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Post-Transplantation Management Strategies

Muhammad Waqas Khan, Ahmed Elmaaz and
Zartash Gul

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Abstract

Relapse is an overwhelmingly difficult and tragic event for patients suffering from hematologic malignancies that have been treated with bone marrow transplantation. More often than not, treatment options are fairly limited in each disease. Selecting the appropriate maintenance therapy gives a chance to delay or avoid these recurrences entirely. Although no perfect combination of drugs has yet been established as a mainstay maintenance therapy post-transplant, the authors here discuss the most effective and safest drugs available for different diseases.

Keywords: post-transplant management, graft versus host disease, graft versus leukemia, hematopoietic stem cell transplant

1. Introduction

The transplantation of multipotent hematopoietic stem cells that are usually derived from bone marrow, umbilical cord, or peripheral blood is a process known as hematopoietic stem cell transplantation (HSCT). It may be autologous or allogeneic and although life-saving, this procedure is not without its drawbacks. Major complications associated with HSCT include graft versus host disease (GVHD), infections, and relapse. Our current discussion is based on strategies employed for prevention of relapse post-transplant in different diseases.

2. Multiple myeloma

The use of autologous hematopoietic stem cell transplantation (A-HSCT) preceded by high-dose chemotherapy is a widely accepted modality for management of multiple myeloma (MM) in patients under the age of 65 years [1–3]. Since recurrence still remains a concern, a need for long-term regimen after transplantation to extend the response and prevent relapse is warranted. Allogenic HSCT has been associated with decreased relapse rates, in part due to its graft versus myeloma effect, but its use is limited by its complications [4]. Thalidomide [5–8], lenalidomide [9–13], proteasome inhibitors, and bortezomib [14–16] are being used as a maintenance therapy following AHSCT. They have shown to significantly decrease the relapse as well as improve the progression free survival (PFS) and overall survival (OS) rates. They have gradually replaced conventional and interferon-based therapy over the past decade due to their limited adverse effect profiles and positive impact on PFS and OS [17]. The mean survival associated with the new modalities approaches eight years post-transplant from the previous duration of three years in the past decades [18]. Several studies have been conducted to comprehensively evaluate the use of these novel agents including the assessment of their degree of response, their depth of response, and their long-term complications.

2.1. Thalidomide

Thalidomide is the first and one of the most widely studied drug following the study and evaluation of post-AHST maintenance therapies in MM. In a Phase II study conducted by Intergroupe Francophone du Myélome (IFM), 597 patients—all younger than 65 years—were divided into three groups [9]. Arm-A did not receive any maintenance therapy, while arm-B received pamidronate. Patients who received a combination of pamidronate and 400 micrograms (mcg) of Thalidomide (once daily following AHSCT) were placed in arm-C. The results showed a 36% PFS in arm-A, 37% in arm-B, and 52% in arm-C ($P < 0.009$). With a median follow-up of 39 months, the OS was 77% in arm-A, 74% in arm-B, and 87% in arm-C with a P-value of <0.04. In another study conducted by Barlogie et al., 7668 patients were divided into two groups; thalidomide versus non-thalidomide. The event-free survival (EFS) was 64% in thalidomide users versus 43% in non-thalidomide group ($P < 0.001$). The OS in the thalidomide group was 57% with 44% in the non-thalidomide group after a 72 months median follow-up ($P = 0.09$). A Phase III trial by Lokhorst et al. [6] compared the EFS between a thalidomide-based regimen and an Interferon-alpha-based regimen with a follow-up of 34 and 22 months, respectively, $P < 0.001$. The results showed no significant difference in the OS between both groups ($P = 0.77$).

The UK Medical Research Council (MRC)—Myeloma XI study divided patients into two separate groups: those with transplant and those without. The PFS was noted to be significantly higher in the transplant group following a median follow-up of 22 months and 15 months, respectively ($P < 0.0001$). No significant difference was noted in the OS between both groups ($P = 0.7$) [5–19]. This may in part be due to a difference in the cytogenetic analysis into high- and low-risk cytogenetic involving chromosome 13 [20]. A detailed analysis showed patients with a chromosome 17p deletion have decreased OS when being treated with thalidomide

indicating that thalidomide should not be used in those individuals (Hazard ratio [HR] 4.55, $P = 0.02$) [5].

A number of other studies have evaluated the use of thalidomide with a corticosteroid in comparison to using a corticosteroid alone. A study of 243 patients by Spencer et al. demonstrated a three-year survival rate; 86% with the thalidomide and corticosteroid group versus 75% in the lone steroid group ($P = 0.004$). The PFS was 42 and 23%, respectively, with a P-value of less than 0.001) [21]. In the Brazilian trial, Maiolino et al. studied 108 patients for duration of 2 years and demonstrated a PFS of 64% in the thalidomide and steroid containing group compared with 30% in dexamethasone only group ($P = 0.002$) [22]. No significant difference was found between both groups in terms of OS ($P = 0.27$). In a similar study by Stewart et al., the PFS in the thalidomide containing group was 32%, while the control group had it at 14% after a median follow-up for 4 years [8]. The survival rate in the thalidomide containing group was 68% in comparison to 60% in the lone dexamethasone group. No significant difference was observed ($P = 0.18$).

Despite the significant improvement in PFS, EFS, and the variable responses in OS rates, the most common long-term complication for thalidomide is peripheral neuropathy, in particular after long-term usage [6, 8, 9, 21]. No optimal duration of thalidomide post-transplant has been suggested by either of the trials.

2.2. Lenalidomide

Due to its higher efficacy and a lower toxicity profile the use of lenalidomide surpasses in tolerance when compared with thalidomide [7]. Although its exact mechanism is not fully understood, several hypotheses have been put forward. One such theory suggests that lenalidomide acts as a natural killer against tumor cells due to their increased cytokine production [23]. Lenalidomide is proven to decrease the production of tumor necrosis factor alpha that in turn tends to increase MM cell growth. It also inhibits the binding of MM cells to the bone marrow cells [24]. Various studies have been conducted to study the effect of lenalidomide on PFS and OS rates post AHSCT in MM. The Cancer and Leukemia Group B (CALGB) conducted a trial labeled CALGB 100104 in which 460 were randomly divided into two groups; one group receiving lenalidomide and the other a placebo with no previous consolidation therapy [12]. The time to progression (TTP) was 46 months in the lenalidomide group compared with 27 months in the placebo group ($P < 0.001$). The OS was significantly higher in patients receiving lenalidomide as compared with those receiving a placebo, 85 and 77%, respectively, ($P = 0.028$). After 36 months of follow-up, the PFS was 66% in the lenalidomide group and 39% in the placebo group. In the IFM 05-02 trial conducted by Attal et al., 614 patients received lenalidomide for a duration of 2 months after AHSCT. They were then divided into two groups: a placebo group and a lenalidomide group [10]. The lenalidomide group had a 41-month TTP versus 23 months in the placebo group with a P-value of <0.001. No difference in OS was found between both the groups, an OS of 73 and 75% in lenalidomide and placebo groups, respectively ($P = 0.7$). Following 45 months of follow-up, the PFS was 43 and 22% ($P < 0.001$), EFS of 40 and 23 months ($P < 0.001$), in the lenalidomide and placebo groups, respectively. The difference in OS in both trials was thought to be due to the difference

in the duration of follow-ups. In a study by Alisna et al., 18 months of follow-up post an AHSCT, 30 patients were started on lenalidomide at a median of 96 days [11]. The PFS was noted to be 63% (95%CI, 43–77%), the OS at 78% (95% CI, 58–90%). A similar study by Kneppers et al. showed a PFS of 60% and an OS of 93%, in 30 patients who were newly diagnosed with MM (HOVON 76 trial) [13]. Lenalidomide was started 12 weeks post an AHSCT for a duration of 24 months.

These studies concluded lenalidomide as an effective maintenance therapy following an AHSCT having significant impact on improving the PFS and OS, particularly on the elderly, patients with an increased risk of MM, and patients receiving a lenalidomide-based induction regimen [25]. Long-term usage was found to be associated with an elevated risk of hematologic complications. A grade 3–4 neutropenia was found in 51% of the patients in comparison with 18% receiving a placebo [10]. Thromboembolic complications were also noted to be markedly higher in comparison to the placebo using group (2% compared with 6%, respectively, $P = 0.01$). The risk of second primary malignancies (SPMs) as acute myeloblastic leukemias (AML) or myelodysplastic syndromes (MDS) has also been reported in various studies [10, 12]. The risk of SPM was significantly higher in patients receiving Melphalan as part of their lenalidomide treatment [27]. A few other studies noted that a lenalidomide-based maintenance therapy post AHSCT was not feasible due to the development of a GVHD [11, 13].

2.3. Bortezomib

A first of its kind, proteasome inhibitor has been used as a maintenance therapy in MM post-transplant. Trials have shown bortezomib's efficacy and its well-defined toxicity profile [14–16]. In a trial by Sonneveld et al. (HOVON 65/GMMG-HD4), 827 patients were divided into two groups; those taking Bortezomib for 2 years after induction (with bortezomib, adriamycin, dexamethasone [PAD]) and HSCT, and a non-Bortezomib group (who took vincristine, adriamycin, and dexamethasone [VAD]) followed by thalidomide [15]. A significant increase in PFS and OS was found on a multivariate analysis (35 and 28 months, respectively, $P = 0.002$), with a hazard ratio (HR) of 0.77 (95% CI, 0.6–1.0, $P = 0.048$) after a 41-month follow-up in the bortezomib group.

In a study conducted by Rosinol et al., 386 patients were divided into three groups in depending on their induction treatment regimens post-HSCT [14]. Thalidomide/dexamethasone (TD), versus bortezomib/thalidomide/dexamethasone (VTD), versus alternate chemotherapy using different regimens in patients <65 years of age who then received a maintenance therapy using bortezomib and thalidomide (VT) versus thalidomide (T) versus interferon, respectively, for 3 years. PFS in the VT group was significantly elevated in comparison with the other groups, although no difference was noted in the OS rates between the three groups. A more recent study by Scheid et al. evaluated the effect of bortezomib post-HSCT in patients with MM and renal impairment using the same management regimen used in the HONOVO 65 trial, using bortezomib for the PAD group and thalidomide for the VAD group [16]. In 746 patients, the serum creatinine was <2 mg/dL, while 81 patients had a serum creatinine of more than 2 mg/dL. The response in the VAD was 63% compared with a response of 81% in the PAD group in patients whose serum creatinine was >2 mg/dL. PFS in the VAD group was noted to

be 16 versus 48% in the PAD group receiving bortezomib, proving the effective use of Borte-zomib as a maintenance therapy in renal impaired patients suffering from MM.

We do not know the exact dose at which bortezomib may be effective during maintenance therapy; we suspect that lower doses might be effective in achieving the desired results.

In another Phase 1 trial by Abidi et al., 12 out of the 15 patients were studied to determine the safest and best-tolerated maintenance dosing of bortezomib post-HSCT [28]. The median duration of follow-up for the entire cohort was 33 months ranging from 12 to 62 months. The study concluded that bortezomib 1 mg/m² administered intravenously and may be subcuta-neously on day(s) 1, 8, and 15 in a 28-day cycle was the best-tolerated maintenance dosing and can be safely given beginning around the hundredth day post-ASCT.

3. Chronic myeloid leukemia (CML)

Allogenic stem cells transplantation (SCT) used to be the first line in management of chronic myeloid leukemia (CML). The survival rate following SCT depends on the phase of the disease in which HSCT was performed; 80% in chronic phase (CP), 40% in accelerated phase (AP), and 20% in blast crisis phase (BP) [29]. Due to the fact that relapses had been a significant problem following SCT, donor leukocyte infusion (DLI) was used to augment the graft versus leukemia (GVL) effect [30]. The introduction of tyrosine kinase inhibitors (TKIs) has replaced the use of DLI due to its effects on bone marrow suppression and GVHD induction. TKIs have proven to greatly improve survival following SCT [31, 32]. Detection of the BCR-ABL transcript levels (the enzyme affected by tyrosine kinase) early on after SCT with the aid of reverse transcriptase polymerase chain reaction (RT-PCR), the probability of relapse after SCT can be predicted giving us an idea regarding the efficacy of TKI post-transplant. High-level positive BCR-ABL is associated with highest relapse probabilities, while negative BCR-ABL has the lowest chances of relapse. Low-level positive BCR-ABL is associated with intermediate risk (total number of BCR-ABL transcripts was <100 per mg RNA and/or the BCR-ABL/ABL ratio was <0.02%) [33].

The efficacy of TKIs following SCT depends on the phase of the disease; prognosis is better if TKIs were used for relapsed CP phase; however, substantially less if used for relapse in the AP or BP phases [31, 32, 34].

The efficacy of imatinib mesylate (IM), the first TKI to be studied has been reported by many studies [35]. Wright et al. studied the response of IM after SCT in CML relapsing patients [36]. Out of 22 patients who received IM for relapse, eight were in CP, while 14 were in AP post-transplant. A complete hematological response was observed in 19 patients, while a complete cytogenetic response was observed in 17 patients. After a 31.5-month follow-up postrelapse, the OS was at 64%. Wright concluded that a complete molecular response following relapse was a predictive factor of the OS (95% CI, 2.3–182). Similarly, Palandri et al. used IM in a total of 16 patients with CML who relapsed post-transplant either in CP or AP for average 31 months. Seventy-five percent of patients achieved a complete molecular response [37],

indicating that IM could be tolerated for longer period of time post-transplant with no major hematological drawbacks. However, peripheral blood counts should be monitored during the duration of treatment for pancytopenia, a leading side effect of TKIs [37]. A study by DeAngelo et al. evaluated 15 patients who received IM for relapse post-transplant, 10 of whom were in CP, one in AP, and four patients in BP [34]. Nine of the ten patients who received IM in CP achieved a complete cytogenetic response after six months. The OS rate was at one 100% after 25 months of follow-up. Kantarjian et al. studied 28 CML relapse patient post-SCT [32], all of whom received IM in a dose range of 400–1000 mg/day. Five patients were in CP, 15 in AP, and 8 in BP. Thirteen patients received DLI at an average of 4 months prior to the use of IM. Complete hematologic response was seen in 100% of the CP patients, 83% in AP, and 43% in BP. The OS was 74% after 1 year of follow-up. The study concluded that no difference was detected in complete response between patients who had received IM and DLI, in comparison to patients who received IM alone. A study by Hess et al. evaluated 44 patients, 37 of whom were in CP before SCT, 18 patients had molecular relapse, while 19 had cytogenetic relapse [38]. IM started post-SCT on an average of 2.1 years yielded a complete molecular response in 62% of the patients after 9 months that further improved with subsequent follow-ups. They also recommended the use of molecular end point in clinical decision making. On the other hand, a study by Olavarria et al. showed that standard PCR techniques were lacking; however, complete molecular response had been significantly high, especially in CP patients [31]. In another study by Olavarria et al., IM was administrated 35 days postrelapse in 22 patients. In a year, all patients had achieved complete molecular remission without cytogenetic relapse during the entire length of IM therapy [33]. Relapse had only been detected after the discontinuation of IM therapy. The length of IM use post-transplant is yet to be determined. These various studies have recommended IM as a feasible, effective, and well-tolerated treatment for relapsing CML patients after SCT. Currently, there is a paucity of data to determine the efficacy of using TKI after SCT for maintenance. However, given its efficacy in relapsed disease, many physicians use this strategy for maintenance.

The available data about the use of second generation TKI, such as dasatinib, is still limited [39]. A study by Klyuchnikov et al. used second-generation TKI dasatinib post HST in 11 patients; out of whom nine had CML, two were in AP, and seven in BP [40]. All the patients had received TKI prior to their SCT-IM, dasatinib, or nilotinib (sometimes in combination). Dasatinib was administrated at a median interval of 1 year post-SCT with a median duration of treatment of 8 months (it was discontinued in one patient due to gastrointestinal bleeding that was thought due to drug-related thrombocytopenia). Responses to dasatinib post-transplant were seen in four out of the nine patients. Five patients failed to respond to dasatinib, while three passed away due to disease progression. One patient had a CNS relapse. The study concluded that second-generation TKI dasatinib is effective in the treatment of relapse of CML post-transplant and is generally well tolerated despite the hematological side effects. Contrary to IM, dasatinib was able to penetrate extramedullary tissues and CNS [41, 42].

4. Philadelphia chromosome positive acute lymphoblastic leukemia (Ph + ALL)

Before the use of allogeneic SCT for the treatment of Philadelphia chromosome positive Acute Lymphoblastic Leukemia (Ph + ALL), patients were usually treated with induction chemotherapy alone. It had poor outcomes in regard to the long-term survival with a median disease-free survival (DFS) range of 5–9 months [43]. SCT has been used as a curative treatment for Ph + ALL postinduction chemotherapy to improve the long-term survival [44]. One such retrospective study compared patients treated with chemotherapy alone, with patients being treated with chemotherapy followed by SCT [45]. The study reported significant survival improvement in patients treated with chemotherapy followed by SCT than patients treated with chemotherapy alone.

Detection of BCR-ABL post-SCT using RT-PCR was found to be a good predictor of minimal residual disease (MRD). Relapse with RT-PCR turned positive 4–6 months prior to the occurrence of relapse in patients who achieved remission after chemotherapy with and without combination with SCT [46].

In a study by Chen et al., the effects of TKI IM on DFS post-SCT in patients with Ph + ALL, 82 patients were evaluated of which 62 patients had received IM at a median of 70 days post-SCT for a median duration of 90 days. In 14 patients, BCR-ABL was positive prior to the use of IM, while 8 patients turned negative after a 1 month use of IM. Relapse rate was 10.2% in the group using IM, while it was 33.1% in non-IM group. The 5-year DFS was 81.5% in IM group in comparison to 33.5% in the non-IM group. Multivariate analysis proved the use of IM post-SCT as a prognostic factor for DFS and OS (P = 0.000) [47]. Twenty-two patients were studied by Carpenter et al. to assess the tolerance of IM use post-SCT [48]: 15 patients with Ph + ALL and seven patients with CML. IM was easily tolerated by 17 out of the 19 adult patients at doses of 400 mg/day. In the pediatric age group, it was tolerated by three children at doses of 260 mg/m^2/day in the first 90 days post-SCT (doses compared with those used in primary therapy for Ph + leukemia). Fourteen patients had positive BCR-ABL before SCT. After an average 1.4-year follow-up, 17 patients were alive with negative BCR-ABL transcripts. In the Ribera et al. study, 30 patients newly diagnosed Ph + ALL received IM with chemotherapy followed by SCT [49]. Transplant was then followed by IM for a median duration of 3.9 months. Twenty-seven patients achieved remission of which 21 patients underwent SCT. Twelve patients received IM after transplant. After a follow-up of 4.1 years, the DFS and the OS were 30 and 30%, respectively. Contrary to previous studies, Ribera et al. showed that adverse effects due to transplant limited the early use of IM post-SCT despite the efficacy of combined IM and chemotherapy as a primary treatment for Ph + ALL.

In another study by Teng et al., a similar TKI, dasatinib was evaluated for the same purpose [50]. Six patients with Ph + ALL were enrolled in the study and received SCT along with 100 mg/day dasatinib for 1 year. All patients achieved complete remission prior to SCT with relapse occurring in three patients only (all extramedullary). Only two patients had adverse effects from dasatinib which was improved by dividing the dose of dasatinib into two 50 mg doses. This study showed that dasatinib was effective and tolerated by Ph + ALL patients after SCT.

5. Acute myeloid leukemia (AML)

Although SCT is considered as a treatment for acute myeloid leukemia (AML) to either induce remission, or to prevent relapse, relapse is perhaps considered to be the most common complication post-SCT in patients with AML especially in the first year after transplant [51]. The duration of remission after SCT is the most important predictor of for survival after relapse [52]. Like ALL, the detection of MRD using RT-PCR could predict the post-transplant relapse in patents with AML and is much more accurate than other classic methods [53]. The 5 years OS was 79% in MRD-negative patients as detected by flow cytometry as opposed to 26% in MRD-positive patients with relapse rates of 58 and 14% after 2 years, respectively [54]. Several modalities have been studied to help control post-transplant relapse in AML patients. Jabbour et al. studied the efficacy and feasibility of Azacitidine (a DNA hypomethylating agent) in nine patients to prevent disease recurrence after SCT and in eight patients as maintenance therapy [55]. It was administrated daily for 5 days and was repeated every 4 weeks for a median duration of follow-up of 11 months. The EFS and OS rates after a year were 55 and 90%, respectively. In a paper by Cruijsen et al., 27 patients with AML who had relapsed post-SCT received Azacitidine for 3 days at a total daily dose of 100 mg which was followed by donor lymphocyte infusion on day 10 [56]. The next course started on day 22. A total of 60 courses of Azacitidine were administered. The OS from the initiation of Azacitidine was 136 days (range of 23–873), and the survival rate after 2 years was 16%. In a study by Bolanos-Meade et al., 10 patients with AML relapse post-SCT receiving Azacitidine 75 mg/m^2/day for 5–7 days were evaluated [57]. Of the 10, six achieved complete remission, one had stable disease, and three progressed after a median of six cycles. After a median follow-up of 624 days, the OS was 422.5 days (range 127–1411). These studies demonstrated that Azacitidine is effective and well tolerated by the patients without exacerbation of GVHD.

A Phase II trial was conducted by De Lima et al. to determine the maintenance dose of azacitidine postallogenic HSCT for recurrent AML or MDS [58]. Forty-five high risk patients with a median age of 60 years were treated. A combination of five different azacitidine was investigated (8, 16, 24, 32, and 40 mg/m^2), on four different schedules. Each scheduled cycle consisted of 5 days of drug administration and 25 days of rest. Reversible thrombocytopenia was found out to be the dose limiting toxicity. The optimal azacitidine combination determined from this study was 32 mg/m^2 administered for four cycles with a median follow-up of 20.5 months. The 1-year event-free survival and OS were 58 and 77%, respectively.

Decitabine (DAC) is a hypomethylating agent that irreversibly binds and inhibits DNA methyltransferase-1, resulting in loss of DNA methylation. Using DAC in maintenance therapy may help eradicate minimal residual disease and facilitate a graft versus leukemia effect by enhancing the effect of T-regulatory lymphocytes. One of the first studies to use Decitabine (DAC) as a maintenance drug postallogenic HSCT in pretreated patients with AML and MDS was conducted in 2012 by Choi et al. [59]. A total of 19 patients with a median age of 60 years were enrolled out of which 14 had AML, and five patients had MDS. All conditioning regimens were myeloablative. Three cohorts had been completed and a final fourth cohort is currently enrolling. Four doses of DAC had been investigated (5, 7.5, 10, and 15 mg/m^2/day)

administered for 5 days in a 6 weeks cycle. The median follow-up post-HSCT was 24 months. Approximately 43% of the patients were able to receive all eight cycles. It was determined that a dose of 15 mg/m^2 administered for 5 days, every 6 weeks was safe. Although results were not statistically significant, an increasing FOXP3 expression was observed in all patients. The lack of toxicities and low GVHD incidence indicated that further studies had to be conducted to determine the exact dosage of DAC required for maintenance.

A more recent and similar study by Pusic et al. [59], DAC was assessed for its safety and efficacy as a maintenance therapy in patients with AML and MDS post-HSCT. Twenty-two patients were enrolled and divided into four cohorts. DAC was administered in four doses (5, 7.5, 10, and 15 mg/m^2/day), for 5 days every 6 weeks, for a maximum of eight cycles. Nine patients completed all eight cycles out of which eight patients remained in CR. DAC maintenance did not clearly impact the rate of chronic GVHD, although a similar trend of increased FOXP3 expression seen. DACs maintenance was associated with acceptable toxicities when given in the postallogenic HSCT setting. Although the maximum tolerated dose was not reached, the dose of 10 mg/m^2 for 5 days every 6 weeks appeared to be the optimal dose.

Sorafenib is a tyrosine kinase inhibitor (TKI) that inhibits the FLT3 tyrosine kinase receptor. The FLT3-ITD mutation is associated with a high relapse rates for patients with AML postallogenic HSCT. Chen et al. [60] conducted a Phase 1 trial using sorafenib as maintenance therapy for post-HSCT in patients with FLT3-ITD AML. The patients received an assortment of conditioning regimens (10 reduced intensity and 12 myeloablative). They were all in morphological remission with predominant donor chimerism post-HSCT before starting maintenance therapy. A dose escalation 3 + 3 cohort design was used to define the maximum tolerated dose (MTD). Ten patients were additionally treated at the MTD. Sorafenib was started between days 45 and 120 post-HSCT and given continuously for 12 cycles, each cycle consisting of 28 days. No significant flares of acute GVHD was observed after starting sorafenib. The 1 year cumulative incidence of chronic GVHD was 42% (90% CI, 23%, 60%). Serial FLT3 ligand levels were measured in seven patients. Median level at baseline and prior to any drug administration was 125 pg/ml, which significantly increased to a median level of 254 pg/ml (P = 0.016) measured on day 29 of cycle 1. The surviving patient median follow-up was 14.5 months post-HSCT. The 1 year PFS is 84% (90% CI, 63–94%) and 1 year OS is 95% (90% CI, 79–99%). Only one patient relapsed post-HSCT. The study concluded Sorafenib may reduce the rate of relapse, was safe to give as maintenance therapy after HSCT for patients with FLT3-ITD AML. The use of maintenance sorafenib and other FLT3 inhibitors post-HSCT warrants further investigation.

6. Non Hodgkins Lymphoma

The use of high-dose chemotherapy followed by ASCT has been in use for a long time as a potential treatment for diffuse large B cell lymphoma (DLBCL). However, it is now mostly restricted to chemosensitive DLBCL [61, 62]. The PARMA trial began with 216 patients who received two courses of DHAP (dexamethasone, Ara-C, cisplatin) confirmed the superiority of dose intensification with autologous bone marrow transplantation over conventional

chemotherapy in patients with relapsed diffuse NHL [62]. In different types of lymphoma, relapse is the most important cause of mortality post-transplant, particularly within the first 9 months post-SCT. This is further demonstrated in a study conducted by Hamdani et al., where patients with DLBCL were compared among autologous HCT outcomes for chemo-sensitive DLBCL patients between 2000 and 2011 [63]. These were divided in two cohorts based on time to relapse from diagnosis. The early rituximab failure (ERF) cohort consisted of patients with primary refractory disease or patients who had first relapse within a year of their initial diagnosis. This group was then compared with those patients who had relapses more than a year after initial diagnosis (late rituximab failure [LRF] cohort). Both the ERF and LRF cohorts included 300 and 216 patients, respectively. Nonrelapse mortality (NRM), OS, PFS values of ERF versus LRF groups at the 3 years were 9% (95% confidence interval [CI], 6–13%) versus 9% (95% CI, 5–13%, 50% (95% CI, 44–56%) versus 67% (95% CI, 60–74%), and 44% (95% CI, 38–50%) versus 52% (95% CI, 45–59%), respectively. On a multivariate analysis, the ERF was not associated with a higher NRM (relative risk [RR], 1.31; $P = 0.34$). The ERF group experienced a higher risk of treatment failure (RR, 2.08; $P < 0.001$) and overall mortality (RR, 3.75; $P < 0.001$) within the first 9 months after autologous HCT. Beyond this period, the PFS and OS were not significantly different between both groups of LRF and ERF. Several studies have evaluated different treatment approaches for relapse post-SCT. In one such study by Haioun et al., 269 patients randomized into two groups receive rituximab maintenance ($n = 139$) for four weeks, or observed without maintenance ($n = 130$) after SCT [64]. Patients were then randomized into two groups of those achieving complete response (CR) ($n = 130$), and those who achieved incomplete or partial response ($n = 139$). After a median follow-up of 4 years from the second randomization, the EFS was 80% in the rituximab arm in comparison to 70% in observation only arm with no statistically significant difference in between both groups ($P = 0.99$), though significant difference was found in both arms of patients who achieved CR post-SCT. In another study by Gisselbrecht et al., of the 477 relapsed patients enrolled, 242 responded to salvage therapy and received SCT and high-dose chemotherapy [65]. They were then assigned to receive either rituximab for 1 year ($n = 122$), or observation alone ($n = 120$). After a median 44 months of follow-up post-SCT, no significant difference was found regarding EFS, PFS, or OS between both groups. Interestingly, significant difference was found in EFS between women (63%) and men (46%) in the rituximab group. This could be explained by the higher concentration of rituximab in females due to their slower body release [66]. The quality of life of 269 patients with DLBCL randomized to receive either rituximab or observation alone post-SCT was done in a study conducted by Heutte et al. [67]. The study showed that Rituximab decreased pain and severity of symptoms, with the long-term difference in quality of life post-SCT was not dependent on rituximab maintenance. As concluded by these studies, rituximab could be used as a maintenance therapy post-SCT as being a feasible and safe option, but does not improve disease control or survival outcome and needs to be investigated further.

Though mantle cell lymphoma (MCL) is still considered a poor prognosis type of non-Hodgkin lymphoma [68], rituximab has proven efficacy in Phase III studies by prolonging disease-free survival and improving clinical response in patients with MCL undergone SCT [69]. Better response was correlated with detection of PCR undetectable markers in bone marrow and peripheral blood after SCT [70–72]. In a study by Andersen et al. [73], 74 patients showed

complete response of 145 patients with SCT, 36 had molecular relapse after a mean of 18.5 months following SCT, and 26 patients got administrated pre-emptive rituximab which could induce a remission of 92%. Median clinical and molecular-free survival was 3.7 and 1.5 years, respectively, stating the importance of PCR analysis for patients with MCL to stratify high-risk group of patients.

7. Hodgkins Lymphoma

As in non-Hodgkin lymphoma, high-dose therapy followed by autologous stem-cell transplantation is the standard of care for relapsed patients of Hodgkin's lymphoma (HL), and for patients who did not respond to the salvage treatment [74]. Studies have shown that SCT could significantly increase the progression-free survival (PFS) [75]. Several treatment approaches have been studied to increase outcome after SCT as radiation before and after SCT and consolidation post-SCT [76, 77]. Brentuximab vedotin, an anti-CD 30 antibody linked to protease cleavage agent has been studied as a post-transplant therapy for HL. A Phase II study by Younes et al. showed that response rate to brentuximab is 75% in relapsed patients with HL and complete response rate was 34% after 2 years [78]. The AETHERA study [79] evaluated brentuximab as an early consolidation therapy post-SCT where 329 patients with relapsed or refractory HL were randomly assigned to receive 16 cycles of 1.8 mg/kg brentuximab vedotin (n = 165), or placebo (n = 164) starting 30–45 days after SCT. PFS was significantly higher in patients in the brentuximab vedotin group compared with those in the placebo group (95% CI 0.40–0.81; P = 0.0013), with median PFS of 42.5 months in brentuximab receiving patients compared with 24.1 months in patients receiving placebo. After 24 months of follow-up, 63% of brentuximab group were alive in comparison with the 51% in the placebo group. The study concluded that the administration of brentuximab early after SCT in relapsed or refractory HL patients had significantly improved EFS and OS.

8. Conclusion

IMiDs have also decreased relapse rates along with a decrease in the PFS and OS rates; increasing the mean survival from the previous 3-year survival to an 8-year post-transplant survival. The combination of thalidomide and steroid is promising and has shown significant improvement in the EFS and PF rates in comparison to a lone steroid therapy, although neuropathy is still a major concern in thalidomide-based regimen for prolonged use. Lenalidomide surpasses in tolerance when compared with thalidomide due to its unique efficacy and toxicity profile and has proven to be an effective maintenance therapy following AHSCT with a significant impact on improving the PFS and OS. Similarly, Bortezomib has its defined efficacy and toxicity profile and showed significant increase in PFS and OS in patients as a maintenance therapy in renal-impaired patients suffering from MM.

MM summary: IMiDs have decreased relapse rates and PFS OS rates. Mean survival with the new modalities is 8 years post-transplant from 3 years.

Thalidomide summary: thalidomide + dexamethasone usage has shown good improvement in EFS and PF rates compared with using dexamethasone alone. OS values are variable. Neuropathy is the major concern in thalidomide-based regimen for long-term use. No optimal duration for thalidomide has been established.

Lenalidomide summary: due to its higher efficacy and a lower toxicity profile the use of lenalidomide surpasses in tolerance when compared with thalidomide. Lenalidomide is an effective maintenance therapy following AHSCT, having and has significant impact on improving the PFS and OS. Long-term usage was found to be associated with an elevated risk of hematologic complications, neutropenia. SPM risk was significantly higher in patients receiving melphalan + lenalidomide.

Bortezomib summary: bortezomibs has a defined efficacy and toxicity profile. Significant increase in PFS and OS in patients using bortezomib post-HSCT. Bortezomib is effective as a maintenance therapy in renal impaired patients suffering from MM. Exact dose of maintenance therapy is not yet known.

CML summary: TKIs have proven to improve survival following SCT. The efficacy of TKIs following SCT depends on the phase of the disease; a good prognosis if TKIs were used for relapse CP phase, less if used for relapse in the AP or BP phases. Dasatinib is effective in the treatment of relapse of CML post-transplant, is well tolerated despite the hematological side effects. Dasatinib can penetrate extramedullary tissues and CNS. Presently, there is an insufficiency of current data required to determine the efficacy of using TKI after SCT for maintenance. Nonetheless, given its efficacy in relapsed disease, many physicians use this strategy for maintenance.

Ph + ALL summary: SCT has been used as a curative treatment for Ph + ALL postinduction chemotherapy to improve the long-term survival. Dasatinib was effective and tolerated by Ph + ALL patients after SCT.

AML summary: the duration of remission after SCT is the most important predictor of for survival after relapse. Azacitidine, decitabine, sorafenib, and other FLT3 inhibitors are effective and well tolerated by the patients without exacerbation of GVHD. Although studies of using FLT3 inhibitors as maintenance therapies are still on going, the data collected so far shows promising results and merits further trials.

NHL summary: high-dose chemotherapy followed by ASCT has been in use for a long time as a potential treatment for DLBCL. A 5-year event-free survival rate was significantly higher in patients who received ASCT and chemotherapy, than patients receiving salvage therapy alone. Rituximab could be used as a maintenance therapy post-SCT as being a feasible and safe option, but does not improve disease control or survival outcome and needs to be investigated.

HL summary: SCT could significantly increase the progression-free survival. Brentuximab early after SCT in relapsed or refractory HL patients had significantly improved EFS and OS.

Conflict of interest

The authors have no conflict of interest, nor have received any funding.

Author details

Muhammad Waqas Khan[1*], Ahmed Elmaaz[2] and Zartash Gul[1*]

*Address all correspondence to: mkh233@uky.edu and gulzh@ucmail.uc.edu

1 Department of Internal Medicine division of Hematology and Bone marrow transplant, University of Kentucky, Kentucky, USA

2 Department of Hematology, Oncology, University of Cincinnati, Cincinnati, Ohio, USA

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