that could be classified with the IPSS system. A multivariate analysis of prognostic factors determined worst outcome for poor performance, older age, thrombocytopenia, anemia, increased bone marrow blasts, leukocytosis, chromosome 7 or complex (≥3) abnormalities, and prior transfusions. This new MDS prognostic model divided patients into 4 prognostic groups with significantly different outcomes with the advantage that it accounts for duration of MDS and prior therapy and is applicable to any patient with MDS at any time during the course of MDS [107].

A Markov decision analysis model designed by Cutler et al. showed that for low and intermediate-1 IPSS groups, delayed transplantation maximized OS; for intermediate-2 and high IPSS groups, HCT at diagnosis maximized OS and was associated with maximal life expectancy [108]. In contrast, other studies have suggested that younger patients with less advanced disease have a better transplantation outcome [105, 109]. An evidence-based review consensus by the American Society of Blood and Marrow Transplantation recommended early HCT for patients with IPSS intermediate-2 or high-risk at diagnosis and selected patients with lower risk disease at diagnosis who have poor prognostic features (such as older age, refractory cytopenias, and/or transfusion dependence) [110]. The American Society of Blood and Marrow Transplantation recommendations are limited as they are based on studies using IPSS score instead of more comprehensive ones; in addition, it only applies to newly diagnosed patients and excludes MDS subjects with treatment-related MDS/t-AML and chronic myelomonocytic leukemia subtype [111].

Factors that determine risk of progression from MDS to t-AML and that more accurately predict disease progression and HCT indication have been studied in the context of MDS phenotype and/or disease biology. With a patient group of 692 MDS patients, a European group analyzed outcome and reported worse OS and relapse rates based on poor cytogenetics [112]. In a multivariate analysis by Chang et al. comparing patients with secondary MDS or transformed to AML(t-AML) to de novo MDS, no significant differences in outcome were shown between the 2 cohorts and overall inferior outcome was shown in patients with secondary MDS/tAML, as the majority of advanced patients has increased frequency of high-risk cytogenetics [113]. Flow cytometric scoring system is predictive of post-HCT outcomes even after adjusting for risk factors such as marrow myeloblast percentage and IPSS score [114]. Cases of MDS classified as AML by microarray-based GEP assays had more aggressive disease and more rapid progression to AML, whereas MDS cases classified as "none-of-the-targets" had a more indolent clinical course [115]. Tumor necrosis factor-α polymorphisms affect HCT outcome in a disease-dependent manner [116]. There are many others risk categorization factors in MDS like FISH, spectral karyotyping, and mutation or deletion analyses [117-119], although clinical significance remains controversial [120]. Development of a revised scoring system is warranted to guide the decision-making process to recommend HCT for such a diverse and heterogeneous clonal condition.

Clinical evolution of disease such us increased transfusion, recurrent infections or bleeding may also precipitate the decision to proceed with HCT. Elevated serum ferritin levels, as reflection of increased body iron storage, have been showed to be associated with decreased OS and DFS, acute GVHD, and infections with myeloablative HCT [121, 122]. Ferritin levels should guide the need of chelation therapy prior to HCT and/or may guide conditioning regimen selection [123]. Co-morbidity as a determinant of HCT outcomes has been elegantly studied by Sorror et al. [124] and applied in the context of AML-MDS [125]. This group investigated the role of comorbidities, among other risk factors, in stratifying and comparing patients conditioned with non-myeloablative or myeloablative regimens. Patients with low HCT-CI scores and either low or high disease risks had probabilities of OS at 2 years of 70% and 57% after nonmyeloablative conditioning compared to 78% and 50% after myeloablative conditioning, respectively. Patients with higher HCT-CI scores (≥ 3) and either low or high disease risks had probabilities of OS of 41% and 29% with nonmyeloablative conditioning compared with 45% and 24% with myeloablative regimens, respectively. After adjusting for pretransplantation differences, stratified outcomes were not significantly different among patients receiving nonmyeloablative compared with myeloablative conditioning, with the exception of lessened nonrelapse mortality (hazard ratio, 0.50; P =.05) in the highest risk group. This group concluded that patients with low comorbidity scores could be candidates for prospective randomized trials comparing nonmyeloablative and myeloablative conditioning regardless of disease status [125]. An additional scoring system has also emphasized the negative influence of comorbidities on HCT outcomes [126].

Based on published literature, patients up to 70 years of age can tolerate allogeneic HCT and age per se should not be a criterion for patient selection and/or intensity of the conditioning regimen rather than performance status, comorbidity, and disease status [127].Results from a

http://dx.doi.org/10.5772/53488

European Group for Blood and Marrow Transplantation (EBMT) report suggested that age is not a contraindication to HCT; the cumulative incidence of non-relapse mortality at 4 years was 36% in the 50- to 60-year-old patient group and 39% for the group 60 years or older (P =. 39], with OS not differing between the groups (34% versus 27%, P =.2). In a multivariate analysis for OS, only advanced stage of the disease at time of transplantation (hazard ratio = 1.55] was associated with inferior survival [128]. Similar results were reported by the CIBMTR; in a multivariate analysis, they showed that OS was inferior with low performance status, mismatched unrelated donors, and unfavorable cytogenetic, but age had no impact [129].

To facilitate HCT access to the majority of MDS patients, a RIC regimen has been developed. The rationale for RIC is to promote graft-versus-leukemia effect without excessive toxicity to minimize TRM. Many RIC regimens have been developed using combinations of busulfan with cyclophosphamide or fludarabine, fludarabine with cyclophosphamide, or low-dose total body irradiation (TBI) (200cG) among others versus the more intense or conventional regimens based on TBI or busulfan/cyclophosphomide-based regimens. Unfortunately, due to the lack randomized prospective trials, it remains unknown which conditioning regimen should be chosen and how "intense and/or reduced" the conditioning should be. In general, the highest tolerable regimen should be chosen since reduced intensity is associated with a higher relapse rate, as suggested in multiple retrospective studies [130-136]. RIC HCT with fludarabine/melphalan and tacrolimus/sirolimus-based GVHD prophylaxis resulted in a relapse incidence of 20.9% with low-grade acute GVHD [137]. An ongoing prospective randomized trial comparing RIC versus myeloablative conditioning has been developed to address selection bias for allogeneic HCT by the EBMT group (NCT00682396).

Disease relapse post-HCT remains a critical issue as long-term outcome is compromised. Approaches to tackle this issue include pre-HCT induction chemotherapy and/or novel agents for high-risk patients or drug maintenance to prevent relapse pre-emptively post-HCT, as opposed to strategies for relapse treatment. Still debatable to date is whether pre-HCT induction chemotherapy has a role to minimize relapse post-HCT for patients with advanced MDS. Unfortunately, this remains unanswered due to lack of randomized and/or definitive data [138-141]. Introduction of novel agents in the pre-HCT setting seems feasible, associated with less toxicity, and may allow for similar post-HCT outcomes when compared to chemotherapy [142].Another approach is to use low-dose 5-azacytidine as maintenance post-HCT. De Lima et al. determined that the optimal combination was 32 mg/m^2 given for at least 4 cycles, with reversible thrombocytopenia as the dose-limiting toxicity. The authors suggested that this treatment prolonged event-free survival (EFS) and OS [143]. In the event of disease relapse post-HCT, azacytidine administration is feasible and may induce durable remissions [144]. DLIs can result in complete remission in some patients, but long-term survival is infrequent [145]. The Azarela trial, a prospective multicenter phase II trial, was developed to test whether a combination of 5-azacytidine and DLI would benefit patients with relapsed MDS post-HCT. Overall response rate was 64% with 20% achieving and staying in CR, 12% achieved partial response, and 32% showed stable disease with low incidence of acute GVHD occurring (24%). These data suggest that salvage therapy with combination azacytidine + DLI is feasible and has significant anti-leukemic activity in relapsed MDS post-HCT [146].

In conclusion, several factors influence HCT indication and timing for MDS patients. Incorporation of evolving prognostic indicators might help to develop treatment algorithms to decide the appropriate timing for allogeneic HCT. The ultimate objective is to proceed with HCT when non-transplantation approaches would result in outcomes lower than those that would result with allogeneic HCT. Currently, novel HCT approaches are allowing the consideration of older patients and/or the use of alternative donors to treat MDS. A remaining question is how to incorporate HCT for those patients that are achieving a CR with hypomethylating agents and/or other novel agents. Development of prospective clinical trial may help to elucidate these questions within a fast evolving field.

5. Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is a bone marrow clonal disease characterized by the rapid proliferation of immature lymphoblasts. Despite initial control of the disease, the majority of adult patients will relapse with poor long-term outcomes. Allogeneic HCT has been used as a salvage therapy for both relapsed patient and high-risk patients with ALL early in the disease process. The availability of unrelated donors and/or alternative stem cell sources and the development of RIC transplants have resulted in far more allogeneic transplants being performed for this rare disease. For adults with ALL, indication and timing of allogeneic HCT remains debatable as defining the optimal role for allogeneic HCT has been limited by the lack of prospective data that can only be gained by large multicenter-national trials.

Historically, allogeneic HCT was reserved for high-risk patients, especially for those with Ph + ALL. Patients with high-risk features benefit from upfront HCT, including those with increased white blood count at presentation (>25,000/μL), chromosomal translocations [t(9;22), t(4;11), t(8;14)], older age (≥30 years), extra-medullary disease at diagnosis, and/or requiring more than 4 weeks to achieve CR [147]. Strategy to take ALL patients in CR1 for t(9;22) and t(1;19) have been supported by a trial by the French Group of Therapy for adult ALL (LALA-94) in a subgroup analysis [148]. Improvement in detection of minimal residual disease has also helped to assess disease risk, as 10% of patients with a rapid MRD decline to lower than 10(-4) or below detection limits at day 11 and day 24 were classified as low risk as their 3-year relapse rate was 0% [149]. Testing MRD with flow cytometry and/or molecular analysis for gene rearrangements may help to guide transplant decisions.

The largest prospective study of HCT in adult ALL was conducted by the Medical Research Council in Great Britain (UKALL XII) and the Eastern Cooperative Oncology Group in the United States (ECOG 2993). In this trial, allogeneic HCT resulted in improved disease control in all adult patients with ALL, with younger patients with low-risk disease benefiting the most with allogeneic HCT [150]. This international collaboration prospectively evaluated the role of allogeneic HCT for adults with ALL and compared autologous HCT with standard chemotherapy. Patients received 2 phases of induction and, if in remission, were assigned to allogeneic HCT if they had a compatible sibling donor. Patients without a donor were randomized to chemotherapy for 2.5 years versus an autologous HCT. A donor versus no-

http://dx.doi.org/10.5772/53488

donor analysis showed that Ph- ALL patients (standard risk) with a donor had a 5-year improved OS of 53% versus 45% for no donor (P =.01). The relapse rate was significantly lower (P ≤.001) with HCT in the standard-risk ALL patients. The survival difference was significant only in standard-risk patients, but not in high-risk patients, who had an impressive reduction in relapse rate but increased non-relapse mortality that abrogated the OS benefit of allogeneic HCT. For the no donor group, patients randomized to chemotherapy had a higher 5-year OS (46%) than those randomized to autologous transplantation (37%; P =.03). In conclusion, MRD allogeneic HCT for ALL in CR1 provide the most potent anti-leukemic therapy and considerable survival benefit for standard-risk patients. We may also conclude that there is no role for a single autologous HCT to replace consolidation/maintenance in any risk group.

For high-risk patients, results are conflicting with a recent large meta-analysis from seven studies of adult high-risk ALL (n=1274) using natural randomization based on donor availability combined with intent-to-treat analyses. This study demonstrated that patients in the donor groups had significantly better survival than patients in the no-donor groups (hazard ratio, 1.29; 95% confidence interval [95% CI], 1.02-1.63 [P =.037]). When only high-risk patients were included in the analysis, the superiority of the survival advantage was even greater (hazard ratio, 1.42; 95% CI, 1.06-1.90 [P =.019]) [151]. In addition, a recent systematic review and meta-analysis supported MRD HCT as the optimal post-remission therapy in ALL patients aged 15 years or over, resulting in improved OS and DFS with a significant reduction of disease relapse but with increased non-relapse mortality[152]. Interpretation of the results of the multicenter international trial has led to advocating early allogeneic HCT for patients with standard risk for some transplantation teams while others have preferred a more personalized approach as reports from various study groups differ and are often contradictory, leading to difficulty in interpreting the data [153, 154].

Historically, allogeneic HCT has been the standard of care for patients with high-risk Ph+ ALL in CR1. With the introduction of TKIs over the past decade, a treatment algorithm introducing TKIs in combination with allogeneic HCT for adult patients with Ph+ ALL is mandated. TKIs have been used in the upfront induction/maintenance chemotherapy setting and as maintenance post-HCT to prevent disease relapse in Ph+ ALL patients. Whether use of TKIs has an impact on OS when combined with HCT or whether TKIs will replace the use of allogeneic HCT remains unanswered to date. Multiple studies have shown the advantage of using imatinib mesylate in the induction/consolidation phase, allowing better remission rates and durable response with minimal toxicity as well as facilitating access and planning for an allogeneic HCT [154-159]. Review of these trials has suggested that over 90% of patients achieved a complete response as previously reviewed [154, 160]. Dasatinib, a multi-target kinase inhibitor of BCR-ABL and SRC family kinases, has been shown to induce responses in patients with imatinib-resistant or intolerant Ph+ ALL. In the START-L trial, major hematologic responses were achieved in 42%(15/36) of patients, 67% of whom remained progression-free when used at a dose of 140 mg. Complete cytogenetic responses were attained by 58% (21/36) of patients. The presence of BCR-ABL mutations conferring imatinib resistance did not preclude a response to dasatinib in this trial [161], suggesting a role for dasatinib to manage Ph+ ALL upfront [161]. Ravandi et al. examined the efficacy and safety of combining chemo-

therapy with dasatinib in patients with Ph+ ALL and determined that 94% achieved CR with an estimated 2-year survival of 64%. The combination of chemotherapy with dasatinib is effective in achieving long-term remissions in patients with newly diagnosed Ph+ ALL[162]. Nilotinib has also been tested for the management of relapsed/refractory Ph+ ALL with encouraging results[163].

TKI treatment is also a promising strategy when used as a consolidation strategy to induce and/or maintain molecular responses to decrease relapse rate after allogeneic HCT. Carpenter el al. reported safety data in 15 patients with Ph+ ALL who were enrolled in a prospective study and given imatinib from the time of engraftment until day 265 after HCT [97]. A clinical trial is currently ongoing to determine the safety of the administration of nilotinib between day 81 and day 365 after HCT in patients with Ph+ leukemia (http://clinicaltrials.gov/show/NCT00702403). Lastly, TKIs have been shown to be effective for management of relapse in Ph+ ALL in the post-HCT setting, although these data are based on few reports [160]. In summary, TKIs should be incorporated as a pre-HCT strategy to facilitate higher response rate and to improve both quality and durability of responses prior to allografting. TKIs are also a reasonable and promising strategy after allogeneic HCT to consolidate and maintain molecular responses that may ultimately improve survival for patients with Ph+ ALL. The optimal duration of therapy post-HCT, particularly in patients with sustained molecular response, remains to be determined. Whether TKI incorporation in the treatment strategy would impact OS is still unclear. In the absence of large prospective randomized trials comparing imatinib-chemotherapy regimens versus allo-HCT as a consolidative strategy, allo-HCT remains the best therapeutic approach that offers a possibility of cure in Ph+ ALL [160].

There is increased interest in developing strategies to minimize toxicity associated with allogeneic HCT, especially after the results of the UK ALL XII ECOG 2993 study, which showed a significant TRM in patients over the age of 35 years despite better control of disease [150]. Several groups have sought to minimize morbidity and mortality in this group of patents through reduced intensity approaches, allowing for access to HCT for majority of Ph+ ALL subjects [164]. Unfortunately, there is no prospective trials using RIC for this disease published in the literature. Few recent retrospective series have been reported with 2-year OS and DFS between 50 and 61.5% [165]. We previously published our initial experience with FLU and BU in adult ALL patients, which showed a 2-year cumulative incidence of relapse of 19% (95% CI 8%-41%) for those transplanted in CR1 and 48% (29%-80%) in those with more advanced disease, with a 2-year OS of 54% (95% CI 39%-69%). Relapse-free survival at 2 years was 63% (95% CI 45%-81%) for patients transplanted in CR1 and 34% (95% CI 11%-57%) for patients transplanted in more advanced disease. We concluded that, compared to irradiation-containing regimens, FLU and PK-targeted BU appear safer and similarly effective in controlling ALL, providing a treatment option for adult patients with ALL [166]. Nonmyeloablative allogeneic HCT approach is promising but its role for management of Ph+ ALL requires further investigations [154].

http://dx.doi.org/10.5772/53488

6. Lymphoma

Both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) represent a large group of diverse diseases. They are characterized by enlarged lymph nodes, splenomegaly, and constitutional symptoms. These disorders can present with bone marrow and extramedullary consequences. As a whole, they respond to combination chemotherapy. For patients who have relapsed or are refractory to initial therapy autologous HCT is the treatment of choice. The Parma group study, established the superiority of high-dose chemotherapy and autologous HCT over conventional salvage chemotherapy in a randomized multi-center trial for relapsed aggressive NHL [167]. Based on this study, autologous HCT became the standard of care for chemotherapy-sensitive relapsed or primary refractory aggressive NHL. There are instances where allogeneic HCT is the preferred approach for lymphoma.

6.1. Non-hodgkin lymphoma

6.1.1. Diffuse large B cell lymphoma (DLBCL)

The number of published studies using allogeneic HCT in DLBCL are limited and do not allow definitive conclusions. Allogeneic HCT has generally been used as treatment for patients who have relapsed after autologous HCT and on occasion for relapsed high-risk or refractory disease. No prospective comparative studies are available in this setting. A retrospective study by the CIBMTR compared the outcomes of DLBCL patients undergoing first autologous HCT (n = 837) or HLA-identical MSD allogeneic HCT with myeloablative conditioning (n =79). Allogeneic HCT was associated with higher TRM but with a similar risk of disease progression compared with lower-risk patients who received autologus HCT. [168] The European Group for Blood and Marrow Transplantation (EBMT) registry published a retrospective analysis of 101 patients. Approximately two-thirds of the patients received a reduced-intensity conditioning (RIC) regimen and 70% had an MSD. Non relapse mortality (NRM) was low with a rate of 28.2%, a relapse rate of 30% and an OS rate of 53%. Patients with a long remission after autologous HCT and with sensitive disease at allogeneic HCT appear to be the best candidates for this approach. [169] Thus, the use of allogeneic transplantation should be reserved for relapsed and refractory DLBCL that is responsive to the last line of therapy.

6.2. Follicular lymphoma (FL)

FL comprises approximately 25% of all newly diagnosed NHL cases. As an indolent lymphoma, the disease course is one of remissions and relapses with chemotherapy, followed inevitably by resistance and transformation to a more aggressive NHL histology. Trials from the several European Groups compared consolidative autologous HCT to chemotherapy ± interferon alfa (IFN-α) maintenance therapy or rituximab. [170-173] As autologous HCT provides no benefit in OS in FL it is currently not recommended as consolidation therapy.

The graft-vs-lymphoma effect afforded by allogeneic HCT is appealing as a potential curative approach in FL. Myeloablative conditioning allogeneic HCT, due to high TRM has not resulted in an improved OS in this disease. [174, 175] RIC allogeneic HCT is associated with a lower

TRM and the graft-vs-lymphoma effect may be beneficial in this indolent disease. Several studies have been published using this approach. The MD Anderson BMT program published results of their single institution trial of 43 patients with relapsed/refractory FL receiving a RIC allogeneic HCT with high doses of rituximab during and after conditioning. The PFS and OS rates were robust at 83% and 85%, respectively. [176] Currently, the BMT-CTN (0701) is confirming these results in a multi-institution trial.

6.3. Mantle cell lymphoma (MCL)

MCL is an aggressive NHL that often is responsive to initial chemotherapy but has a very high relapse rate and is incurable with conventional chemotherapy. With intensified induction regimens and the addition of rituximab, a higher proportion of patients achieve complete remission; however, long term cures are rare. [177] Autologous HCT provides very good control of the disease particularly in patients who received transplants in CR1. [178, 179] The Mantle Cell Lymphoma International Prognostic Index (MIPI) predicted good outcomes for patients in the good- and intermediate-risk. Unfortunately the poor-risk group had a disappointing survival, suggesting that these patients may be better suited for allogeneic HCT. [180]

To reduce toxicity and mortality in these heavily pretreated and older patients, RIC allogeneic HCT has been proposed with promising results. Treatment with a nonmyeloablative conditioning regimen and allogeneic HCT in 33 patients with relapsed and refractory MCL resulted in an OS rate of 65%. None of the patients transplanted in CR had relapsed after a median follow-up of 2 years. [181] Long term follow upof RIC allogeneic HCT in 35 patients with relapsed or refractory MCL demonstrated a low TRM rate and outcomes in which median OS had not been reached. [182] Finally, The British Society for Blood and Marrow Transplantation published the results of a retrospective analysis of 70 heavily pretreated patients with relapsed/refractory MCL who received RIC allogeneic HCT with or without alemtuzumab with or without DLI to boost the graft vs-lymphoma effect. The 3-year OS rate for patients who received donor lymphocyte infusions for relapse was 79%. [183] All of these studies demonstrated a plateau on the survival curves. Based on these reports, allogeneic HCT appears to be effective therapy for relapsed and refractory MCL and the only one associated with long-term remission. It will be necessary to complete a prospective, randomized study to define the role of upfront allogeneic HCT in MCL patients.

6.4. T-cell lymphoma

T-cell NHL (Peripheral T-cell lymphoma-not otherwise specified, angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL)) are a heterogeneous group of lymphomas which for the most part have an inferior prognosis when compared to B-cell NHL after CHOP therapy. With the exception of anaplastic large-cell kinase-positive (ALK) positive anaplastic large-cell lymphoma, T-cell NHL Carries a poor prognosis with low DFS and OS with standard chemotherapy. Several studies have demonstrated the use of autologous HCT in T-cell lymphoma has similar results to DLBCL. [184-189].

http://dx.doi.org/10.5772/53488

Allogeneic HCT has been proposed for the treatment of T-cell Lymphoma because of the potential graft-vs-lymphoma effect. There are limited studies in this field but the results have been promising. A retrospective analysis from France on 77 patients who underwent allogeneic HCT for PTCL resulted in a 5-year OS rates of 57%. Myeloablative conditioning was used in the majority of the patients. Patients with AITL had the best outcome, with a 5-year OS rate of 80%. Risk of relapse was low; however, the high TRM limited the benefit of the myeloablative approach. [190] RIC allogeneic HCT was published a prospective phase II trial using a reduced intensity regimen in 17 patients with PTCL. As expected TRM was low and the estimated 3-year OS was 81%. [191] In summary, the use of RIC allogeneic HCT through a lower TRM and allows transplant in older and heavily pretreated patients with reasonable OS. Certain T-cell entities such as hepatosplenic T-cell lymphoma, adult T-cell leukemia/ lymphoma, and systemic extranodal NK/T-cell lymphoma carry such a poor prognosis that allogeneic HCT is justified as part of the initial treatment. The use of prognostic indexes such help identify patients with extremely high risk of relapse who may also benefit from an allograft. Only prospective multicenter trials will define the role of allogeneic HCT in these aggressive lymphomas.

6.5. Hodgkin lymphoma

Combination chemotherapy with or without radiation therapy results in long-term DFS and OS for about 80% of newly diagnosed patients with HL. [192] As in NHL autologous HCT is well established for the treatment of disease. [193] An approach to minimize relapse after autologous HCT for high-risk patients using the anti-CD30 antibody (brentuximab) conjugated to an anti-tubulin drug (vedotin) [SGN-35][194] is currently being studied in a randomized phase III placebo-controlled trial as maintenance therapy following autologous HCT.

Because of prior intensive therapy, RIC allogeneic HCT is an appropriate option in candidates for patients with HL. [195-198] Recent retrospective analyses demonstrate improved PFS and OS compared to additional salvage therapy for patients treated with this approach after relapse following autologous HCT. [197, 199] More importantly, outcomes with MRD vs MUD do not appear to be different. [196, 198]

7. Conditioning regimens

7.1. Myeloablative conditioning

Allogeneic bone marrow transplantation is the most intensive post-remission therapy used for management of malignant disorders over the past decades. Toxicity of a conditioning regimen can impact on overall morbidity, including interstitial pneumonitis, sinusoidal obstruction syndrome/veno-occlusive disease, and may lead to an increased incidence of GVHD. Despite current understanding of the transplantation process, the optimal chemotherapy and/or radiation conditioning regimen remains unknown. Few data from comparative or randomized studies are available to address this issue. Allogeneic hematopoietic cells serve a dual purpose, not only to restore hematopoiesis but also to impose immunologic effects against malignant

clones, a process known as graft versus leukemia. This has led to the development of a conditioning regimen that will minimize toxicity with preservation of graft versus leukemia effect as the main mechanism of action to eradicate disease.

The spectrum of conditioning intensity has been defined in three categories: 1) myeloablative, which causes irreversible marrow aplasia if transplantation is not performed; 2) nonmyeloablative, which cause minimal marrow suppression; and 3) RIC, which causes cytopenias of intermediate duration [200]. Assignment to these categories is based on the duration of cytopenia and on the requirement for stem cell support. Myeloablative regimens cause irreversible cytopenia, and stem cell support is mandatory. Nonmyeloablative regimens cause minimal cytopenia and can be given also without stem cell support. RIC causes cytopenias of variable duration and should be given with stem cell support, although cytopenia may not be irreversible. Compared with high-dose MA preparative regimens, NMA or RIC regimens are associated with shorter inpatient hospital stays, reduced need for transfusions [201], and a shorter duration of neutropenia with fewer bacterial infections [202-204]. There is current trend to adopt less-toxic conditioning regimens to allow access for patients to undergo HCT who has been previously been excluded because of age or comorbidities. Standardized classification of conditioning regimen intensities will allow comparisons across studies and interpretation of study results [200].

Myeloablative regimens, a combination of agents expected to produce profound pancytopenia and myeloablation within 1-3 weeks from administration, have caused pancytopenia that is long lasting, usually irreversible, and in most instances fatal, unless hematopoiesis is restored by hemopoietic stem cell infusion [200]. Early use of this approached invested on the theory of dose intensity to eradicate disease. [205]. The two most commonly used myeloablative conditioning regimens for allografts for leukemia/lymphoma use a combination of high-dose busulfan combined with cyclophosphamide and cyclophosphamide in combination with TBI. The Cyclophosphamide-TBI regimen uses a cyclophosphamide dose of 120 mg/kg and 10–15 Gy TBI [23] and busulfan-cyclophosphamide uses a busulfan dose of 16 mg/kg orally and Cy 120 mg/kg [206]. From the available data, there are no significant differences in survival with these two regimens. There is also no evidence that intensified conditioning improves survival, as a higher dose of TBI is associated with increased toxicity [205]. Cyclophosphamide or TBI has also been tested in addition to other chemotherapy agents like melphalan, thiotepa, etoposide, and dimethylbusulfan. The problem with myeloablative conditioning is the high TRM that ultimately jeopardizes overall success. The risk of TRM after a myeloablative regimen has decreased over time, attributed to improved HLA-typing and better supportive care [207]. Neither regimen explored in the myeloablative setting is suitable for all the situations and a particular regimen should be selected depending on the clinical situations if myeloablative approaches are still an option nowadays [208] with the introduction of less toxic transplantation approaches.

Several attempts have been made in the past 30 years to limit early transplant toxicity, by reducing the intensity of the conditioning regimen as previously reviewed [200]. Within the past 20 years, the introduction of fludarabine (Flu) [209, 210] and further dose reductions of alkylating agents [211, 212] or TBI has led to minimized toxicity.

http://dx.doi.org/10.5772/53488

These regimens were designed to allow access to HCT for older patients or because of comorbidities that would preclude HCT. Enthusiasm in the transplant community has led to adoption of these reduced toxicity modalities [213]. A workshop convened by the CIBMTR addressed the dose spectrum, which defines a RIC regimen [214]. A total of 56 participants were surveyed, and 67% agreed that a RIC regimen should cause reversible myelosuppression when administered without stem cell support, result in low nonhematologic toxicity, and, after transplantation, result in mixed donor–recipient chimerism at the time of first assessment in most patients. Likewise, the majority (71%) agreed or strongly agreed that regimens including <500 cGy of TBI as a single fraction or 800 cGy in fractionated doses, busulfan dose <9 mg/kg, melphalan dose <140 mg/m^2, and thiotepa dose < 10 mg/kg should be considered RIC regimens. However, only 32% agreed or strongly agreed that the combination of carmustine, etoposide, cytarabine, and melphalan (BEAM) should be considered a RIC regimen. These results demonstrate that, although HCT professionals have not reached a consensus on what constitutes a RIC regimen, most accept currently used criteria and operational definitions [214].

RIC is an intermediate category of regimens that causes pancytopenia and requires stem cell support if prolonged and autologous recovery is possible. An improved rate of toxicity is achieved by reducing the dose of alkylating agents or TBI by at least 30%. Most often, these regimens combine Flu with an alkylating agent, melphalan [215],Bu [211],thiotepa[212] in reduced doses, or Flu with reduced-dose TBI [216]. Decreased TRM has been successfully achieved with this approach [217, 218] Among the published phase II trials, leukemia relapse remained consistently the main cause of treatment failure after RIC or nonmyeloablative conditioning, with 2- to 4-year relapse rates ranging from 30% to 61%. Mohty et al.recently updated results of the first prospective trial directly comparing RIC allogeneic HCT versus consolidation chemotherapy in patients with AML using “genetic allocation.” In an intent-to-treat analysis, leukemia-free survival was superior in the donor group (60% versus 23% at 7 years; P =.003) but with a significant relapse risk [219]. Recent retrospective analysis demonstrated that RIC has similar outcomes to MAC in patients with AML or MDS. [217, 220] Because of prior therapy and older age, as described above in the Lymphoma section RIC allogeneic HCT is appropriate for most those patients. Allogeneic transplantation has evolved significantly in the last 40 plus years of use as stem cell therapy. To further improve its outcomes patients should be selected early and the appropriate regimen should be used to optimize the anti-malignancy effect.

Author details

Hugo F. Fernandez and Lia Perez

Moffitt Cancer Center and Research Institute, Tampa, Florida, USA

References

[1] Howlader N NA, Krapcho M, Neyman N, Aminou R, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). , National Cancer Institute. Bethesda, MD, , . *SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations)*.based on November 2011 SEER data submission, posted to the SEER web site, 2012.

[2] Rai KR, Holland JF, Glidewell OJ, Weinberg V, Brunner K, Obrecht JP, et al. Treatment of acute myelocytic leukemia: a study by cancer and leukemia group B. Blood. 1981 Dec;58(6):1203-12.

[3] A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. AML Collaborative Group. British journal of haematology. 1998 Oct;103(1): 100-9.

[4] Weick JK, Kopecky KJ, Appelbaum FR, Head DR, Kingsbury LL, Balcerzak SP, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. Blood. 1996 Oct 15;88(8):2841-51.

[5] Vogler WR, Velez-Garcia E, Weiner RS, Flaum MA, Bartolucci AA, Omura GA, et al. A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukemia: a Southeastern Cancer Study Group Study. J Clin Oncol. 1992 Jul;10(7):1103-11.

[6] Pautas C, Thomas X, Merabet F, Raffoux E, Bourhis JH, de Botton S, et al. Randomized Comparison of Standard Induction with Daunorubicin (DNR) for 3 Days vs Idarubicin (IDA) for 3 or 4 Days in AML pts Aged 50 to 70 and of Maintenance with Interleukin 2. Final Analysis of the ALFA 9801 Study. ASH Annual Meeting Abstracts. 2007 November 16, 2007;110(11):162-.

[7] Ohtake S, Miyawaki S, Fujita H, Kiyoi H, Shinagawa K, Usui N, et al. Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study. Blood. 2011 Feb 24;117(8):2358-65.

[8] Fernandez HF, Sun Z, Yao X, Litzow MR, Luger SM, Paietta EM, et al. Anthracycline dose intensification in acute myeloid leukemia. The New England journal of medicine. 2009 Sep 24;361(13):1249-59.

[9] Lowenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. The New England journal of medicine. 2009 Sep 24;361(13):1235-48.

[10] Lee JH, Joo YD, Kim H, Bae SH, Kim MK, Zang DY, et al. A randomized trial comparing standard versus high-dose daunorubicin induction in patients with acute myeloid leukemia. Blood. 2011 Oct 6; 118(14):3832-41.

[11] Ganzel C, Rowe JM. Prognostic factors in adult acute leukemia. Hematology/oncology clinics of North America. 2011 Dec;25(6):1163-87.

[12] Schlenk RF, Dohner K, Krauter J, Frohling S, Corbacioglu A, Bullinger L, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. The New England journal of medicine. 2008 May 1;358(18):1909-18.

[13] Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood. 2001 Sep 15;98(6): 1752-9.

[14] Patel JP, Gonen M, Figueroa ME, Fernandez H, Sun Z, Racevskis J, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. The New England journal of medicine. 2012 Mar 22;366(12):1079-89.

[15] Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010 Jan 21;115(3):453-74.

[16] Armand P, Kim HT, Zhang MJ, Perez WS, Dal Cin PS, Klumpp TR, et al. Classifying cytogenetics in patients with acute myelogenous leukemia in complete remission undergoing allogeneic transplantation: a Center for International Blood and Marrow Transplant Research study. Biol Blood Marrow Transplant. 2012 Feb;18(2):280-8.

[17] Byrd JC, Dodge RK, Carroll A, Baer MR, Edwards C, Stamberg J, et al. Patients with t(8;21)(q22;q22) and acute myeloid leukemia have superior failure-free and overall survival when repetitive cycles of high-dose cytarabine are administered. J Clin Oncol. 1999 Dec;17(12):3767-75.

[18] Lugthart S, Groschel S, Beverloo HB, Kayser S, Valk PJ, van Zelderen-Bhola SL, et al. Clinical, Molecular, and Prognostic Significance of WHO Type inv(3)(q21q26.2)/t(3;3) (q21;q26.2) and Various Other 3q Abnormalities in Acute Myeloid Leukemia. J Clin Oncol. 2010 Aug 9.

[19] Schnittger S, Kinkelin U, Schoch C, Heinecke A, Haase D, Haferlach T, et al. Screening for MLL tandem duplication in 387 unselected patients with AML identify a prognostically unfavorable subset of AML. Leukemia. 2000 May;14(5):796-804.

[20] Ley TJ, Ding L, Walter MJ, McLellan MD, Lamprecht T, Larson DE, et al. DNMT3A mutations in acute myeloid leukemia. N Engl J Med. 2010 Dec 16;363(25):2424-33.

[21] Yanada M, Matsuo K, Suzuki T, Kiyoi H, Naoe T. Prognostic significance of FLT3 internal tandem duplication and tyrosine kinase domain mutations for acute myeloid leukemia: a meta-analysis. Leukemia. 2005 Aug;19(8):1345-9.

[22] Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. The New England journal of medicine. 1994 Oct 6;331(14): 896-903.

[23] Thomas ED, Buckner CD, Banaji M, Clift RA, Fefer A, Flournoy N, et al. One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation. Blood. 1977 Apr;49(4):511-33.

[24] Thomas ED, Buckner CD, Clift RA, Fefer A, Johnson FL, Neiman PE, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission. N Engl J Med. 1979 Sep 13;301(11):597-9.

[25] Clift R, Buckner CD, Bianco J, Petersen F, Appelbaum F. Marrow transplantation in patients with acute myeloid leukemia. Leukemia. 1992;6 Suppl 2:104-9.

[26] Clift RA, Buckner CD. Marrow transplantation for acute myeloid leukemia. Cancer Invest. 1998;16(1):53-61.

[27] Clift RA, Buckner CD, Appelbaum FR, Bearman SI, Petersen FB, Fisher LD, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. Blood. 1990 Nov 1;76(9): 1867-71.

[28] Zittoun RA, Mandelli F, Willemze R, de Witte T, Labar B, Resegotti L, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. The New England journal of medicine. 1995 Jan 26;332(4):217-23.

[29] Cassileth PA, Harrington DP, Appelbaum FR, Lazarus HM, Rowe JM, Paietta E, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. The New England journal of medicine. 1998 Dec 3;339(23):1649-56.

[30] 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 Dec 15;96(13):4075-83.

[31] 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: sys-

tematic review and meta-analysis of prospective clinical trials. Jama. 2009 Jun 10;301(22):2349-61.

[32] Cornelissen JJ, van Putten WL, Verdonck LF, Theobald M, Jacky E, Daenen SM, et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? Blood. 2007 May 1;109(9): 3658-66.

[33] Yanada M, Matsuo K, Emi N, Naoe T. Efficacy of allogeneic hematopoietic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission: a metaanalysis. Cancer. 2005 Apr 15;103(8):1652-8.

[34] Kurosawa S, Yamaguchi T, Miyawaki S, Uchida N, Kanamori H, Usuki K, et al. A Markov decision analysis of allogeneic hematopoietic cell transplantation versus chemotherapy in patients with acute myeloid leukemia in first remission. Blood. 2011 Feb 17;117(7):2113-20.

[35] Cornelissen JJ, Breems D, van Putten WL, Gratwohl AA, Passweg JR, Pabst T, et al. Comparative analysis of the value of allogeneic hematopoietic stem-cell transplantation in acute myeloid leukemia with monosomal karyotype versus other cytogenetic risk categories. J Clin Oncol. 2012 Jun 10;30(17):2140-6.

[36] Krauter J, Heil G, Hoelzer D, Ottmann OG, Martin H, Lubbert M, et al. Treatment of Patients up to 60 Years with High Risk AML: Final Results of the AML SHG-Hannover 01/99 Trial. ASH Annual Meeting Abstracts. 2006 November 16, 2006;108(11): 433-.

[37] Ho VT, Kim HT, Aldridge J, Liney D, Kao G, Armand P, et al. Use of matched unrelated donors compared with matched related donors is associated with lower relapse and superior progression-free survival after reduced-intensity conditioning hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2011 Aug;17(8): 1196-204.

[38] Lee SJ, Kang BW, Moon JH, Chae YS, Kim JG, Jung JS, et al. Comparable analysis of outcomes for allogeneic peripheral blood stem cell transplantation from matched related and matched unrelated donors in acute myeloid leukemia. Acta haematologica. 2012;127(2):81-9.

[39] Sierra J, Bjerke J, Hansen J, Martin P, Petersdorf E, Woolfrey A, et al. Marrow transplants from unrelated donors as treatment for acute leukemia. Leukemia & lymphoma. 2000 Nov;39(5-6):495-507.

[40] Horowitz MM. High-resolution typing for unrelated donor transplantation: how far do we go? Best Pract Res Clin Haematol. 2009 Dec;22(4):537-41.

[41] Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. The New England journal of medicine. 2010 Nov 25;363(22):2091-101.

[42] Cutler C, Antin JH. Sirolimus for GVHD prophylaxis in allogeneic stem cell transplantation. Bone marrow transplantation. 2004 Sep;34(6):471-6.

[43] Cutler C, Li S, Ho VT, Koreth J, Alyea E, Soiffer RJ, et al. Extended follow-up of methotrexate-free immunosuppression using sirolimus and tacrolimus in related and unrelated donor peripheral blood stem cell transplantation. Blood. 2007 Apr 1;109(7): 3108-14.

[44] Pidala J, Kim J, Jim H, Kharfan-Dabaja MA, Nishihori T, Fernandez H, et al. A randomized phase II study to evaluate tacrolimus in combination with sirolimus or methotrexate after allogeneic hematopoietic cell transplantation. Haematologica. 2012 Jun 11.

[45] Finke J, Bethge WA, Schmoor C, Ottinger HD, Stelljes M, Zander AR, et al. Standard graft-versus-host disease prophylaxis with or without anti-T-cell globulin in haematopoietic cell transplantation from matched unrelated donors: a randomised, open-label, multicentre phase 3 trial. Lancet Oncol. 2009 Sep;10(9):855-64.

[46] Juliusson G, Antunovic P, Derolf A, Lehmann S, Mollgard L, Stockelberg D, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. Blood. 2009 Apr 30;113(18):4179-87.

[47] Frohling S, Schlenk RF, Kayser S, Morhardt M, Benner A, Dohner K, et al. Cytogenetics and age are major determinants of outcome in intensively treated acute myeloid leukemia patients older than 60 years: results from AMLSG trial AML HD98-B. Blood. 2006 Nov 15;108(10):3280-8.

[48] Herr AL, Labopin M, Blaise D, Milpied N, Potter M, Michallet M, et al. HLA-identical sibling allogeneic peripheral blood stem cell transplantation with reduced intensity conditioning compared to autologous peripheral blood stem cell transplantation for elderly patients with de novo acute myeloid leukemia. Leukemia. 2007 Jan;21(1): 129-35.

[49] Schetelig J, Bornhauser M, Schmid C, Hertenstein B, Schwerdtfeger R, Martin H, et al. Matched unrelated or matched sibling donors result in comparable survival after allogeneic stem-cell transplantation in elderly patients with acute myeloid leukemia: a report from the cooperative German Transplant Study Group. J Clin Oncol. 2008 Nov 10;26(32):5183-91.

[50] Eom KS, Kim HJ, Cho BS, Choi SM, Lee DG, Lee SE, et al. Hematopoietic stem cell transplant following remission induction chemotherapy including gemtuzumab ozogamicin is a feasible and effective treatment option in elderly patients with acute myeloid leukemia. Leukemia & lymphoma. 2011 Dec;52(12):2321-8.

[51] Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. The New England journal of medicine. [Clinical Trial Clinical Trial, Phase I Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2001 Apr 5;344(14):1031-7.

[52] Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. [Practice Guideline Research Support, Non-U.S. Gov't Review]. 2006 Sep 15;108(6):1809-20.

[53] Giralt SA, Arora M, Goldman JM, Lee SJ, Maziarz RT, McCarthy PL, et al. Impact of imatinib therapy on the use of allogeneic haematopoietic progenitor cell transplantation for the treatment of chronic myeloid leukaemia. British journal of haematology. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. 2007 Jun;137(5):461-7.

[54] Hehlmann R, Berger U, Pfirrmann M, Heimpel H, Hochhaus A, Hasford J, et al. Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia. Blood. 2007 Jun 1;109(11):4686-92.

[55] Bittencourt H, Funke V, Fogliatto L, Magalhaes S, Setubal D, Paz A, et al. Imatinib mesylate versus allogeneic BMT for patients with chronic myeloid leukemia in first chronic phase. Bone Marrow Transplant. 2008 Nov;42(9):597-600.

[56] Michor F, Hughes TP, Iwasa Y, Branford S, Shah NP, Sawyers CL, et al. Dynamics of chronic myeloid leukaemia. Nature. 2005 Jun 30;435(7046):1267-70.

[57] Roeder I, Horn M, Glauche I, Hochhaus A, Mueller MC, Loeffler M. Dynamic modeling of imatinib-treated chronic myeloid leukemia: functional insights and clinical implications. Nat Med. 2006 Oct;12(10):1181-4.

[58] Bhatia R, Holtz M, Niu N, Gray R, Snyder DS, Sawyers CL, et al. Persistence of malignant hematopoietic progenitors in chronic myelogenous leukemia patients in complete cytogenetic remission following imatinib mesylate treatment. Blood. 2003 June 15, 2003;101(12):4701-7.

[59] Chu S, McDonald T, Lin A, Chakraborty S, Huang Q, Snyder DS, et al. Persistence of leukemia stem cells in chronic myelogenous leukemia patients in prolonged remission with imatinib treatment. Blood. 2011 Nov 17;118(20):5565-72.

[60] Pavlu J, Szydlo RM, Goldman JM, Apperley JF. Three decades of transplantation for chronic myeloid leukemia: what have we learned? Blood. 2011 Jan 20;117(3):755-63.

[61] Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. Journal of clinical oncology : official journal of the American

Society of Clinical Oncology. [Practice Guideline Review]. 2009 Dec 10;27(35): 6041-51.

[62] Saussele S, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, Schwerdtfeger R, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood. [Clinical Trial, Phase IV Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2010 Mar 11;115(10):1880-5.

[63] Deininger M, Schleuning M, Greinix H, Sayer HG, Fischer T, Martinez J, et al. The effect of prior exposure to imatinib on transplant-related mortality. Haematologica. 2006 Apr;91(4):452-9.

[64] Lee SJ, Kukreja M, Wang T, Giralt SA, Szer J, Arora M, et al. Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. Blood. 2008 Oct 15;112(8):3500-7.

[65] Zaucha JM, Prejzner W, Giebel S, Gooley TA, Szatkowski D, Kalwak K, et al. Imatinib therapy prior to myeloablative allogeneic stem cell transplantation. Bone marrow transplantation. [Clinical Trial Comparative Study]. 2005 Sep;36(5):417-24.

[66] Perz JB, Khorashad JS, Marin D, Apperley JF, Olavarria E. Imatinib preceding allogeneic stem cell transplantation in chronic myeloid leukemia. Haematologica. [Letter]. 2006 Aug;91(8):1145-6.

[67] Oehler VG, Gooley T, Snyder DS, Johnston L, Lin A, Cummings CC, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. Blood. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2007 Feb 15;109(4):1782-9.

[68] Shimoni A, Kroger N, Zander AR, Rowe JM, Hardan I, Avigdor A, et al. Imatinib mesylate (STI571) in preparation for allogeneic hematopoietic stem cell transplantation and donor lymphocyte infusions in patients with Philadelphia-positive acute leukemias. Leukemia. 2003 Feb;17(2):290-7.

[69] Magro L, Mohty M, Catteau B, Coiteux V, Chevallier P, Terriou L, et al. Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease. Blood. [Multicenter Study Research Support, Non-U.S. Gov't]. 2009 Jul 16;114(3): 719-22.

[70] Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, Raimondi R, et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood. [Clinical Trial Research Support, Non-U.S. Gov't]. 2009 Jul 16;114(3):709-18.

[71] Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006 Dec 7;355(23):2408-17.

[72] Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med. 2001 Apr 5;344(14):1038-42.

[73] Kantarjian HM, Cortes J, O'Brien S, Giles FJ, Albitar M, Rios MB, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. Blood. 2002 May 15;99(10):3547-53.

[74] Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med. 2002 Feb 28;346(9):645-52.

[75] Brave M, Goodman V, Kaminskas E, Farrell A, Timmer W, Pope S, et al. Sprycel for chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. Clin Cancer Res. 2008 Jan 15;14(2):352-9.

[76] Hazarika M, Jiang X, Liu Q, Lee SL, Ramchandani R, Garnett C, et al. Tasigna for chronic and accelerated phase Philadelphia chromosome--positive chronic myelogenous leukemia resistant to or intolerant of imatinib. Clin Cancer Res. 2008 Sep 1;14(17):5325-31.

[77] Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010 Jun 17;362(24):2260-70.

[78] Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010 Jun 17;362(24):2251-9.

[79] Velev N, Cortes J, Champlin R, Jones D, Rondon G, Giralt S, et al. Stem cell transplantation for patients with chronic myeloid leukemia resistant to tyrosine kinase inhibitors with BCR-ABL kinase domain mutation T315I. Cancer. 2010 Aug 1;116(15): 3631-7.

[80] Basak G, Torosian T, Snarski E, Niesiobedzka J, Majewski M, Gronkowska A, et al. Hematopoietic stem cell transplantation for T315I-mutated chronic myelogenous leukemia. Ann Transplant. 2010 Apr-Jun;15(2):68-70.

[81] Sanchez-Guijo FM, Lopez-Jimenez J, Gonzalez T, Santamaria C, Gonzalez M, Del Canizo MC. Multitargeted sequential therapy with MK-0457 and dasatinib followed by stem cell transplantation for T315I mutated chronic myeloid leukemia. Leuk Res. 2009 Jun;33(6):e20-2.

[82] Jabbour E, Cortes J, Santos FP, Jones D, O'Brien S, Rondon G, et al. Results of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia pa-

tients who failed tyrosine kinase inhibitors after developing BCR-ABL1 kinase domain mutations. Blood. 2011 Mar 31;117(13):3641-7.

[83] Cortes J, Talpaz M, Bixby D, Deininger M, Shah N, Flinn IW, et al. A Phase 1 Trial of Oral Ponatinib (AP24534) In Patients with Refractory Chronic Myelogenous Leukemia (CML) and Other Hematologic Malignancies: Emerging Safety and Clinical Response Findings. American Society of Haematology Annual meeting. 2010(210).

[84] Palandri F, Castagnetti F, Testoni N, Luatti S, Marzocchi G, Bassi S, et al. Chronic myeloid leukemia in blast crisis treated with imatinib 600 mg: outcome of the patients alive after a 6-year follow-up. Haematologica. 2008 December 1, 2008;93(12): 1792-6.

[85] Palandri F, Castagnetti F, Alimena G, Testoni N, Breccia M, Luatti S, et al. The long-term durability of cytogenetic responses in patients with accelerated phase chronic myeloid leukemia treated with imatinib 600 mg: the GIMEMA CML Working Party experience after a 7-year follow-up. Haematologica. 2009 February 1, 2009;94(2): 205-12.

[86] Silver RT, Cortes J, Waltzman R, Mone M, Kantarjian H. Sustained durability of responses and improved progression-free and overall survival with imatinib treatment for accelerated phase and blast crisis chronic myeloid leukemia: long-term follow-up of the STI571 0102 and 0109 trials. Haematologica. 2009 May 1, 2009;94(5):743-4.

[87] Gratwohl A, Brand R, Apperley J, Crawley C, Ruutu T, Corradini P, et al. Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Haematologica. 2006 2006 Apr;91(4):513-21.

[88] Hehlmann R. How I treat CML blast crisis. Blood. 2012 Jul 26;120(4):737-47.

[89] Bornhauser M, Kiehl M, Siegert W, Schetelig J, Hertenstein B, Martin H, et al. Dose-reduced conditioning for allografting in 44 patients with chronic myeloid leukaemia: a retrospective analysis. British journal of haematology. [Multicenter Study]. 2001 Oct;115(1):119-24.

[90] Or R, Shapira MY, Resnick I, Amar A, Ackerstein A, Samuel S, et al. Nonmyeloablative allogeneic stem cell transplantation for the treatment of chronic myeloid leukemia in first chronic phase. Blood. 2003 January 15, 2003;101(2):441-5.

[91] Baron F, Storb R. Current roles for allogeneic hematopoietic cell transplantation following nonmyeloablative or reduced-intensity conditioning. Clinical advances in hematology & oncology : H&O. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2005 Oct;3(10):799-819.

[92] Warlick E, Ahn KW, Pedersen TL, Artz A, de Lima M, Pulsipher M, et al. Reduced intensity conditioning is superior to nonmyeloablative conditioning for older chronic

myelogenous leukemia patients undergoing hematopoietic cell transplant during the tyrosine kinase inhibitor era. Blood. 2012 Apr 26;119(17):4083-90.

[93] Asnafi V, Rubio MT, Delabesse E, Villar E, Davi F, Damaj G, et al. Prediction of relapse by day 100 BCR-ABL quantification after allogeneic stem cell transplantation for chronic myeloid leukemia. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK. [Clinical Trial Comparative Study Research Support, Non-U.S. Gov't]. 2006 May;20(5):793-9.

[94] Ballestrero A, Cirmena G, Dominietto A, Garuti A, Rocco I, Cea M, et al. Peripheral blood vs. bone marrow for molecular monitoring of BCR-ABL1 levels in chronic myelogenous leukemia, a retrospective analysis in allogeneic bone marrow recipients. International Journal of Laboratory Hematology. 2010;32(4):387-91.

[95] Lange T, Deininger M, Brand R, Hegenbart U, Al-Ali H, Krahl R, et al. BCR-ABL transcripts are early predictors for hematological relapse in chronic myeloid leukemia after hematopoietic cell transplantation with reduced intensity conditioning. Leukemia. 2004 Sep;18(9):1468-75.

[96] Klyuchnikov E, Schafhausen P, Kroger N, Brummendorf TH, Osanmaz O, Asenova S, et al. Second-generation tyrosine kinase inhibitors in the post-transplant period in patients with chronic myeloid leukemia or Philadelphia-positive acute lymphoblastic leukemia. Acta haematologica. 2009;122(1):6-10.

[97] Carpenter PA, Snyder DS, Flowers ME, Sanders JE, Gooley TA, Martin PJ, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. Blood. [Clinical Trial Research Support, N.I.H., Extramural]. 2007 Apr 1;109(7):2791-3.

[98] Olavarria E, Siddique S, Griffiths MJ, Avery S, Byrne JL, Piper KP, et al. Posttransplantation imatinib as a strategy to postpone the requirement for immunotherapy in patients undergoing reduced-intensity allografts for chronic myeloid leukemia. Blood. [Clinical Trial Research Support, Non-U.S. Gov't]. 2007 Dec 15;110(13):4614-7.

[99] DeAngelo DJ, Hochberg EP, Alyea EP, Longtine J, Lee S, Galinsky I, et al. Extended follow-up of patients treated with imatinib mesylate (gleevec) for chronic myelogenous leukemia relapse after allogeneic transplantation: durable cytogenetic remission and conversion to complete donor chimerism without graft-versus-host disease. Clinical cancer research : an official journal of the American Association for Cancer Research. 2004 Aug 1;10(15):5065-71.

[100] Kantarjian HM, O'Brien S, Cortes JE, Giralt SA, Rios MB, Shan J, et al. Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. Blood. [Clinical Trial Research Support, Non-U.S. Gov't]. 2002 Sep 1;100(5):1590-5.

[101] Savani BN, Montero A, Kurlander R, Childs R, Hensel N, Barrett AJ. Imatinib synergizes with donor lymphocyte infusions to achieve rapid molecular remission of CML

relapsing after allogeneic stem cell transplantation. Bone marrow transplantation. 2005 Dec;36(11):1009-15.

[102] Garcia-Manero G. Myelodysplastic syndromes: 2012 update on diagnosis, risk-stratification, and management. American Journal of Hematology. 2012;87(7):692-701.

[103] Platzbecker U, Schetelig J, Finke J, Trenschel R, Scott BL, Kobbe G, et al. Allogeneic Hematopoietic Cell Transplantation in Patients Age 60-70 Years with De Novo High-Risk Myelodysplastic Syndrome or Secondary Acute Myelogenous Leukemia: Comparison with Patients Lacking Donors Who Received Azacitidine. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2012;18(9):1415-21.

[104] Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes. Blood. 1997 March 15, 1997;89(6):2079-88.

[105] Alessandrino EP, Della Porta MG, Bacigalupo A, Van Lint MT, Falda M, Onida F, et al. WHO classification and WPSS predict posttransplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Blood. 2008 August 1, 2008;112(3):895-902.

[106] Malcovati L, Germing U, Kuendgen A, Della Porta MG, Pascutto C, Invernizzi R, et al. Time-Dependent Prognostic Scoring System for Predicting Survival and Leukemic Evolution in Myelodysplastic Syndromes. J Clin Oncol. 2007 August 10, 2007;25(23): 3503-10.

[107] Kantarjian H, O'Brien S, Ravandi F, Cortes J, Shan J, Bennett JM, et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. Cancer. 2008;113(6):1351-61.

[108] Cutler CS, Lee SJ, Greenberg P, Deeg HJ, Pérez WS, Anasetti C, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004 July 15, 2004;104(2):579-85.

[109] Mandelli F, Vignetti M, Suciu S, Stasi R, Petti MC, Meloni G, et al. Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: the EORTC and GIMEMA Groups Study AML-10. J Clin Oncol. 2009 Nov 10;27(32):5397-403.

[110] Oliansky DM, Antin JH, Bennett JM, Deeg HJ, Engelhardt C, Heptinstall KV, et al. The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of Myelodysplastic Syndromes: An Evidence-Based Review. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2009;15(2):137-72.

[111] Appelbaum FR. The role of hematopoietic cell transplantation as therapy for myelodysplasia. Best Practice & Research Clinical Haematology. 2011;24(4):541-7.

[112] Onida F, Brand R, Van Biezen A, Barge R, Verdonck L, Finke J, et al. Impact of cytogenetics on outcome of patients with MDS or secondary AML undergoing allogeneic HSCT from HLA-identical siblings: a retrospective analysis of the EBMT-CLWP. Blood (ASH Annual Meeting Abstracts). 2006;108(11):A750-A.

[113] Chang C, Storer BE, Scott BL, Bryant EM, Shulman HM, Flowers ME, et al. Hematopoietic cell transplantation in patients with myelodysplastic syndrome or acute myeloid leukemia arising from myelodysplastic syndrome: similar outcomes in patients with de novo disease and disease following prior therapy or antecedent hematologic disorders. Blood. 2007 August 15, 2007;110(4):1379-87.

[114] Scott BL, Wells DA, Loken MR, Myerson D, Leisenring WM, Deeg HJ. Validation of a flow cytometric scoring system as a prognostic indicator for posttransplantation outcome in patients with myelodysplastic syndrome. Blood. 2008 October 1, 2008;112(7): 2681-6.

[115] Mills KI, Kohlmann A, Williams PM, Wieczorek L, Liu W-m, Li R, et al. Microarray-based classifiers and prognosis models identify subgroups with distinct clinical outcomes and high risk of AML transformation of myelodysplastic syndrome. Blood. 2009 July 30, 2009;114(5):1063-72.

[116] Newell LF, Gooley T, Hansen JA, Stirewalt DL, Petersdorf EW, Deeg HJ. Tumor Necrosis Factor Polymorphism Affects Transplantation Outcome in Patients with Myelodysplastic Syndrome but Not in Those with Chronic Myelogenous Leukemia, Independent of the Presence of HLA-DR15. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2010;16(12):1700-6.

[117] Bejar R, Stevenson K, Abdel-Wahab O, Galili N, Nilsson B, Garcia-Manero G, et al. Clinical Effect of Point Mutations in Myelodysplastic Syndromes. New England Journal of Medicine. 2011;364(26):2496-506.

[118] Yoshida K, Sanada M, Shiraishi Y, Nowak D, Nagata Y, Yamamoto R, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. Nature. [10.1038/nature10496]. 2011;478(7367):64-9.

[119] Malcovati L, Papaemmanuil E, Bowen DT, Boultwood J, Della Porta MG, Pascutto C, et al. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. Blood. 2011 December 8, 2011;118(24):6239-46.

[120] Bacher U, Haferlach C, Kroger N, Schnittger S, Kern W, Wiedemann B, et al. Diagnostic tools in the indications for allogeneic stem cell transplantation in myelodysplastic syndromes. Biol Blood Marrow Transplant. 2010 Jan;16(1):1-11.

[121] Armand P, Kim HT, Cutler CS, Ho VT, Koreth J, Alyea EP, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. Blood. 2007 15 May 2007;109(10):4586-8.

[122] Pullarkat V, Blanchard S, Tegtmeier B, Dagis A, Patane K, Ito J, et al. Iron overload adversely affects outcome of allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2008;42(12):799-805.

[123] Cutler C. Allogeneic Hematopoietic Stem-Cell Transplantation for Myelodysplastic Syndrome. ASH Education Program Book. 2010 December 4, 2010;2010(1):325-9.

[124] Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005 October 15, 2005;106(8):2912-9.

[125] Sorror ML, Sandmaier BM, Storer BE, Maris MB, Baron F, Maloney DG, et al. Comorbidity and Disease Status–Based Risk Stratification of Outcomes Among Patients With Acute Myeloid Leukemia or Myelodysplasia Receiving Allogeneic Hematopoietic Cell Transplantation. Journal of Clinical Oncology. 2007 September 20, 2007;25(27):4246-54.

[126] Boehm A, Sperr WR, Leitner G, Worel N, Oehler L, Jaeger E, et al. Comorbidity predicts survival in myelodysplastic syndromes or secondary acute myeloid leukaemia after allogeneic stem cell transplantation. European Journal of Clinical Investigation. 2008;38(12):945-52.

[127] Kröger N. Allogeneic stem cell transplantation for elderly patients with myelodysplastic syndrome. Blood. 2012 June 14, 2012;119(24):5632-9.

[128] Lim Z, Brand R, Martino R, van Biezen A, Finke J, Bacigalupo A, et al. Allogeneic Hematopoietic Stem-Cell Transplantation for Patients 50 Years or Older With Myelodysplastic Syndromes or Secondary Acute Myeloid Leukemia. Journal of Clinical Oncology. 2010 January 20, 2010;28(3):405-11.

[129] McClune BL, Weisdorf DJ, Pedersen TL, Tunes da Silva G, Tallman MS, Sierra J, et al. Effect of Age on Outcome of Reduced-Intensity Hematopoietic Cell Transplantation for Older Patients With Acute Myeloid Leukemia in First Complete Remission or With Myelodysplastic Syndrome. Journal of Clinical Oncology. 2010 April 10, 2010;28(11):1878-87.

[130] Rodrigo M, Simona I, Ronald B, Thekla J, Anja van B, Jürgen F, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood. 2006;108(3):836-46.

[131] Scott BL, Sandmaier BM, Storer B, Maris MB, Sorror ML, Maloney DG, et al. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodys-

plastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. Leukemia. 2006;20(1):128-35.

[132] Kojima R, Kami M, Kanda Y, Kusumi E, Kishi Y, Tanaka Y, et al. Comparison between reduced intensity and conventional myeloablative allogeneic stem-cell transplantation in patients with hematologic malignancies aged between 50 and 59 years. Bone Marrow Transplant. 2005;36(8):667-74.

[133] Martino R, Iacobelli S, Brand R, Jansen T, van Biezen A, Finke J, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood. 2006 August 1, 2006;108(3):836-46.

[134] de Lima M, Anagnostopoulos A, Munsell M, Shahjahan M, Ueno N, Ippoliti C, et al. Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation. Blood. 2004 August 1, 2004;104(3):865-72.

[135] Luger SM, Ringden O, Zhang MJ, Perez WS, Bishop MR, Bornhauser M, et al. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. Bone Marrow Transplant. 2012;47(2):203-11.

[136] Shimoni A, Hardan I, Shem-Tov N, Yeshurun M, Yerushalmi R, Avigdor A, et al. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. Leukemia. 2005;20(2):322-8.

[137] Nakamura R, Palmer JM, O'Donnell MR, Stiller T, Thomas SH, Chao J, et al. Reduced intensity allogeneic hematopoietic stem cell transplantation for MDS using tacrolimus/sirolimus-based GVHD prophylaxis. Leukemia Research. 2012;36(9):1152-6.

[138] Nakai K, Kanda Y, Fukuhara S, Sakamaki H, Okamoto S, Kodera Y, et al. Value of chemotherapy before allogeneic hematopoietic stem cell transplantation from an HLA-identical sibling donor for myelodysplastic syndrome. Leukemia. 2005;19(3): 396-401.

[139] Field T, Perkins J, Huang Y, Kharfan-Dabaja MA, Alsina M, Ayala E, et al. 5-Azacitidine for myelodysplasia before allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2009;45(2):255-60.

[140] Buchholz S, Dammann E, Stadler M, Krauter J, Beutel G, Trummer A, et al. Cytoreductive treatment with clofarabine/ara-C combined with reduced-intensity conditioning and allogeneic stem cell transplantation in patients with high-risk, relapsed, or refractory acute myeloid leukemia and advanced myelodysplastic syndrome. European Journal of Haematology. 2012;88(1):52-60.

[141] De Padua Silva L, de Lima M, Kantarjian H, Faderl S, Kebriaei P, Giralt S, et al. Feasibility of allo-SCT after hypomethylating therapy with decitabine for myelodysplastic syndrome. Bone Marrow Transplant. 2009;43(11):839-43.

[142] Gerds AT, Gooley TA, Estey EH, Appelbaum FR, Deeg HJ, Scott BL. Pretransplantation Therapy with Azacitidine vs Induction Chemotherapy and Posttransplantation Outcome in Patients with MDS. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2012;18(8): 1211-8.

[143] de Lima M, Giralt S, Thall PF, de Padua Silva L, Jones RB, Komanduri K, et al. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome. Cancer. 2010;116(23):5420-31.

[144] Jabbour E, Giralt S, Kantarjian H, Garcia-Manero G, Jagasia M, Kebriaei P, et al. Low-dose azacitidine after allogeneic stem cell transplantation for acute leukemia. Cancer. 2009;115(9):1899-905.

[145] Campregher PV, Gooley T, Scott BL, Moravec C, Sandmaier B, Martin PJ, et al. Results of donor lymphocyte infusions for relapsed myelodysplastic syndrome after hematopoietic cell transplantation. Bone Marrow Transplant. 2007;40(10):965-71.

[146] Schroeder T, Czibere AG, Kröger N, Platzbecker U, Bug G, Uharek L, et al. Combining Azacitidine (Vidaza®, Aza) and Donor Lymphocyte Infusions (DLI) as First Salvage Treatment in Patients (PTS) With Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS) Relapsing After Allogeneic Hematopoietic Stem Cell Transplantation (allo-SCT): Interim-Analysis From the Azarela-Trial (NCT-00795548). Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2011;17(2):S159.

[147] Jamieson CHM, Amylon MD, Wong RM, Blume KG. Allogeneic hematopoietic cell transplantation for patients with high-risk acute lymphoblastic leukemia in first or second complete remission using fractionated total-body irradiation and high-dose etoposide: A 15-year experience. Experimental Hematology. 2003;31(10):981-6.

[148] Thomas X, Boiron JM, Huguet F, Dombret H, Bradstock K, Vey N, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol. 2004 Oct 15;22(20):4075-86.

[149] Bruggemann M, Raff T, Flohr T, Gokbuget N, Nakao M, Droese J, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. Blood. 2006 Feb 1;107(3):1116-23.

[150] Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolida-

tion/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008 February 15, 2008;111(4):1827-33.

[151] Yanada M, Matsuo K, Suzuki T, Naoe T. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a metaanalysis. Cancer. 2006 Jun 15;106(12): 2657-63.

[152] Ram R, Gafter-Gvili A, Vidal L, Paul M, Ben-Bassat I, Shpilberg O, et al. Management of adult patients with acute lymphoblastic leukemia in first complete remission: systematic review and meta-analysis. Cancer. 2010 Jul 15;116(14):3447-57.

[153] Rowe JM. Interpreting Data on Transplant Selection and Outcome in Adult Acute Lymphoblastic Leukemia (ALL). Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2011;17(1):S76-S83.

[154] Fielding AK. Philadelphia-Positive Acute Lymphoblastic Leukemia—Is Bone Marrow Transplant Still Necessary? Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2011;17(1):S84-S8.

[155] Thomas DA, Faderl S, Cortes J, O'Brien S, Giles FJ, Kornblau SM, et al. Treatment of Philadelphia chromosome–positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. Blood. 2004 June 15, 2004;103(12):4396-407.

[156] Wassmann B, Pfeifer H, Goekbuget N, Beelen DW, Beck J, Stelljes M, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ALL). Blood. 2006 September 1, 2006;108(5):1469-77.

[157] de Labarthe A, Rousselot P, Huguet-Rigal F, Delabesse E, Witz F, Maury S, et al. Imatinib combined with induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome–positive acute lymphoblastic leukemia: results of the GRAAPH-2003 study. Blood. 2007 February 15, 2007;109(4):1408-13.

[158] Yanada M, Sugiura I, Takeuchi J, Akiyama H, Maruta A, Ueda Y, et al. Prospective monitoring of BCR-ABL1 transcript levels in patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia undergoing imatinib-combined chemotherapy. Br J Haematol. 2008 Nov;143(4):503-10.

[159] Lee S, Kim YJ, Min CK, Kim HJ, Eom KS, Kim DW, et al. The effect of first-line imatinib interim therapy on the outcome of allogeneic stem cell transplantation in adults with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2005 May 1;105(9):3449-57.

[160] Abou Mourad YR, Fernandez HF, Kharfan-Dabaja MA. Allogeneic hematopoietic cell transplantation for adult Philadelphia-positive acute lymphoblastic leukemia in

the era of tyrosine kinase inhibitors. Biol Blood Marrow Transplant. 2008 Sep;14(9): 949-58.

[161] Ottmann O, Dombret H, Martinelli G, Simonsson B, Guilhot F, Larson RA, et al. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome–positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. Blood. 2007 October 1, 2007;110(7):2309-15.

[162] Ravandi F, O'Brien S, Thomas D, Faderl S, Jones D, Garris R, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia. Blood. 2010 September 23, 2010;116(12):2070-7.

[163] Ottmann OG, Larson RA, Kantarjian HM, le Coutre P, Baccarani M, Haque A, et al. Nilotinib in Patients (pts) with Relapsed/Refractory Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) Who Are Resistant or Intolerant to Imatinib. ASH Annual Meeting Abstracts. 2007 November 16, 2007;110(11):2815-.

[164] Mohty M, Labopin M, Volin L, Gratwohl A, Socie G, Esteve J, et al. Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. Blood. 2010 Nov 25;116(22): 4439-43.

[165] Bachanova V, Verneris MR, DeFor T, Brunstein CG, Weisdorf DJ. Prolonged survival in adults with acute lymphoblastic leukemia after reduced-intensity conditioning with cord blood or sibling donor transplantation. Blood. 2009 March 26, 2009;113(13): 2902-5.

[166] Santarone S, Pidala J, Di Nicola M, Field T, Alsina M, Ayala E, et al. Fludarabine and Pharmacokinetic-Targeted Busulfan before Allografting for Adults with Acute Lymphoid Leukemia. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2011;17(10):1505-11.

[167] Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995 Dec 7;333(23):1540-5.

[168] Lazarus HM, Zhang MJ, Carreras J, Hayes-Lattin BM, Ataergin AS, Bitran JD, et al. A comparison of HLA-identical sibling allogeneic versus autologous transplantation for diffuse large B cell lymphoma: a report from the CIBMTR. Biol Blood Marrow Transplant. 2010 Jan;16(1):35-45.

[169] van Kampen RJ, Canals C, Schouten HC, Nagler A, Thomson KJ, Vernant JP, et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell trans-

plantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. J Clin Oncol. 2011 Apr 1;29(10):1342-8.

[170] Gyan E, Foussard C, Bertrand P, Michenet P, Le Gouill S, Berthou C, et al. High-dose therapy followed by autologous purged stem cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by the GOELAMS with final results after a median follow-up of 9 years. Blood. 2009 Jan 29;113(5):995-1001.

[171] Lenz G, Dreyling M, Schiegnitz E, Forstpointner R, Wandt H, Freund M, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. Blood. 2004 Nov 1;104(9):2667-74.

[172] Sebban C, Mounier N, Brousse N, Belanger C, Brice P, Haioun C, et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). Blood. 2006 Oct 15;108(8):2540-4.

[173] Ladetto M, De Marco F, Benedetti F, Vitolo U, Patti C, Rambaldi A, et al. Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. Blood. 2008 Apr 15;111(8):4004-13.

[174] van Besien K, Loberiza FR, Jr., Bajorunaite R, Armitage JO, Bashey A, Burns LJ, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood. 2003 November 15, 2003;102(10):3521-9.

[175] Hosing C, Saliba RM, McLaughlin P, Andersson B, Rodriguez MA, Fayad L, et al. Long-term results favor allogeneic over autologous hematopoietic stem cell transplantation in patients with refractory or recurrent indolent non-Hodgkin's lymphoma. Ann Oncol. 2003 May 1, 2003;14(5):737-44.

[176] Khouri IF, McLaughlin P, Saliba RM, Hosing C, Korbling M, Lee MS, et al. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. Blood. 2008 Jun 15;111(12):5530-6.

[177] Romaguera JE, Fayad LE, Feng L, Hartig K, Weaver P, Rodriguez MA, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol. 2010 Jul;150(2):200-8.

[178] Vandenberghe E, Ruiz de Elvira C, Loberiza FR, Conde E, Lopez-Guillermo A, Gisselbrecht C, et al. Outcome of autologous transplantation for mantle cell lymphoma:

a study by the European Blood and Bone Marrow Transplant and Autologous Blood and Marrow Transplant Registries. Br J Haematol. 2003 Mar;120(5):793-800.

[179] Geisler CH, Kolstad A, Laurell A, Andersen NS, Pedersen LB, Jerkeman M, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood. 2008 Oct 1;112(7): 2687-93.

[180] Geisler CH, Kolstad A, Laurell A, Raty R, Jerkeman M, Eriksson M, et al. The Mantle Cell Lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first-line immunochemotherapy and autologous stem cell transplantation (ASCT). Blood. 2010 Feb 25;115(8):1530-3.

[181] Maris MB, Sandmaier BM, Storer BE, Chauncey T, Stuart MJ, Maziarz RT, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood. 2004 Dec 1;104(12): 3535-42.

[182] Tam CS, Bassett R, Ledesma C, Korbling M, Alousi A, Hosing C, et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood. 2009 Apr 30;113(18):4144-52.

[183] Cook G, Smith GM, Kirkland K, Lee J, Pearce R, Thomson K, et al. Outcome following Reduced-Intensity Allogeneic Stem Cell Transplantation (RIC AlloSCT) for relapsed and refractory mantle cell lymphoma (MCL): a study of the British Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2010 Oct;16(10): 1419-27.

[184] Blystad AK, Enblad G, Kvaloy S, Berglund A, Delabie J, Holte H, et al. High-dose therapy with autologous stem cell transplantation in patients with peripheral T cell lymphomas. Bone marrow transplantation. 2001 Apr;27(7):711-6.

[185] Rodriguez J, Caballero MD, Gutierrez A, Gandarillas M, Sierra J, Lopez-Guillermo A, et al. High dose chemotherapy and autologous stem cell transplantation in patients with peripheral T-cell lymphoma not achieving complete response after induction chemotherapy.The GEL-TAMO experience. Haematologica. 2003 Dec;88(12):1372-7.

[186] Rodriguez J, Caballero MD, Gutierrez A, Marin J, Lahuerta JJ, Sureda A, et al. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. Ann Oncol. 2003 December 1, 2003;14(12): 1768-75.

[187] Corradini P, Tarella C, Zallio F, Dodero A, Zanni M, Valagussa P, et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia. 2006 Sep;20(9):1533-8.

[188] Mercadal S, Briones J, Xicoy B, Pedro C, Escoda L, Estany C, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol. 2008 May;19(5):958-63.

[189] Reimer P, Rudiger T, Geissinger E, Weissinger F, Nerl C, Schmitz N, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol. 2009 Jan 1;27(1):106-13.

[190] Le Gouill S, Milpied N, Buzyn A, De Latour RP, Vernant JP, Mohty M, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol. 2008 May 10;26(14):2264-71.

[191] Corradini P, Dodero A, Zallio F, Caracciolo D, Casini M, Bregni M, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol. 2004 Jun 1;22(11):2172-6.

[192] Advani R. Optimal therapy of advanced Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program. 2011;2011:310-6.

[193] Bierman PJ, Anderson JR, Freeman MB, Vose JM, Kessinger A, Bishop MR, et al. High-dose chemotherapy followed by autologous hematopoietic rescue for Hodgkin's disease patients following first relapse after chemotherapy. Ann Oncol. 1996 Feb;7(2):151-6.

[194] Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012 Jun 20;30(18):2183-9.

[195] Sarina B, Castagna L, Farina L, Patriarca F, Benedetti F, Carella AM, et al. Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability. Blood. 2010 May 6;115(18):3671-7.

[196] Robinson SP, Sureda A, Canals C, Russell N, Caballero D, Bacigalupo A, et al. Reduced intensity conditioning allogeneic stem cell transplantation for Hodgkin's lymphoma: identification of prognostic factors predicting outcome. Haematologica. 2009 Feb;94(2):230-8.

[197] Thomson KJ, Peggs KS, Smith P, Cavet J, Hunter A, Parker A, et al. Superiority of reduced-intensity allogeneic transplantation over conventional treatment for relapse of Hodgkin's lymphoma following autologous stem cell transplantation. Bone marrow transplantation. 2008 May;41(9):765-70.

[198] Devetten MP, Hari PN, Carreras J, Logan BR, van Besien K, Bredeson CN, et al. Unrelated donor reduced-intensity allogeneic hematopoietic stem cell transplantation

for relapsed and refractory Hodgkin lymphoma. Biol Blood Marrow Transplant. 2009 Jan;15(1):109-17.

[199] Sureda A, Canals C, Arranz R, Caballero D, Ribera JM, Brune M, et al. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study - a prospective clinical trial by the Grupo Espanol de Linfomas/Trasplante de Medula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Haematologica. 2012 Feb;97(2):310-7.

[200] Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the Intensity of Conditioning Regimens: Working Definitions. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2009;15(12):1628-33.

[201] Weissinger F, Sandmaier BM, Maloney DG, Bensinger WI, Gooley T, Storb R. Decreased transfusion requirements for patients receiving nonmyeloablative compared with conventional peripheral blood stem cell transplants from HLA-identical siblings. Blood. 2001 December 15, 2001;98(13):3584-8.

[202] Fukuda T, Hackman RC, Guthrie KA, Sandmaier BM, Boeckh M, Maris MB, et al. Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. Blood. 2003 October 15, 2003;102(8):2777-85.

[203] Hogan WJ, Maris M, Storer B, Sandmaier BM, Maloney DG, Schoch HG, et al. Hepatic injury after nonmyeloablative conditioning followed by allogeneic hematopoietic cell transplantation: a study of 193 patients. Blood. 2004 January 1, 2004;103(1):78-84.

[204] Junghanss C, Marr KA, Carter RA, Sandmaier BM, Maris MB, Maloney DG, et al. Incidence and outcome of bacterial and fungal infections following nonmyeloablative compared with myeloablative allogeneic hematopoietic stem cell transplantation: A matched control study. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2002;8(9):512-20.

[205] Clift RA, Buckner CD, Appelbaum FR, Sullivan KM, Storb R, Thomas ED. Long-term follow-Up of a randomized trial of two irradiation regimens for patients receiving allogeneic marrow transplants during first remission of acute myeloid leukemia. Blood. 1998;92(4):1455-6.

[206] Santos GW, Tutschka PJ, Brookmeyer R, Saral R, Beschorner WE, Bias WB, et al. Marrow transplantation for acute nonlymphocytic leukemia after treatment with busulfan and cyclophosphamide. N Engl J Med. 1983;309(22):1347-53.

[207] Bacigalupo A, Sormani M, Lamparelli T, Gualandi F, Occhini D, Bregante S, et al. Reducing transplant-related mortality after allogeneic hematopoietic stem cell transplantation. Haematologica. 2004 2004 Oct;89(10):1238-47.

[208] Gupta V, Lazarus HM, Keating A. Myeloablative conditioning regimens for AML allografts: 30 years later. Bone Marrow Transplant. 0000;32(10):969-78.

[209] Giralt S, Estey E, Albitar M, Besien Kv, Rondón G, Anderlini P, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood. 1997;89(12):4531-6.

[210] Giralt S, Thall PF, Khouri I, Wang X, Braunschweig I, Ippolitti C, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. Blood. 2001;97(3):631-7.

[211] Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalli G, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood. 1998;91(3):756-63.

[212] Corradini P, Zallio F, Mariotti J, Farina L, Bregni M, Valagussa P, et al. Effect of age and previous autologous transplantation on nonrelapse mortality and survival in patients treated with reduced-intensity conditioning and allografting for advanced hematologic malignancies. J Clin Oncol. 2005;23(27):6690-8.

[213] Bacigalupo A. Third EBMT/AMGEN Workshop on reduced-intensity conditioning allogeneic haemopoietic stem cell transplants (RIC-HSCT), and panel consensus. Bone Marrow Transplant. 2004;33(7):691-6.

[214] Giralt S, Ballen K, Rizzo D, Bacigalupo A, Horowitz M, Pasquini M, et al. Reduced-Intensity Conditioning Regimen Workshop: Defining the Dose Spectrum. Report of a Workshop Convened by the Center for International Blood and Marrow Transplant Research. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2009;15(3):367-9.

[215] Sudhir T, Charles C, Karl P, Gulnaz B, Premini M, Gordon C, et al. Allogeneic stem-cell transplantation using a reduced-intensity conditioning regimen has the capacity to produce durable remissions and long-term disease-free survival in patients with high-risk acute myeloid leukemia and myelodysplasia. J Clin Oncol. 2005;23(36): 9387-93.

[216] Christoph S, Michael S, Rainer S, Bernd H, Eva M-W, Donald B, et al. Long-term survival in refractory acute myeloid leukemia after sequential treatment with chemotherapy and reduced-intensity conditioning for allogeneic stem cell transplantation. Blood. 2006;108(3):1092-9.

[217] Aoudjhane M, Labopin M, Gorin NC, Shimoni A, Ruutu T, Kolb HJ, et al. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey

from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). Leukemia. 2005;19(12):2304-12.

[218] Charles C, Richard S, Marc L, Andrea B, Andrzej L, Mats B, et al. Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. Blood. 2005;106(9):2969-76.

[219] Mohty M, de Lavallade H, El-Cheikh J, Ladaique P, Faucher C, Furst S, et al. Reduced intensity conditioning allogeneic stem cell transplantation for patients with acute myeloid leukemia: long term results of a /`donor/' versus /`no donor/' comparison. Leukemia. 2008;23(1):194-6.

[220] Luger SM, Ringden O, Zhang MJ, Perez WS, Bishop MR, Bornhauser M, et al. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. Bone marrow transplantation. 2012 Feb;47(2):203-11.