Published in final edited form as:

Expert Rev Hematol. 2010 February 1; 3(1): 23–33. doi:10.1586/ehm.09.73.

Optimizing reduced-intensity conditioning regimens for myeloproliferative neoplasms

Aravind Ramakrishnan, MD and

Associate in Clinical Research, Fred Hutchinson Cancer Research Center, Acting Instructor, University of Washington School of Medicine, 1100 Fairview Avenue N, D1-100, PO Box 19024, Seattle, WA 98109-1024, USA, Tel.: +1 206 667 2908, Fax: +1 206 667 6124, aramakri@fhcrc.org

Brenda M Sandmaier, MD[†]

Member, Clinical Research Division, Fred Hutchinson Cancer Research Center, Professor, University of Washington School of Medicine, 1100 Fairview Avenue N, D1-100, PO Box 19024, Seattle, WA 98109-1024, USA, Tel.: +1 206 667 4961, Fax: +1 206 667 6124 bsandmai@fhcrc.org

Abstract

The myeloproliferative neoplasms (MPNs) are a group of clonal disorders that arise from a pluripotent hematopoietic stem cell and are characterized by excess cellular proliferation. These disorders tend to be chronic in nature and can terminate over time into a bone marrow failure syndrome characterized by marrow fibrosis or transform into a leukemic phase. MPNs are predominantly diseases of the elderly and this is one reason why until very recently the standard treatment was supportive care. The only curative modality for these disorders is allogeneic hematopoietic cell transplantation. The introduction of reduced-intensity conditioning regimens now allows this life-saving therapy to be offered to elderly patients who were previously considered ineligible for high-dose conditioning owing to age or comorbidity. In this review, we will summarize the current strategies and future directions regarding the use of reduced-intensity conditioning regimens in the treatment of MPNs.

Keywords

bcr-abl; graft-versus-leukemia; JAK-2; myeloproliferative neoplasm; reduced-intensity conditioning; stem cell transplant

The myeloproliferative neoplasms (MPNs) consist of a group of clonal disorders that are thought to arise from a malignant hematopoietic stem cell. These disorders are rare, with an annual incidence of six to ten out of 100,000 people, and generally affect the elderly with a peak incidence in the fifth to seventh decade of life [1]. In the initial stages of the disease, there is abnormal proliferation of the myeloid compartment, and bone marrow examination reveals hypercellularity. In general, these disorders are considered to be chronic in nature, as patients

© 2010 Expert Reviews Ltd

[†]Author for correspondence, Clinical Research Division, Fred Hutchinson Cancer Research, Center, University of Washington School of Medicine, 1100 Fairview Avenue N, D1-100, PO Box 19024, Seattle, WA 98109-1024, USA, Tel.: +1 206 667 4961, Fax: +1 206 667 6124, bsandmai@fhcrc.org.

Financial & competing interests disclosure

This work was supported in part by PHS grants DK082783, HL36444, and CA18029 from the NIH. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

can live with these neoplasms for years to decades. However, they all have the common ability to terminate in a marrow failure syndrome characterized by marrow fibrosis, or transform into acute leukemia [2].

The most recent WHO classification of MPN is shown in Table 1 [3]. The four classic and most commonly diagnosed MPNs are chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF), and they will be discussed later in this article. In addition, very rare disorders, such as chronic eosinophilic leukemia, chronic neutrophilic leukemia and mastocytosis are also MPNs. There are very few data regarding the role of transplantation in these rarer MPNs, and they will not be considered in this review.

The majority of the MPNs have mutations/rearrangements involving receptor or cytoplasmic tyrosine kinases that are involved in the pathogenesis of the neoplasm (Table 1) [3]. There has been great interest in targeting these abnormalities in the hope of curing the disease. The best example of this is CML. Prior to the last decade, the standard of care for patients with CML who had HLA-matched donors was to proceed to hematopoietic stem cell transplantation (HCT) as soon as possible, as this was the only known long-term curative therapy [4]. With the introduction of effective tyrosine kinase inhibitors, such as imatinib, dasatinib and nilotinib, in the last decade, the majority of CML patients do not proceed to HCT early after diagnosis. However, tyrosine kinase inhibitors are not curative, and HCT still plays an important role in the treatment of this disease, as will be discussed below [5].

Polycythemia vera, ET and PMF are related disorders that often have considerable clinical overlap [6]. In 2005, four groups simultaneously and independently identified an activating mutation (V617F) in the JAK-2 kinase in the majority of patients with PV, as well as in a significant percentage of patients with ET and PMF [7–10]. Although the JAK-2 mutation is important in the pathogenesis of these disorders, other factors also contribute to the varying clinical spectrum of MPN [11]. Although patients can be managed conservatively for many years, the majority of patients will develop marrow failure or leukemia [12]. Although JAK-2 inhibitors have shown activity *in vitro* [13] and current clinical trials show some promise [14–20], HCT remains the only curative therapy [12].

Reduced-intensity regimens

Unfortunately, the majority of patients with MPN are elderly and cannot withstand the toxicities associated with conventional high-dose conditioning regimens. In the last decade, reduced-intensity conditioning (RIC) regimens have been developed in an effort to extend this curative therapy to the elderly [21]. Readers are also referred to a number of excellent reviews that have been published recently on this topic [22–29]. Observations in the late 1970s to early 1980s led to the rationale for the development of RIC regimens [30]. Initially, it was thought that high-dose chemotherapy or radiation was an essential component of eradicating the underlying disease. However, it was later noted that the development of graft-versus-host disease (GVHD) after HCT was strongly associated with the lowest relapse rates [31–33]. The observation that recipients of T-cell-depleted grafts had a higher risk of relapse, and studies in which patients who relapsed post-HCT and achieved remission after donor lymphocyte infusion (DLI), both confirmed that donor T cells play an important role in the graft-versus-tumor (GVT) effect [34–37]. Furthermore, studies in which conditioning regimens were intensified in the hope of decreasing relapse only yielded more toxicity and did not impact survival [38,39]. These findings have led to a major paradigm shift in the field of HCT towards RIC regimens, which rely heavily on maximizing GVT to eradicate disease while minimizing toxicity [40].

Although the omission of high-dose myeloablative therapy is associated with significantly decreased nonrelapse mortality (NRM), in some cases this comes at the cost of higher relapse

rates. This is especially true when the tumor is associated with rapid proliferation or the burden of disease is very high at the time of HCT [41]. Therefore, in an effort aimed at minimizing NRM as much as possible without increasing relapse rates, a spectrum of RIC regimens have been introduced, with varying intensities ranging from very low, to moderate, to very high.

There is broad agreement that RIC regimens are characterized by a few general principles: these regimens cause reversible myelosuppression when given without stem cell support, they have limited nonhematopoietic organ toxicity, and they will result in a state of mixed chimerism at the time of the first evaluation post-transplant [42]. Based on results in a preclinical canine model, investigators at our center have further decreased conditioning intensity and developed a non-myeloablative conditioning regimen that consists of fludarabine, 2-Gy total-body irradiation (TBI) and post-grafting cyclosporine, and mycophenolate mofetil (MMF) [43,44]. In contrast to conventional RIC regimens that include some amount of debulking chemotherapy, the aim of non-myeloablative conditioning is to provide profound immunosuppression to prevent graft rejection, and this type of transplant relies entirely on GVT to eradicate the underlying malignancy [25].

The Center for International Blood and Marrow Transplantation (CIBMTR) definition for retrospective analysis defines a RIC as any regimen that includes the following: a TBI dose of 5 Gy or less if given as a single fraction or 8 Gy if given in a fractionated manner, a busulfan dose of 9 mg/kg or less, a melphalan dose 140 mg/m² or less, a thiotepa dose no greater than 10 mg/kg, and the BEAM regimen (carmustine, etoposide, cytarabine and melphalan) [45]. A recent survey of transplant professionals indicated that the majority of respondents agreed with the general principles and most of the CIBMTR definitions; however, only 32% considered the BEAM regimen to be a RIC regimen. The conclusion of this study was that a consensus needs to be achieved on what constitutes a myeloablative regimen so that RIC regimens could be better defined. Current efforts are underway by the CIBMTR and European Bone Marrow Transplant Registry (EBMT) to address these issues [42].

Specific results in CML

As discussed earlier, in the pre-tyrosine kinase era, it was recommended that CML patients proceed to HCT as soon as possible [4]. However, the introduction of effective tyrosine kinase inhibitors has led to a dramatic reduction in the number of transplants performed for CML. Thus, currently, patients with CML only proceed to transplant if they have failed or are intolerant of these drugs [5]. However, tyrosine kinase therapy needs to be taken for the patients entire life, is very expensive and is not curative. Furthermore, patients who present in accelerated phase or blast crisis very rarely achieve a complete cytogenetic response with imatinib [46]. Treatment with second-generation tyrosine kinase inhibitors, such as dasatinib, can increase the rate of complete cytogenetic response to 20–30%, but the median duration of this response is very short, usually a few months [46,47]. Thus, HCT still plays a large role in the treatment of CML in these patients, especially in advanced disease [46,48].

In comparison with acute leukemia, there are only a few studies of RIC regimens in CML, but this disease is quite sensitive to the GVT effect, as demonstrated by the success of DLI [36]; therefore, RIC might be particularly effective in this disease. Results of currently published RIC studies are summarized in Table 2 [49–54]. It should be noted that the majority of these studies were performed in the pre-tyrosine kinase inhibitor era.

These studies all suggest that RIC regimens are effective in the treatment of early-stage CML with low NRM. However, results of RIC in advanced CML are not as encouraging. This is particularly highlighted by a study from the MD Anderson Cancer Center (MDACC; TX, USA), which reported long-term results of patients with CML treated with a variety of fludarabine/melphalan-based RIC regimens [54]. The majority of patients had advanced

disease: chronic phase (CP)1 (20%), CP2 (26%), accelerated phase (AP; 45%) and blast crisis (BC; 8%). Early toxicity was seen with NRM of 33, 39 and 48% at 100 days, 2 and 5 years, respectively. The 5-year overall survival (OS) and relapse-free survival (RFS) were 33 and 20%. Data from the EBMT and the Seattle Consortium are also similar in that patients with advanced disease have poor outcomes. These results highlight the need to optimize RIC with addition of novel agents for more advanced disease.

It is also well known that minimal residual disease post-conventional HCT using quantitative PCR for *bcr-abl* transcript level can accurately predict relapse. In the myeloablative setting, detection of *bcr-abl* transcripts 6–12 months post-HCT is an independent predictor of relapse and would warrant further intervention, such as DLI or tyrosine kinase therapy. Although molecular remission can be achieved within 1 month using even non-myeloablative conditioning, in general, it is delayed with reduced-intensity approaches [55,56]. This is usually because of the fact that many patients develop mixed chimerism after RIC. In the majority of cases, conversion to full donor T-cell chimerism is associated with clearance of minimal residual disease [49,51,56]. The kinetics of this conversion to a full donor chimera is slower when using RIC versus conventional myeloablative conditioning and usually depends on the intensity of conditioning. Thus, patients may have detectable *bcr-abl* transcripts up to 1 year post-transplant but eventually achieve a complete molecular remission [29,51]. As discussed earlier, the stage of disease at transplant also affects the outcomes post-RIC, as patients with advanced disease often have early detection of minimal residual and rapid relapse after transplant. Therefore, molecular remission can be induced using RIC and non-myeloablative approaches, and is useful in predicting relapse. However, the kinetics are likely to depend on the stage of disease prior to transplant and the intensity of the conditioning regimen.

Specific results in myelofibrosis

The majority of patients with PV and ET can be managed conservatively for many years and are not routinely recommended to proceed to transplant until they develop myelofibrosis or leukemia. Patients with myelofibrosis can also have a chronic course and the timing of recommending a transplant can be a difficult decision. A variety of scoring systems have been developed to help determine prognosis in patients with myelofibrosis, including the Dupriez (Lille), Mayo, and International Working Group (IWG) scoring systems for myelofibrosis (Table 3–Table 5) [57–59]. Patients with intermediate- or high-risk disease are generally considered to have poor long-term prognosis and should be considered for HCT [12]. The majority of conventional high-dose transplant series for myelofibrosis report a high rate of NRM up to 40%, which increases in older patients especially. Specifically, there have been increased rates of veno-occlusive disease of the liver owing to pre-existing hepatosplenomegaly [60]. A study from our center reported results on 104 patients transplanted for a diagnosis of primary or secondary myelofibrosis [61]. Although the majority of patients received myeloablative regimens, most commonly BuCY, nine patients received non-myeloablative conditioning with fludarabine and 2-Gy TBI. This cohort comprised of elderly patients up to the age of 70 years who had other comorbid conditions. The overall survival in this group was 56%, which did not differ statistically from patients who received a conventional transplant. These results were encouraging and suggested that a GVT effect does exist in MPN.

Thus, there has been considerable interest in RIC in this disease. The Myeloproliferative Disease Consortium is currently conducting a prospective Phase II trial evaluating RIC in myelofibrosis, and the results of this study should add to our understanding.

Results of currently published RIC studies are summarized in Table 6 [62–67]. These studies suggest that RIC is effective in the treatment of myelofibrosis with low NRM. There have been concerns regarding engraftment using RIC given that most patients have considerable marrow

fibrosis; however, published data suggest that engraftment is not a problem with RIC or even non-myeloablative conditioning [60]. Similar to conventional HCT, rapid regression of marrow fibrosis is also seen after RIC [68]. There has also been some concern that splenomegaly, especially when it is profound, can increase the risk of graft failure or can lead to delayed engraftment [69,70]. However, recent studies suggest that even with profound splenomegaly, engraftment was not a problem and that spleen size decreased over time and paralleled the reduction in marrow fibrosis [71]. Although these results are encouraging, they still highlight the need for improvement in patients with advanced disease.

Expert commentary

Although results of RIC regimens are promising in MPN, results in advanced disease are still poor, similar to high-dose regimens. A number of issues are currently being studied to optimize RIC for better results. These are reviewed below.

Incorporation of new methods of delivery, novel agents & targeted therapies into conditioning regimens

It has long been known that the use of oral busulfan leads to varying levels of plasma concentrations owing to differences in bioavailability and pharmacokinetics. Patients who have low concentrations have a higher risk for relapse/graft rejection and those with higher levels have more toxicity. A study from our center identified that targeting of oral busulfan to a level of 900 ng/ml resulted in better results [72]. Similarly, the use of intravenous busulfan has been reported to reduce hepatotoxicity [73]. In addition, alternative agents with better toxicity profiles are being incorporated into conditioning regimens. The alkylating drug treosulfan has significant cytotoxicity against malignant myeloid cells while having limited non-ematologic toxicities. Treosulfan is also more advantageous compared with oral busulfan as it has a more predictable pharmacologic profile [74,75]. Current studies are underway in the use of this drug in conditioning regimens in a variety of malignancies [76,77]. Cyclophosphamide is also being eliminated in more RIC regimens as it has been demonstrated that metabolites of this drug may increase morbidity and mortality [78]. Fludarabine, a potent immunosuppressive agent that has a favorable toxicity profile, is being incorporated into the majority of RIC regimens as it favors engraftment of donor T cells [79–81].

Targeted therapies are also being added to conditioning in the hope that these agents will decrease relapse rates without increasing NRM. Investigators at the FHCRC recently reported results with a RIC regimen of 2-Gy TBI, fludarabine and I¹³¹ radiolabeled anti-CD45 antibody in elderly patients with high-risk leukemia or myelodysplasia [82]. The use of this radiolabeled antibody allows for delivery of very high-intensity therapy to the target organ, while sparing toxicity in nonhematopoietic tissues. This regimen was used to transplant 58 patients (median age: 63 years) with advanced MDS and AML from HLA-matched related (n = 22) and unrelated (n = 36) donors. A total of 20 patients (35%) had refractory disease that either was primary refractory (n = 8) or was in relapse after prior remission (n = 12) at the time of transplant. According to Southwest Oncology Group criteria, 55% of the patients had high-risk cytogenetic abnormalities. The maximum tolerated dose of the antibody was estimated to be 24 Gy delivered to the liver, which allowed us to deliver an average of 36 Gy to the marrow space and 102 Gy to the spleen. After a median follow-up of 2.6 years, the 1-year probabilities of OS, RFS and NRM were 41, 40 and 22% in this very high-risk population of elderly patients which is very encouraging. Similarly, investigators at MDACC have incorporated gemtuzumab ozogamicin, a monoclonal antibody against the CD33 antigen conjugated to calicheamicin, into a RIC regimen of fludarabine and melphalan, and early results show some promise [83]. Further preclinical studies are also being conducted to identify the optimal radioisotope/toxins to use in conjugation with antibodies [84–87]. More studies will be needed to determine if these therapies will be effective in MPN.

Finally, the addition of tyrosine kinase inhibitor therapy prior to and after transplant is also being studied to determine if relapse rates can be reduced. In CML, the use of tyrosine kinase inhibitors is clearly effective in controlling disease in patients who have relapsed following allogeneic transplant [88–90]. After RIC, the maximal GVT effect does not occur immediately, and rapidly proliferative diseases may relapse early [21]. Thus, there has been interest in the use of adjunctive therapies, such as tyrosine kinase inhibitors, to modify the kinetics of the disease post-transplant until the GVT effect can occur. Furthermore, a study from our center reported that prophylactic administration of imatinib post-myeloablative transplant for *bcr-abl*-positive diseases was safe and effective at reducing relapse [91]. One publication from the UK reported results on 22 patients transplanted with a RIC regimen on fludarabine–busulfan–alemtuzumab followed by 11 months of post-transplant imatinib [92]. The rate of acute GVHD was 5%; there was no chronic GVHD seen with NRM of 4% at 1 year. Of the 21 patients who completed 11 months of imatinib, 15 patients relapsed and required DLI. With a median follow-up of 3 years, OS was 87%. There is also some evidence that imatinib is effective in the treatment of chronic GVHD and may explain the very low rates of GVHD seen in this study [93]. Further studies are needed to determine the optimal tyrosine kinase inhibitor and the length of time needed for treatment, but this strategy does appear quite promising. Furthermore, novel drugs, such as aurora kinase inhibitors, which are effective in imatinib-refractory disease, will also need to be studied [94]. Similarly, several JAK-2 inhibitors are now being introduced into clinical trials and do have significant activity in JAK-2-positive MPN [13–20,95]. Studies will be needed to determine if the use of JAK-2 inhibitors post-transplant will also be effective at decreasing relapse rates.

Separating GVT from GVHD

As discussed earlier, the first evidence of a GVT effect in humans was shown in the late 1970s [31]. In this study, patients with acute and chronic GVHD after high-dose conditioning had lower rates of relapse when compared with patients who had no GVHD. Furthermore, patients who only developed chronic GVHD had the highest rates of survival after HCT [32]. A recent retrospective analysis from our center looking at 322 patients who underwent non-myeloablative HCT, also identified chronic GVHD as being highly associated with decreased risk of relapse [40]. In this analysis, acute GVHD was associated with higher NRM but did not influence relapse rates. Similar analyses from other groups looking at RIC transplants in a variety of hematologic malignancies also suggest that only the occurrence of chronic GVHD is associated with better disease-free survival [50,96–98]. Consequently, attempts to minimize severe, acute GVHD without affecting chronic GVHD may decrease NRM even further, without impacting survival when using RIC.

A common method used to decrease acute GVHD is the use of antibodies targeted against donor T cells [99]. The most commonly used agents are anti-thymocyte globulin or alemtuzumab, which targets the CD52 antigen found on T lymphocytes and natural killer cells [100]. Although these antibodies are quite effective at decreasing the incidence of GVHD, the rates of relapse/disease progression are also higher [50,100–102]. Furthermore, the rates of certain infectious complications can be significantly higher, particularly CMV infection with the use of alemtuzumab [103].

Another method proposed by the Stanford group is the use of total lymphoid irradiation of 8 Gy combined with ATG [104]. This regimen was translated from murine studies where the conditioning prevented mice from developing GVHD by increasing the proportion of regulatory natural killer T cells [105]. This regimen was used to treat 111 patients with hematologic and lymphoid malignancies using HLA-matched related and unrelated donors. The rates of acute GVHD were 2% for related and 10% for unrelated donors. The incidence of chronic GVHD was 27% and NRM at 1 year was 4%. The 36-month probabilities of OS

and RFS were 60 and 40%, respectively. With relatively short follow-up, the results suggest that this regimen is associated with very low levels of acute GVHD while apparently preserving GVT [104]. Further studies will be needed to determine if this regimen would be effective in MPN.

The current drugs that are most commonly used for GVHD prophylaxis are the calcineurin inhibitors, methotrexate and MMF [99]. Although these drugs are effective, GVHD continues to be a problem, and the use of newer pharmacologic agents that limit GVHD without compromising GVT has generated a great deal of interest. In a recent retrospective analysis, the use of rapamycin as GVHD prophylaxis after RIC was associated with improved survival in patients with lymphoma [106]. In addition to direct anti-tumor effects, rapamycin may also affect Tregs, and this drug is currently being studied further [107]. The proteasome inhibitor bortezomib and the histone deacetylase inhibitor SAHA have both been studied in murine models of transplantation and have been shown to reduce GVHD without compromising GVT [108,109]. However, these studies need to be interpreted with caution as similar effects of keratinocyte growth factor in murine models did not translate to human clinical trials [110, 111]. In a recent Phase I study, the combination of bortezomib, tacrolimus and methotrexate was evaluated as GVHD prophylaxis after HLA-mismatched HCT and the rate of acute GVHD was very low at 13% [112]. These data are quite promising, but further studies with these novel agents in human trials will be needed to show their efficacy.

Finally, the infusion of mesenchymal stem cells (MSCs) is also being studied in modulating GVHD. These are fibroblastoid cells derived from the marrow and have potent immunomodulatory properties in animal models of transplantation [113,114]. The use of MSCs in humans was first reported in 2004 in a case report where the infusion of haploidentical MSC resulted in resolution of steroid-refractory GVHD [114]. At present, clinical trials are underway to study the use of third-party MSCs in the treatment of GVHD and their effects on GVT.

Impact of comorbidities

Given that the majority of patients with MPNs are elderly, comorbid medical conditions are often a major cause of NRM. Sorror *et al.* have developed a useful tool, the Hematopoietic Cell Transplantation-Specific Comorbidity Index that risk-stratifies patients into several groups to help identify patients that would have increased NRM [115]. Patients with higher comorbidity scores have higher rates of NRM when conditioned with increasing intensity [116].

Five-year view

Over the last decade, the introduction of RIC has made significant strides toward reducing the NRM associated with transplantation. However, relapse rates are still high when using RIC, especially when the stage of disease is advanced. Over the next 5 years, we anticipate that relapse rates will decline, especially as the role of tyrosine kinase inhibitors in the peri- and post-transplant period is better defined. Currently, imatinib is the most studied drug in CML. However, the second-generation tyrosine kinase inhibitors nilotinib and dasatinib are also being used widely, and more drugs are in development. Further studies will be needed to define the ideal inhibitor, dose and duration of therapy. Similarly, the JAK2 inhibitors are just entering the clinic, and further study is required regarding their potential role in maintenance therapy after transplantation. We also anticipate the incorporation of novel chemotherapeutic agents, such as treosulfan, and targeted therapies, such as monoclonal antibodies, into conditioning regimens that aim to maximize efficacy while minimizing toxicity.

Key issues

- The only curative modality for myeloproliferative neoplasms (MPNs) is hematopoietic stem cell transplantation (HCT).
- Reduced-intensity conditioning (RIC) regimens rely heavily on maximizing graft-versus-tumor (GVT) effects to eradicate disease while minimizing toxicity.
- The introduction of RIC allows this curative therapy to be offered to elderly patients previously considered ineligible for HCT owing to advanced age or comorbidity.
- A variety of RIC regimens have been used to transplant patients with MPN. Decreasing conditioning intensity is associated with lower nonrelapse mortality but often at the cost of increased relapse rates.
- Future regimens incorporating novel agents and targeted therapies are being investigated; the addition of tyrosine kinase inhibitors in the peritransplant period is promise.
- The addition of novel agents post-transplant that allow for the separation of GVT from graft-versus-host disease is under investigation.
- The Hematopoietic Cell Transplantation-Specific Comorbidity Index is a useful tool in determining the appropriate intensity of the conditioning regimen.
- Future studies are needed that incorporate these novel approaches to further define the appropriate conditioning that minimizes toxicity while maximizing efficacy.

Acknowledgments

The authors would like to thank Bonnie Larson, Helen Crawford and Sue Carbonneau for assistance with the preparation and editing of the manuscript.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1. Hoffman R, Prchal JT, Samuelson S, Ciurea SO, Rondelli D. Philadelphia chromosome-negative myeloproliferative disorders: biology and treatment. *Biol. Blood Marrow Transplant* 2007;13:64–72. [PubMed: 17222772]
2. Tefferi, A. Classification, diagnosis and management of myeloproliferative disorders in the JAK2V617F era. In: Gewirtz, AM.; Winter, JN.; Zuckerman, K., editors. *Hematology 2007: American Society of Hematology Education Program Book*. Washington, DC, USA: American Society of Hematology; 2006. p. 240-245.
3. Swerdlow, SH., editor. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: WHO; 2008.
4. Appelbaum FR, Clift R, Radich J, Anasetti C, Buckner CD. Bone marrow transplantation for chronic myelogenous leukemia. *Semin. Oncol* 1995;22:405–411. [PubMed: 7638637]
5. Maziarz RT. Who with chronic myelogenous leukemia to transplant in the era of tyrosine kinase inhibitors? *Curr. Opin. Hematol* 2008;15:127–133. [PubMed: 18300759]
6. Zhan H, Spivak JL. The diagnosis and management of polycythemia vera, essential thrombocythemia, and primary myelofibrosis in the JAK2 V617F era. *Clin. Adv. Hematol. Oncol* 2009;7:334–342. [PubMed: 19521323]

7. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. *N. Engl. J. Med* 2005;352:1779–1790. [PubMed: 15858187] • Identification of the JAK2 mutation.
8. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell* 2005;7:387–397. [PubMed: 15837627] • Identification of the JAK2 mutation.
9. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet* 2005;365:1054–1061. [PubMed: 15781101] • Identification of the JAK2 mutation.
10. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature* 2005;434:1144–1148. [PubMed: 15793561] • Identification of the JAK2 mutation.
11. Levine RL, Pardanani A, Tefferi A, Gilliland DG. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. *Nat. Rev. Cancer* 2007;7:673–683. [PubMed: 17721432]
12. Scott B, Deeg HJ. Hemopoietic cell transplantation as curative therapy of myelodysplastic syndromes and myeloproliferative disorders. *Best Pract. Res. Clin. Haematol. J* 2006;19:519–522.
13. Pardanani A, Hood J, Lasho T, et al. TG101209, a small molecule JAK2-selective kinase inhibitor potently inhibits myeloproliferative disorder-associated JAK2V617F and MPLW515L/K mutations. *Leukemia* 2007;21:1658–1668. [PubMed: 17541402]
14. Goh KC, Ong WC, Hu C, et al. SB1518: a potent and orally active JAK2 inhibitor for the treatment of myeloproliferative disorders. *Blood* 2007;110:165A–166A. 538.
15. Mesa RA, Verstovsek S, Kantarjian HM, et al. INCB018424, a selective JAK1/2 inhibitor, significantly improves the compromised nutritional status and frank cachexia in patients with myelofibrosis (MF). *Blood* 2008;112(11):621–622.
16. Moliterno AR, Roboz GJ, Carroll M, Luger S, Hexner E, Bensen-Kennedy DM. An open-label study of CEP-701 in patients with JAK2 V617F-positive polycythemia vera and essential thrombocytosis. *Blood* 2008;112(11):44.
17. Paquette R, Sokol L, Shah NP, et al. A Phase I study of XL019, a selective JAK2 inhibitor, in patients with polycythemia vera. *Blood* 2008;112(11):971.
18. Pardanani AD, Gotlib J, Jamieson C, et al. A Phase I study of TG101348, an orally bioavailable JAK2-selective inhibitor, in patients with myelofibrosis. *Blood* 2008;112(11):43–44.
19. Verstovsek S, Kantarjian HM, Pardanani AD, et al. The JAK inhibitor, INCB018424, demonstrates durable and marked clinical responses in primary myelofibrosis (PMF) and post-polycythemia/essential thrombocythemia myelofibrosis (Post PV/ETMF). *Blood* 2008;112(11):1762.
20. Verstovsek S, Pardanani AD, Shah NP, et al. A Phase I study of XL019, a selective JAK2 inhibitor, in patients with primary myelofibrosis and post-polycythemia vera/essential thrombocythemia myelofibrosis. *Blood* 2008;112(11):206–207.
21. Scott, BL.; Sandmaier, BM. Outcomes with myeloid malignancies. In: Berliner, N.; Linker, C.; Schiffer, CA., editors. *Hematology 2006: American Society of Hematology Education Program Book*. Washington, DC, USA: American Society of Hematology; 2006. p. 381-389.
22. Baron F, Storb R. Current roles for allogeneic hematopoietic cell transplantation following non-myeloablative or reduced-intensity conditioning. *Clin. Adv. Hematol. Oncol* 2005;3:799–813. [PubMed: 16258490]
23. Barrett AJ, Savani BN. Stem cell transplantation with reduced-intensity conditioning regimens: a review of ten years experience with new transplant concepts and new therapeutic agents. *Leukemia* 2006;20:1661–1672. [PubMed: 16871277]
24. Finke J, Nagler A. Viewpoint: what is the role of allogeneic haematopoietic cell transplantation in the era of reduced-intensity conditioning – is there still an upper age limit? A focus on myeloid neoplasia. *Leukemia* 2007;21:1357–1362. [PubMed: 17508002]
25. Sandmaier BM, Mackinnon S, Childs RW. Reduced intensity conditioning for allogeneic hematopoietic cell transplantation: current perspectives. *Biol. Blood Marrow Transplant* 2007;13:87–97. [PubMed: 17222778]
26. Antin, JH. Reduced-Intensity Stem Cell Transplantation: “...whereof a little more than a little is by much too much”. *King Henry IV, part 1, I, 2*. In: Gewirtz, AM.; Winter, JN.; Zuckerman, K., editors.

- Hematology 2007: American Society of Hematology Education Program Book. Washington, DC, USA: American Society of Hematology; 2007. p. 47-54.
27. Alousi A, de Lima M. Reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation. Clin. Adv. Hematol. Oncol 2007;5:560–570. [PubMed: 17679930]
 28. Storb R. Reduced-intensity conditioning transplantation in myeloid malignancies. Curr. Opin. Oncol 2009;21:S3–S5. [PubMed: 19561410]
 29. Storb, RF.; Champlin, R.; Riddell, SR.; Murata, M.; Bryant, S.; Warren, EH. Non-myeloablative transplants for malignant disease. In: Schechter, GP.; Broudy, VC.; Williams, ME., editors. Hematology 2001: American Society of Hematology Education Program Book. Washington, DC, USA: The American Society of Hematology; 2001. p. 375-391.
 30. Baron F, Storb R. The immune system as a foundation for immunologic therapy and hematologic malignancies: a historical perspective. Best Pract. Res. Clin. Haematol. J 2006;19:637–653.
 31. Weiden PL, Flournoy N, Thomas ED, et al. Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. N. Engl. J. Med 1979;300:1068–1073. [PubMed: 34792] •• First demonstration of the graft-versus-tumor (GVT) effect.
 32. Weiden PL, Sullivan KM, Flournoy N, Storb R, Thomas ED. the Seattle Marrow Transplant Team. Antileukemic effect of chronic graft-versus-host disease. Contribution to improved survival after allogeneic marrow transplantation. N. Engl. J. Med 1981;304:1529–1533. [PubMed: 7015133] •• First demonstration that chronic graft-versus-host disease (GVHD) improves long-term survival.
 33. Weiden PL, Flournoy N, Sanders JE, Sullivan KM, Thomas ED. Antileukemic effect of graft-versus-host disease contributes to improved survival after allogeneic marrow transplantation. Transplant. Proc 1981;13:248–251. [PubMed: 7022833]
 34. Martin PJ, Hansen JA, Buckner CD, et al. Effects of *in vitro* depletion of T cells in HLA-identical allogeneic marrow grafts. Blood 1985;66:664–672. [PubMed: 3896348]
 35. Maraninchi D, Gluckman E, Blaise D, et al. Impact of T-cell depletion on outcome of allogeneic bone-marrow transplantation for standard-risk leukaemias. Lancet 1987;2:175–178. [PubMed: 2885638]
 36. Kolb HJ, Mittermüller J, Clemm Ch, et al. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. Blood 1990;76:2462–2465. [PubMed: 2265242] •• Efficacy of donor lymphocyte infusion demonstrated in chronic myelogenous leukemia.
 37. Kolb HJ, Schattenberg A, Goldman JM, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. European Group for Blood and Marrow Transplantation Working Party Chronic Leukemia. Blood 1995;86:2041–2050. [PubMed: 7655033]
 38. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. Blood 1990;76:1867–1871. [PubMed: 2224134]
 39. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with chronic myeloid leukemia in the chronic phase: a randomized trial of two irradiation regimens. Blood 1991;77:1660–1665. [PubMed: 2015394]
 40. Baron F, Maris MB, Sandmaier BM, et al. Graft-versus-tumor effects after allogeneic hematopoietic cell transplantation with non-myeloablative conditioning. J. Clin. Oncol 2005;23:1993–2003. [PubMed: 15774790] •• Chronic GVHD improves survival in non-myeloablative transplants.
 41. Kahl C, Storer BE, Sandmaier BM, et al. Relapse risk among patients with malignant diseases given allogeneic hematopoietic cell transplantation after non-myeloablative conditioning. Blood 2007;110:2744–2748. [PubMed: 17595333]
 42. Giralt S, Ballen K, Rizzo D, 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. Biol. Blood Marrow Transplant 2009;15:367–369. [PubMed: 19203728]
 43. Storb R, Yu C, Wagner JL, et al. Stable mixed hematopoietic chimerism in DLA-identical littermate dogs given sublethal total body irradiation before and pharmacological immunosuppression after marrow transplantation. Blood 1997;89:3048–3054. [PubMed: 9108426] •• Nonmyeloablative conditioning optimized in the canine transplant model.
 44. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-

tumor effects. *Blood* 2001;97:3390–3400. [PubMed: 11369628] •• Nonmyeloablative conditioning in elderly patients.

45. Giralt S, Logan B, Rizzo D, et al. Reduced-intensity conditioning for unrelated donor progenitor cell transplantation: long-term follow-up of the first 285 reported to the National Marrow Donor Program. *Biol. Blood Marrow Transplant* 2007;13:844–852. [PubMed: 17580263]
46. Radich JP. The biology of CML blast crisis. In: Gewirtz, AM.; Winter, JN.; Zuckerman, K., editors. *Hematology 2007: American Society of Hematology Education Program Book*. Washington, DC, USA: American Society of Hematology; 2007. p. 384–391.
47. Cortes J, Rousselot P, Kim DW, et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or intolerant chronic myeloid leukemia in blast crisis. *Blood* 2007;109:3207–3213. [PubMed: 17185463]
48. Radich JP, Olavarria E, Apperley JF. Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia. *Hematol. Oncol. Clin. North Am. J* 2004;18:685–702.
49. Or R, Shapira MY, Resnick I, et al. Nonmyeloablative allogeneic stem cell transplantation for the treatment of chronic myeloid leukemia in first chronic phase. *Blood* 2003;101:441–445. [PubMed: 12393604]
50. Crawley C, Lalancette M, Szydlo R, et al. Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. *Blood* 2005;105:4532–4539. [PubMed: 15731182]
51. Weisser M, Schleuning M, Ledderose G, et al. Reduced-intensity conditioning using TBI (8 Gy), fludarabine, cyclophosphamide and ATG in elderly CML patients provides excellent results especially when performed in the early course of the disease. *Bone Marrow Transplant* 2004;34:1083–1088. [PubMed: 15489879]
52. Ruiz-Arguelles GJ, Gomez-Almaguer D, Morales-Toquero A, et al. The early referral for reduced-intensity stem cell transplantation in patients with Ph1 (+) chronic myelogenous leukemia in chronic Phase in the imatinib era: results of the Latin American Cooperative Oncohematology Group (LACOHG) prospective, multicenter study. *Bone Marrow Transplant* 2005;36:1043–1047. [PubMed: 16247424]
53. Kerbaux FR, Storb R, Hegenbart U, et al. Hematopoietic cell transplantation from HLA-identical sibling donors after low-dose radiation-based conditioning for treatment of CML. *Leukemia* 2005;19:990–997. [PubMed: 15800667]
54. Kebriaei P, Detry MA, Giralt S, et al. Long-term follow-up of allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning for patients with chronic myeloid leukemia. *Blood* 2007;110:3456–3462. [PubMed: 17652620]
55. Lange T, Deininger M, Brand 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;18:1468–1475. [PubMed: 15241437]
56. Uzunel M, Mattsson J, Brune M, Johansson JE, Aschan J, Ringden O. Kinetics of minimal residual disease and chimerism in patients with chronic myeloid leukemia after non-myeloablative conditioning and allogeneic stem cell transplantation. *Blood* 2003;101:469–472. [PubMed: 12393598]
57. Dupriez B, Morel P, Demory JL, et al. Prognostic factors in agnogenic myeloid metaplasia: a report on 195 cases with a new scoring system. *Blood* 1996;88:1013–1018. [PubMed: 8704209]
58. Dingli D, Schwager SM, Mesa RA, Li CY, Tefferi A. Prognosis in transplant-eligible patients with agnogenic myeloid metaplasia: a simple CBC-based scoring system. *Cancer* 2006;106:623–630. [PubMed: 16369987]
59. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood* 2009;113:2895–2901. [PubMed: 18988864]
60. Papageorgiou SG, Castleton A, Bloor A, Kottaridis PD. Allogeneic stem cell transplantation as treatment for myelofibrosis. *Bone Marrow Transplant* 2006;38:721–727. [PubMed: 17013423]
61. Kerbaux DMB, Gooley TA, Sale GE, et al. Hematopoietic cell transplantation as curative therapy for idiopathic myelofibrosis, advanced polycythemia vera, and essential thrombocythemia. *Biol. Blood Marrow Transplant* 2007;13:355–365. [PubMed: 17317589]

62. Devine SM, Hoffman R, Verma A, et al. Allogeneic blood cell transplantation following reduced-intensity conditioning is effective therapy for older patients with myelofibrosis with myeloid metaplasia. *Blood* 2002;99:2255–2258. [PubMed: 11877308]
63. Kröger N, Holler E, Kobbe G, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Blood*. 2009 DOI:10.1182/blood-2009-2007-234880 (Epub ahead of print).
64. Rondelli D, Barosi G, Bacigalupo A, et al. Allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning in intermediate- or high-risk patients with myelofibrosis with myeloid metaplasia. *Blood* 2005;105:4115–4119. [PubMed: 15671439]
65. Merup M, Lazarevic V, Nahi H, et al. Different outcome of allogeneic transplantation in myelofibrosis using conventional or reduced-intensity conditioning regimens. *Br. J. Haematol* 2006;135:367–373. [PubMed: 16972981]
66. Snyder DS, Palmer J, Stein AS, et al. Allogeneic hematopoietic cell transplantation following reduced intensity conditioning for treatment of myelofibrosis. *Biol. Blood Marrow Transplant* 2006;12:1161–1168. [PubMed: 17085309]
67. Laport GG, Sandmaier BM, Storer BE, et al. Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation for adult patients with myelodysplastic syndrome and myeloproliferative disorders. *Biol. Blood Marrow Transplant* 2008;14:246–255. [PubMed: 18215785]
68. Kroger N, Thiele J, Zander A, et al. Rapid regression of bone marrow fibrosis after dose-reduced allogeneic stem cell transplantation in patients with primary myelofibrosis. *Exp. Hematol* 2007;35:1719–1722. [PubMed: 17976523]
69. Barosi G, Ambrosetti A, Centra A, et al. Splenectomy and risk of blast transformation in myelofibrosis with myeloid metaplasia. *Blood* 1998;91:3630–3636. [PubMed: 9572998]
70. Guardiola P, Anderson JE, Bandini G, et al. Allogeneic stem cell transplantation for agnogenic myeloid metaplasia: a European Group for Blood and Marrow Transplantation, Société Française de Greffe de Moelle, Gruppo Italiano per il Trapianto del Midollo Osseo, and Fred Hutchinson Cancer Research Center collaborative study. *Blood* 1999;93:2831–2838. [PubMed: 10216077]
71. Ciurea SO, Sadegi B, Wilbur A, et al. Effects of extensive splenomegaly in patients with myelofibrosis undergoing a reduced intensity allogeneic stem cell transplantation. *Br. J. Haematol* 2008;141:80–83. [PubMed: 18324970]
72. Slattery JT, Clift RA, Buckner CD, et al. Marrow transplantation for chronic myeloid leukemia: the influence of plasma busulfan levels on the outcome of transplantation. *Blood* 1997;89:3055–3060. [PubMed: 9108427]
73. Kashyap A, Wingard J, Cagnoni P, et al. Intravenous versus oral busulfan as part of a busulfan/cyclophosphamide preparative regimen for allogeneic hematopoietic stem cell transplantation: decreased incidence of hepatic venoocclusive disease (HVD), HVD-related mortality, and overall 100-day mortality. *Biol. Blood. Marrow. Transplant* 2002;8:493–500. [PubMed: 12374454]
74. Bacher U, Klyuchnikov E, Wiedemann B, Kroeger N, Zander AR. Safety of conditioning agents for allogeneic haematopoietic transplantation. *Expert Opin. Drug Saf* 2009;8:305–315. [PubMed: 19505263]
75. Cutting R, Mirelman A, Vora A. Treosulphan as an alternative to busulphan for myeloablative conditioning in paediatric allogeneic transplantation. *Br. J. Haematol* 2008;143:748–751. [PubMed: 19036020]
76. Kroger N, Shimoni A, Zabelina T, et al. Reduced-toxicity conditioning with treosulfan, fludarabine and ATG as preparative regimen for allogeneic stem cell transplantation (alloSCT) in elderly patients with secondary acute myeloid leukemia (sAML) or myelodysplastic syndrome (MDS). *Bone Marrow Transplant* 2006;37:339–344. [PubMed: 16415898]
77. Shimoni A, Hardan I, Shem-Tov N, Rand A, Yerushalmi R, Nagler A. Fludarabine and treosulfan: a novel modified myeloablative regimen for allogeneic hematopoietic stem-cell transplantation with effective antileukemia activity in patients with acute myeloid leukemia and myelodysplastic syndromes. *Leuk. Lymphoma* 2007;48:2352–2359. [PubMed: 18067010]

78. McDonald GB, Slattery JT, Bouvier ME, et al. Cyclophosphamide metabolism, liver toxicity, and mortality following hematopoietic stem cell transplantation. *Blood* 2003;101:2043–2048. [PubMed: 12406916]
79. Carella AM, Champlin R, Slavin S, McSweeney P, Storb R. Mini-allografts: ongoing trials in humans (editorial). *Bone Marrow Transplant* 2000;25:345–350. [PubMed: 10723575]
80. Carella AM, Giralt S, Slavin S. Low intensity regimens with allogeneic hematopoietic stem cell transplantation as treatment of hematologic neoplasia. *Haematologica* 2000;85:304–313. [PubMed: 10702821]
81. Champlin R, Khouiri I, Kornblau S, et al. Allogeneic hematopoietic transplantation as adoptive immunotherapy. Induction of graft-versus-malignancy as primary therapy. *Hematol. Oncol. Clin. North Am.* 1999;13:1041–1057.
82. Pagel JM, Gooley TA, Rajendran J, et al. Allogeneic hematopoietic cell transplantation after conditioning with ¹³¹I-anti-CD45 antibody plus fludarabine and low-dose total body irradiation for elderly patients with advanced acute myeloid leukemia or high-risk myelodysplastic syndrome. *Blood*. 2009 DOI:10.1182/blood-2009-2003-213298 (Epub ahead of print).
83. de Lima M, Champlin RE, Thall PF, et al. Phase I/II study of gemtuzumab ozogamicin added to fludarabine, melphalan and allogeneic hematopoietic stem cell transplantation for high-risk CD33 positive myeloid leukemias and myelodysplastic syndrome. *Leukemia* 2008;22:258–264. [PubMed: 17989720]
84. Green DJ, Pagel JM, Nemecek ER, et al. Pretargeting CD45 enhances the selective delivery of radiation to hematolymphoid tissues in nonhuman primates. *Blood* 2009;114:1226–1235. [PubMed: 19515724]
85. Nakamae H, Wilbur DS, Hamlin DK, et al. Biodistribution, myelosuppression, and toxicities in mice treated with an anti-CD45 antibody labeled with the α -emitting radionuclides bismuth-213 or astatine-211. *Cancer Res* 2009;69:2408–2415. [PubMed: 19244101]
86. Pagel JM. Radioimmunotherapeutic approaches for leukemia: the past, present and future. *Cytotherapy* 2008;10:13–20. [PubMed: 18202970]
87. Walter RB, Boyle KM, Appelbaum FR, Bernstein ID, Pagel JM. Simultaneously targeting CD45 significantly increases cytotoxicity of the anti-CD33 immunoconjugate, gemtuzumab ozogamicin, against acute myeloid leukemia (AML) cells and improves survival of mice bearing human AML xenografts. *Blood* 2008;111:4813–4816. [PubMed: 18326813]
88. Kantarjian HM, O'Brien S, Cortes JE, et al. Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. *Blood* 2002;100:1590–1595. [PubMed: 12176876]
89. Olavarria E, Ottmann OG, Deininger M, et al. Response to imatinib in patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. *Leukemia* 2003;17:1707–1712. [PubMed: 12970768]
90. Hess G, Bunjes D, Siegert W, et al. Sustained complete molecular remissions after treatment with imatinib-mesylate in patients with failure after allogeneic stem cell transplantation for chronic myelogenous leukemia: results of a prospective Phase II open-label multicenter study. *J. Clin. Oncol* 2005;23:7583–7593. [PubMed: 16234522]
91. Carpenter PA, Snyder DS, Flowers MED, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. *Blood* 2007;109:2791–2793. [PubMed: 17119111]
92. Olavarria E, Siddique S, Griffiths MJ, et al. Posttransplantation imatinib as a strategy to postpone the requirement for immunotherapy in patients undergoing reduced-intensity allografts for chronic myeloid leukemia. *Blood* 2007;110:4614–4617. [PubMed: 17881635]
93. Magro L, Catteau B, Coiteux V, Bruno B, Jouet JP, Yakoub-Agha I. Efficacy of imatinib mesylate in the treatment of refractory sclerodermatous chronic GVHD. *Bone Marrow Transplant* 2008;42:757–760. [PubMed: 18762765]
94. Giles FJ, Cortes J, Jones D, Bergstrom D, Kantarjian H, Freedman SJ. MK-0457, a novel kinase inhibitor, is active in patients with chronic myeloid leukemia or acute lymphocytic leukemia with the T315I BCR-ABL mutation. *Blood* 2007;109:500–502. [PubMed: 16990603]

95. Shah NP, Olszynski P, Sokol L, et al. A Phase I study of XL019, a selective JAK2 inhibitor, in patients with primary myelofibrosis, post-polycythemia vera, or post-essential thrombocythemia myelofibrosis. *Blood* 2008;112(11):44.
96. Martino R, Caballero MD, Simón JA, et al. Evidence for a graft-versus-leukemia effect after allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning in acute myelogenous leukemia and myelodysplastic syndromes. *Blood* 2002;100:2243–2245. [PubMed: 12200391]
97. Kroger N, Perez-Simon JA, Myint H, et al. Relapse to prior autograft and chronic graft-versus-host disease are the strongest prognostic factors for outcome of melphalan/fludarabine-based dose-reduced allogeneic stem cell transplantation in patients with multiple myeloma. *Biol. Blood Marrow Transplant* 2004;10:698–708. [PubMed: 15389436]
98. Blaise DP, Boiron JM, Faucher C, et al. Reduced intensity conditioning prior to allogeneic stem cell transplantation for patients with acute myeloblastic leukemia as a first-line treatment. *Cancer* 2005;104:1931–1938. [PubMed: 16178004]
99. Barrett AJ, Le Blanc K. Prophylaxis of acute GVHD: manipulate the graft or the environment? *Baillieres Best Pract. Res. Clin. Haematol* 2008;21:165–176.
100. Ho, VT. Graft manipulation: T cell depletion and tumor cell purging. In: Soiffer, RJ., editor. *Hematopoietic Stem Cell Transplantation*. NJ, USA: Human Press; 2008. p. 653–686.
101. Mohty M, Bay JO, Faucher C, et al. Graft-versus-host disease following allogeneic transplantation from HLA-identical sibling with antithymocyte globulin-based reduced-intensity preparative regimen. *Blood* 2003;102:470–476. [PubMed: 12649133]
102. Goldman JM, Gale RP, Horowitz MM, et al. Bone marrow transplantation for chronic myelogenous leukemia in chronic phase: increased risk of relapse associated with T-cell depletion. *Ann. Intern. Med* 1988;108:806–814. [PubMed: 3285744]
103. Chakrabarti S, Mackinnon S, Chopra R, et al. High incidence of cytomegalovirus infection after non-myeloablative stem cell transplantation: potential role of Campath-1H in delaying immune reconstitution. *Blood* 2002;99:4357–4363. [PubMed: 12036862]
104. Kohrt HE, Turnbull BB, Heydari K, et al. TLI and ATG conditioning with low risk of graft-versus-host disease retains antitumor reactions after allogeneic hematopoietic cell transplantation from related and unrelated donors. *Blood* 2009;114:1099–1109. [PubMed: 19423725]
105. Lan F, Zeng D, Higuchi M, Huie P, Higgins JP, Strober S. Predominance of NK1.1⁺TCR $\alpha\beta$ ⁺ or DX5⁺TCR $\alpha\beta$ ⁺ T cells in mice conditioned with fractionated lymphoid irradiation protects against graft-versus-host disease: “natural suppressor” cells. *J. Immunol* 2001;167:2087–2096. [PubMed: 11489992]
106. Armand P, Gannamaneni S, Kim HT, et al. Improved survival in lymphoma patients receiving sirolimus for graft-versus-host disease prophylaxis after allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning. *J. Clin. Oncol* 2008;26:5767–5774. [PubMed: 19001324]
107. Valmori D, Tosello V, Souleimanian NE, et al. Rapamycin-mediated enrichment of T cells with regulatory activity in stimulated CD4⁺ T cell cultures is not due to the selective expansion of naturally occurring regulatory T cells but to the induction of regulatory functions in conventional CD4⁺ T cells. *J. Immunol* 2006;177:944–949. [PubMed: 16818749]
108. Sun K, Welniak LA, Panoskaltis-Mortari A, et al. Inhibition of acute graft-versus-host disease with retention of graft-versus-tumor effects by the proteasome inhibitor bortezomib. *Proc. Natl Acad. Sci* 2004;101:8120–8125. [PubMed: 15148407]
109. Reddy P, Maeda Y, Hotary K, et al. Histone deacetylase inhibitor suberoylanilide hydroxamic acid reduces acute graft-versus-host disease and preserves graft-versus-leukemia effect. *Proc. Natl Acad. Sci. USA* 2004;101:3921–3926. [PubMed: 15001702]
110. Krijanovski OI, Hill GR, Cooke KR, et al. Keratinocyte growth factor separates graft-versus-leukemia effects from graft-versus-host disease. *Blood* 1999;94:825–831. [PubMed: 10397751]
111. Blazar BR, Weisdorf DJ, DeFor T, et al. Phase 1/2 randomized, placebo-control trial of palifermin to prevent graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). *Blood* 2006;108:3216–3222. [PubMed: 16835378]

112. Koreth J, Stevenson KE, Kim HT, et al. Bortezomib, tacrolimus, and methotrexate for prophylaxis of graft-versus-host disease after reduced-intensity conditioning allogeneic stem cell transplantation from HLA-mismatched unrelated donors. *Blood* 2009;114:3956–3959. [PubMed: 19713456]
113. Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nat. Rev. Immunol* 2008;8:726–736. [PubMed: 19172693]
114. Le Blanc K, Rasmusson I, Sundberg B, et al. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. *Lancet* 2004;363:1439–1441. [PubMed: 15121408]
115. Sorrow ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 2005;106:2912–2919. [PubMed: 15994282] •• Reports on the development of Hematopoietic cell transplantation-specific comorbidity index.
116. Sorrow ML, Sandmaier BM, Storer BE, et al. Comorbidity and disease status-based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. *J. Clin. Oncol* 2007;25:4246–4254. [PubMed: 17724349]

Table 1

WHO classification of myeloproliferative neoplasms.

Neoplasm	Known associated abnormalities in cytoplasmic/receptor tyrosine kinases
Chronic myelogenous leukemia	<i>bcr-abl</i>
Polycythemia vera	<i>JAK2</i> V617F
Essential thrombocythemia	<i>JAK2</i> V617F, <i>MPL</i> W151 L/K
Primary myelofibrosis	<i>JAK2</i> V617F, <i>MPL</i> W151 L/K
Chronic eosinophilic leukemia, not otherwise specified	<i>PDGFRA</i> , <i>PDGFRB</i> , <i>FGFR1</i>
Chronic neutrophilic leukemia	
Mastocytosis	<i>KIT</i> D816V
Myeloproliferative neoplasm (unclassifiable)	

Table 2

Results of reduced-intensity conditioning in chronic myelogenous leukemia.

Study group	Regimen	Median age (years)	Patients (n)	Disease phase	Donor type (%)	Stem cell source (%)	Severe acute GVHD (III-IV) (%)	Chronic GVHD (%)	OS (%)	RFS (%)	NRM (%)	Ref.
Hadassah-Hebrew University	Flu 150 mg/m ² Bu 8 mg/kg ATG 20-40 mg/kg	35	24	CP1 = 24 >CP1 = 0	MRD: 79 MUD: 21	PBSC: 100	29	55	85	85	13	[49]
EBMT	Flu/Bu/ATG Flu/TBI Flu/Mel/Cy Flu/Mel Flu/Cy	50	186	CP1 = 118 >CP1 = 68	MRD: 67 MUD: 25	PBSC: 72 BM: 28	9	43	58	37	23.3 (2 year)	[50]
University of Munich	8 Gy given in 2 fractions of 4 Gy Flu/Cy/ATG	51	35	CP1 = 26 >CP1 = 9	MRD: 54 MUD: 46	BM: 88 PBSC: 12	14	23	59	49	28 (1 year)	[51]
LACOHG	Flu/Bu/Cy	41	24	CP1 = 24 >CP1 = 0	MRD: 100	PBSC: 100	0	30	92	92	8	[52]
Seattle Consortium	2-Gy TBI 2-Gy TBI Flu 90	58	24	CP1 = 14 >CP1 = 10	MRD: 100	PBSC: 100	12	32	54	54	21	[53]
MDACC	Flu/Ara-C Flu/Mel 140 Flu/Ara-C/Mel 140 Mel/Ara-C		64	CP1 = 13 >CP1 = 51	MRD: 47 MUD: 53	PBSC: 41 BM: 59	16	51	33	20	48	[54]

Ara-C: Cytarabine; ATG: Anti-thymocyte globulin; BM: Bone marrow; Bu: Busulfan; Cy: Cyclophosphamide; EBMT: European Bone Marrow Transplant Registry; Flu: Fludarabine; GVHD: Graft-versus-host disease; LACOHG: Latin American Cooperative Oncohematology Group; MDACC: MD Anderson Cancer Center; Mel: Melphalan; MRD: Matched related donor; MUD: Matched unrelated donor; NRM: Nonrelapse mortality; OS: Overall survival; PBSC: Peripheral blood stem cell; RFS: Relapse-free survival; TBI: Total-body irradiation.

Table 3

Dupriez system for myelofibrosis.

Factor number	Risk group	Cases (%)	Median survival (months)
0	Low	47	93
1	Intermediate	45	26
2	High	8	13

Adverse factors include hemoglobin below 10 g/dl and white blood cell count less than $4 \times 10^9/l$ or more than $30 \times 10^9/l$.

Table 4

Mayo scoring system for myelofibrosis.

Factor number	Risk group	Cases (%)	Median survival (months)
0	Low	51	155
1	Intermediate	23	69
≥ 2	High	26	24

Adverse factors include hemoglobin level less than 10 g/dl, white blood cell count below $4 \times 10^9/l$ or above $30 \times 10^9/l$ and platelet count less than $100 \times 10^9/l$.

Table 5

International Working Group scoring system for myelofibrosis.

Factor number	Risk group	Cases (%)	Median survival (months)
0	Low	22	135
1	Intermediate-1	29	95
2	Intermediate-2	28	48
≥ 3	High	21	27

Adverse factors include an age over 65 years, presence of constitutional symptoms, hemoglobin level less than 10 g/dl, white blood cell count more than $25 \times 10^9/l$ and peripheral blood blasts greater than 1%.

Table 6

Results of reduced-intensity conditioning in myelofibrosis.

Study group	Regimen	Disease	Median age (years)	Patients (n)	Dupriez score	Donor type (%)	Stem cell source (%)	Acute GVHD (III–IV) (%)	Chronic GVHD (%)	OS (%)	RFS (%)	NRM (%)	Ref.
University of Illinois	Flu/Mel	PMF	56	4	Int = 3 High = 1	MRD: 100	PBSC: 100	0	75	100	100	0	[62]
Hamburg	Flu/Bu/ATG	PMF + secondary	55	103	Low = 17 Int = 55 High = 31	MRD: 32 MUD: 68	PBSC: 96 BM: 3 Both: 1	11	43	67	51	16 (1 year)	[63]
MPD Research Consortium	Flu/Mel Flu/TBI Flu/TT TT/Cy	PMF + secondary	54	21	Int = 21	MRD: 85 MUD: 10	PBSC: 85 BM: 15	9	72	85	81	10	[64]
Swedish Group	Flu/Bu/ATG Flu/Mel/Cy/ATG	PMF + secondary	56	10	Low = 2 Int = 6 2 points with AML	MRD: 70 MUD: 30		10	50	90	90	10	[65]
City of Hope	Flu/Mel Flu/TBI	PMF + secondary	54	9	Low = 1 Int = 4 High = 4	MRD: 22 MUD: 44 MMUD: 34	PBSC: 88 BM: 12	45	56	56	45	45	[66]
Seattle Consortium	TBI Flu/TBI	PMF PV, ET, CML	58	27		MRD: 41 MUD: 69	PBSC: 100	10	37	43	37	37 (3 years)	[67]

AML: Acute myeloid leukemia; ATG: Anti-thymocyte globulin; BM: Bone marrow; Bu: Busulfan; CML: Chronic myeloid leukemia; Cy: Cyclophosphamide; ET: Essential thrombocythemia; Flu: Fludarabine; GVHD: Graft-versus-host disease; Int: Intermediate; Mel: Melphalan; MMUD: Mismatched unrelated donor; MRD: Matched related donor; MUD: Matched unrelated donor; NRM: Nonrelapse mortality; OS: Overall survival; PBSC: Peripheral blood stem cell; PMF: Primary myelofibrosis; PV: Polycythemia vera; RFS: Relapse-free survival; TBI: Total-body irradiation; TT: Thiohepa.