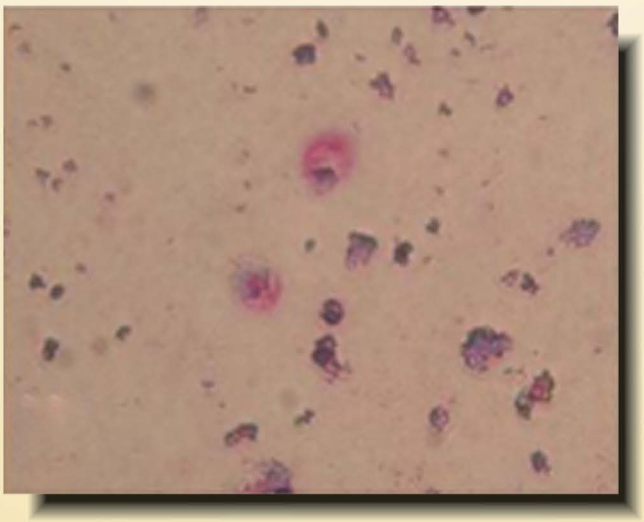
RECENT ADVANCES IN HEMATOLOGY-3

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Chapter

3 Role of Autologous Stem Cell Transplantation in Hematological Malignancies

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SUMMARY

High dose chemotherapy followed by autologous stem cell transplantation (ASCT) has been in use since past two decades. Its role has been clearly defined in young patients of multiple myeloma without significant co-morbidities and chemosensitive relapse Hodgkin's and non-Hodgkin's lymphoma. For many other hematological and solid malignancies single center data is promising. This is also being explored for a number of nonmalignant conditions particularly autoimmune diseases. While the morbidity and mortality of ASCT has come down significantly in the past decade, relapse continues to be a major cause of failure. Identification of patients at high-risk of relapse and use of novel approaches to reduce the relapse risk are likely to be areas of research in future studies.

KEYWORDS

Autologous stem cell transplantation, Acute myeloblastic leukemia, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Multiple myeloma

INTRODUCTION

Autologous stem cell transplantation (ASCT) is currently a standard treatment for young patients of multiple myeloma without major co-morbidities, Hodgkin's and non-Hodgkin's lymphoma with chemo-sensitive relapse and high-risk/advanced neuroblastoma. In addition, ASCT is being used for treatment of acute myeloid leukemia, poor risk/relapsed germ cell tumors and many other solid tumors. The morbidities and mortality due to ASCT have come down significantly in the past few years due to improved supportive care, use of peripheral blood derived stem cells (in place of bone marrow) and proper case selection. We here review role of ASCT in hematological malignancies.

EVALUATION

Potential recipients of ASCT are evaluated for the underlying disease (remission status) and for any major organ dysfunction. This includes assessment of cardiac, renal, lung and liver function. Evaluation for viral

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infections (hepatitis B and C, CMV, etc.) is also done. Patients with moderate to severe major organ dysfunction or those with active infection are at high risk for transplant-related complications or reactivation of infection and are not suitable candidates for ASCT. It is important to carefully record details of chemotherapeutic drugs received in past and any history of major infection such as fungal/tubercular and allo-immunization to platelets.[1]

Stem Cell Mobilization

For ASCT , peripheral blood stem cells are harvested as a routine, rarely in a few patients bone marrow harvest may need to be done due to technical reasons or if PB stem cells collection is not adequate. For this purpose, PB stem cells have to be mobilized from the BM. This is done by giving to patient granulocyte colony-stimulating factor (G-CSF) in a dose of 10 μg/kg/day in 2 divided doses, subcutaneously for 4-5 days. On day 5-6, PB stem cells are collected by leukapheresis using an apheresis (cell separator) machine. A PB-stem cell harvest contains substantially more CD34+ cells and 10 times more lymphocytes than a BM harvest. The recovery of neutrophil and platelet numbers is quicker in recipients of PB-derived stem cells than in those receiving BM. Neither anesthesia nor hospitalization is required. Once harvested, the PB stem cells are cryopreserved at – 80°C using 7.5% dimethyl sulphoxide (DMSO) or liquid nitrogen.[2] The patient is then administered high dose chemotherapy (HDCT). Depending upon the half-life of the chemotherapeutic drugs used, the PB stem cells can be re-infused either after 24 hours (melphalan) or a longer interval (5-7 days).

The precise number of PB stem cells (mononuclear cells) required is not known. In practice, for BM, approximately 3×10^8 nucleated cells/kg of the recipient's body weight and for PB 5×10^8 mononuclear cells/kg or $\geq 2 \times 10^6$/kg CD34+ cells (marker for stem cells) are harvested.

Some centers use cyclophosphamide 2-4 Gm/m^2 followed by G-CSF. Patient is monitored daily with blood counts. Once total WBC count is about 2000/cmm, stem cell harvest is initiated and continued on alternate day basis till target number of stem cells is collected. In most patients 1-2 harvests may be adequate, about 10-20% of patients may need ≥ 3 harvests to achieve the target number. Recently, Stiff et al (2009) have reported use of Plerixafor, (a bicyclam molecule which is a reversible inhibitor of hemopoietic stem cell adhesion to stromal cells mediated through CXCR4 binding to stromal derived factor -1-α) with G-CSF for mobilization of stem cells in patients of NHL and myeloma who were heavily pretreated. Adequate number of stem cells (2×10^6/kg) could be achieved in 96% of patients.[3] This molecule may be of value in patients who are heavily pre-treated and in whom adequate number of stem cells is not mobilized with G-CSF alone.

The primary concern with autologous HSCT is relapse due to re-infusion of malignant cells along with progenitor cells. Various methods including *in vitro* treatment with chemotherapeutic drugs or monoclonal antibodies have been used to remove the contaminating tumor cells

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(purging). Retrospective analyses suggest that purging leads to decreased rates of relapse in patients with acute myeloblastic leukemia (AML) and non-Hodgkin lymphoma (NHL).

PREPARATORY REGIMEN

Prior to ASCT, the patient's own BM is destroyed by giving high dose chemotherapy (HDCT) with or without total body irradiation (TBI). This is done to (i) eradicate the malignant cells (cytoreduction) and to (ii) possibly to create space (niche) within the BM microenvironment to allow engraftment of stem cells. For autologous transplantation immunosuppression is not required and the preparatory regimen is used to provide maximum dose intensity with a goal of eradicating the malignancy. In earlier period, most patients have received cyclophosphamide and TBI (Cy–TBI) as the preparatory regimen. Fractionation of TBI (total dose 1200-1500 cGy) was used to reduce toxicity to the normal tissues. A combination of busulphan (4 mg/kg/day × 4 days; total 16 mg/kg) and cyclophosphamide (60 mg/kg/day × 2 days; total 120 mg/kg; Bu–Cy2) is effective for allogeneic and autologous SCT, and has been popular in the past two decades. The same regimens are used for autologous SCT.

For patients of myeloma, high dose melphalan 200 mg/m^2 is currently the standard. For patients with Hodgkin's and non-Hodgkin's lymphoma – BEAM (BCNU, etoposide , cytosine arabinoside and melphalan) or CVB (cyclophosphamide, VP-16 (etoposide) and BCNU) are commonly used. Radiation based preparatory regimens[4] used earlier are no longer popular in view of long-term toxicity of radiation.

STEM CELL INFUSION

After completion of the preparatory regimen, there is a 24-48 hours period (called rest period) prior to infusion of the stem cells. For patients undergoing ASCT the stem cells are removed from the deep freezer, thawed at room temperature in a water bath and re-infused into the patient. Some patients may experience nausea, dizziness or a suffocating feeling—all side-effects related to the use of DMSO for cryopreservation of stem cells. These patients require strict isolation after infusion (transplantation) of the stem cells.

Most centers use prophylactic antibiotics (quinolones—ciprofloxacin), antifungals (oral fluconazole or itraconazole) and antiviral drugs (oral acyclovir).

Complications Following ASCT

In addition to infections secondary to severe myelosuppression a number of other complications can occur (Table 3.1).

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Table 3.1. Complications of autologous stem cell transplantation

- **Acute**
  - Infection
  - *Regimen-related complications*
    - Gastrointestinal: Nausea/vomiting, diarrhea, mucositis:
    - Pulmonary and cardiac disease
    - Hemorrhagic cystitis disease
    - Veno-occlusive disease
- ***Late***
  - Relapse
  - Sterility
  - Myelodysplasia/Secondary leukemia

Infections

Infections can be divided into three categories based on the time of their occurrence after transplant. In the first 30 days, most bacterial infections are due to chemotherapy-induced neutropenia. Fungal infections tend to occur during the first 3-4 months after SCT. The commonly encountered organisms include *Candida species (C. albicans and C. tropicalis)* and *Aspergillus*. The risk of *Pneumocystis carinii*-induced interstitial pneumonia may be reduced to < 10% by chemoprophylaxis with oral trimethoprim–sulphamethoxazole given 2-3 times per week, starting after engraftment (when the neutrophils are >1000/cmm) and continued for 6-12 months. In patients allergic to sulphamethoxazole, pentamidine (300 mg) once a month can be given. In ASCT patients risk of bacterial infections diminishes with hematopoietic recovery. However, recovery of humoral and cell-mediated immunity may take 3-12 months; therefore, such patients may be at risk for viral infections, particularly *Varicella zoster*. Reactivation of *Mycobacterium tuberculosis* infection can also occur infrequently.

Mucositis

Oral mucositis is common in the second week after ASCT. Patients with grade III-IV oral mucositis may need parenteral opioids for pain relief and parenteral alimentation to maintain an adequate calorie intake. Spielberger et al in a randomized trial reported the use of recombinant human keratinocyte growth factor (pelifermin) to decrease mucosal injury. Both severity (grade III-IV, 63% *vs* 98%, p< 0.001) and the median duration of mucositis (6 days *vs* 9 days, p< 0.01) were significantly less in the group receiving pelifermin compared with placebo.[5]

In another study, the severity of oral mucositis was reduced following administration of amifostine in myeloma patients who underwent ASCT using highdose melphalan for conditioning.[6]

Pulmonary Complications

Diffuse pulmonary hemorrhage manifests as dyspnea (92%), fever (67%), cough (56%), hemoptysis (15%) and hypoxia. Pulmonary infiltrates are

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seen on chest X-ray and CT scan during the first 30 days after ASCT. This syndrome is probably related to pulmonary injury due to HDCT and is most frequently seen in patients who receive autologous HSCT. The condition seems to respond to corticosteroids.[1]

Engraftment Syndrome

A clinical picture similar to capillary leak syndrome may occur during the second or third week following engraftment. It is characterized by excessive weight gain, ascites and edema (similar to noncardiogenic pulmonary edema) and is associated with kidney and liver abnormalities, suggesting a common injury to multiple organs. The pathogenesis of this disorder is poorly understood; a pivotal contribution by circulating leukocytes is a possibility.[7] Treatment with prophylactic steroids may prevent the engraftment syndrome.

Hemorrhagic Cystitis

This occurs most often following the use of preparatory regimens containing ifosphamide or cyclophosphamide, which cause marked chemical inflammation of the bladder mucosa. Infection with a virus (polyoma, BK virus or adenovirus) has also been implicated. Its incidence varies from 7% to 70%. Mild cystitis (grade I, dysuria and microscopic hematuria) is self-limiting and occurs early (during or immediately after conditioning) and can be prevented with diuresis and 2-mercaptoethane sulphonate (Mesna). However, overt cystitis (grade > II, gross hematuria, clot retention, urinary tract obstruction and impairment of renal function) is clinically more important. This occurs late and has a protracted course requiring regular bladder irrigation and repeated cystoscopy, and is a cause of substantial morbidity. A variety of uroprotective measures including alkaline diuresis, frequent voiding, urethral catheterization and bladder irrigation and the use of Mesna reduces the risk of hemorrhagic cystitis.[8]

Veno-occlusive Disease

Veno-occlusive disease of the liver is a common regimen-related toxicity characterized by jaundice (serum bilirubin > 2 mg/dl), tender hepatomegaly, ascites and unexplained weight gain (> 2%of baseline body weight) within 20 days of HSCT.[9] The incidence varies from 15% to 25%, being lower in autologous compared with allogeneic SCT. The median time of onset is day 8-10 post-transplant (generally before day 21). The course may range from mild, reversible disease to severe disease associated with multi-organ failure with a poor prognosis. It occurs due to injury to the sinusoidal endothelial cells and hepatocytes with subsequent damage to the zone 3 central veins of the hepatic acinus. Early changes include deposition of fibrinogen, factor VIII and fibrin within the venular walls and sinusoids. As the process of venular micro-thrombosis,

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fibrin deposition, ischemia and fibrinogenesis advances, widespread zonal disruption leads to portal hypertension, hepatorenal syndrome, multiorgan failure and death.

Patients with elevated transaminases prior to ASCT, and those with persistent fever during the cytoreductive phase are at high-risk for developing severe disease. Management of mild/moderate disease requires fluid restriction and diuretics. Treatment of severe disease is unsatisfactory. Therefore, efforts have been directed towards its prevention by using drugs that interrupt the coagulation cascade or those that diminish the influence of thrombogenic factors. Richardson et al reported the use of defibrotide, a single-strand polydeoxyribonucleotide with fibrinolytic, antithrombotic and anti-ischemic properties. Complete resolution of severe disease was seen in 36% with a 35% survival at day 100. 27 Younger age, autologous HSCT and abnormal portal flow predicted survival whereas busulphan-based conditioning and encephalopathy predicted a worse outcome. Similar results with defibrotide have also been reported in children.[10]

CLINICAL RESULTS

Acute Myeloblastic Leukemia (AML)

Following induction chemotherapy 60-75% of patients with AML achieve complete remission (CR) (Table 3.2). This is followed by 3-4 cycles of consolidation chemotherapy with high dose cytosine arabinoside (15-18 g/m^2). AML is a heterogeneous disease with widely different risk for relapse following standard treatment. Cytogenetic abnormality and time to achieve CR are two important prognostic factors. In addition, age and a variety of molecular markers have been defined.[11] Table 3.3 gives various cytogenetic abnormalities. Morra et al[12] for the Italian Society of Hematology and Italian Group for Bone Marrow transplantation have recently described guidelines for clinical management of AML patients

Table 3.2: Response criteria in acute myeloid leukemia[12]

Response criterion	*Neutrophils (ul)*	*Platelets (ul)*	*BM Blasts (%)*	*Other*
Morpholgical CR	>1000	>100,000	<5	Transfusion Independent No EMD
Cytogenetic CR	>1000	>100,000	<5	Cytogenetics Normal, no EMD
Molecular CR	>1000	>100,000		Molecular negative NO EMD
Partial remission	>1000	>100,000	5-25	Blasts < 5%, if Auer rods positive

EMD—extramedullary disease, BM—bone marrow,CR—complete remission

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Table 3.3: Cytogenetic molecular risk in acute myeloid leukemia

Risk	*Pattern*
Low risk	Inv (16)/ t (16;16); CBFB/MYH11
	* t (8;21); AML1/ETO
	Normal karyotype: NPM+,FLT3–
	Normal karyotype: CEBPA+
Intermediate	+8 (isolated)
	t (9; 11)
	Normal karyotype
High	Complex karyotype
	–7/7q;5/5q–
	t (11q21-23)/MLL;MLLampl;
	CALM/AF10
	Inv (3)/ t (3;3)
	t (6;9)
	t (9;22)
	t (8;16); inv (8)
	t (3;5)
	Normal karyotype: FLT3+

* Core binding factors leukemia, in the absence of KIT mutations

(other than acute promyelocytic leukemia). These are summarized in Tables 3.3 and 3.4 Breems et al in a prospective randomized trial evaluated role of autologous SCT vs chemotherapy for AML patients less than 60 years of age in CR1. patients who achieved CR after two courses of induction chemotherapy and who were not eligible for an HLA matched sibling transplant were randomized after a third consolidation cycle of chemotherapy to either autologous SCT or no further treatment.

No significant difference was observed in disease-free survival and overall survival between the two arms.[13]

Acute Promyelocytic Leukemia (APML)

AML with t (15;17) (q22;q12) is a molecularly defined disease entity. Current treatment strategies based on all transretinoic acid and anthracycline based induction, anthracycline based consolidation and maintenance therapy without any transplantation results in excellent CR (up to 90%) and overall survival (up to 85%). Even in high-risk subsets of APML the relapse rates does not exceed 20-25%. Hence stem cell transplant has no role in consolidation in first line treatment of APML. Nonrandomized studies show that autologous SCT can offer an effective salvage treatment when performed in second molecular remission.[14]

Autologous HSCT could be considered in AML patients in first complete remission, poor risk category, if HLA-matched sibling donor is not available. For patients with normal cytogenetics, allogeneic HSCT should be considered if the patient requires 2 cycles to achieve complete remission. Karyotypes (> 3 abnormalities), have poor CR and leukemia-free survival (LFS) rates with chemotherapy and should be

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Table 3.4: Indications for HSCT in acute myeloid leukemia (AML)[12]

Myeloablative allogeneic SCT from a fully matched sibling donor	In CR1 to (i) All children with intermediate to high-risk cytogenetics (ii) To all adults with high-risk cytogenetics, under age 55 years without major co-morbidities (iii) To adults under 40 years without severe comorbidities, with intermediate cytogenetics with the exception of NPM1 mutant and FLT3 –ITD negative cases (iv) Achievement of CR1 after 2 courses of induction chemotherapy irrespective of cytogenetic risk. Provided they are under 55 years and do not have severe comorbidities.
Allogeneic SCT from an unrelated donor	All adults in CR1 under 30 years of age, (i) with high-risk cytogenetics, (ii) achieved CR after second course. Not recommended for patients above 50 years who achieved CR. Children with (i) AML-M7, (ii) complex cytogenetics, monosomy 7, (iii) a high level of MRD measured by flow cytometry after consolidation chemotherapy.
Alternative donors (e.g. mismatched-related, cord blood)	(i) At a center with active programme for adults without related or unrelated donor but have high-risk cytogenetics (ii) Children who are candidates for transplant as above but lack a donor.
Allogeneic SCT with RIC regimen	High-risk patients aged > 55 years OR with severe comorbidities.
Autologous peripheral blood SCT	Favorable (Low-risk): CR1: Not recommended CR2: Allogeneic SCT is choice, if match is not available or if allo-SCT can not be carried out due to practical reasons then autologous SCT can provide effective therapy. For patients aged < 60 years, eligible for high dose chemotherapy but who are not candidate for allogeneic SCT from a fully matched donor or lack a donor. Not recommended for children with Down syndrome. Time for transplant should be done within 6 months of achieving CR.

SCT—stem cell transplantation, MRD—minimal residual disease, RIC—reduced intensity transplant

considered for allogeneic HSCT. Many investigators prefer to transplant patients with intermediate risk cytogenetics such as +8, –Y, +6, Del 12p, normal karyotype if an HLA-identical sibling is available. Patients in the second CR or those with an untreated relapse can be cured with allogeneic HSCT with 3-year LFS rates of 22-30%. About 10-20% of

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patients with primary chemorefractory AML can be salvaged with allogeneic HSCT.

Thus, allogeneic SCT from an HLA-identical sibling remains treatment of choice for young patients with high-risk cytogenetics in CR1. Next best option is unrelated matched donor transplant. For those not having match, autologous SCT would be a reasonable option.

Acute Lymphoblastic Leukemia (ALL)

About 80% of children with good risk ALL are now cured with standard chemotherapy. Therefore, allogeneic HSCT is usually reserved for (i) children < 15 years of age with cytogenetic abnormalities such as t(4;11) and Philadelphia (Ph) chromosome, t (9;22), (ii) children in the second or third remission and (iii) young adults between 15 and 21 years of age who have a high leukocyte count at diagnosis and have the Ph chromosome. Such patients are considered at high-risk for relapse with standard chemotherapy. The best results for allogeneic SCT in ALL are reported in children and adults in first remission; the LFS is 60% and 52% respectively.[15] Allogeneic HSCT might also cure a proportion of patients (15%) with ALL in whom remission could not be achieved with conventional chemotherapy.[15]

Results with autologous SCT are not superior to chemotherapy alone in patients with high-risk ALL. For adult patients with Ph+ ALL, early allogeneic SCT from a sibling donor is the treatment of choice; 27-65% of patients in first CR achieve long-term survival. Survival decreases to 17% and 5% for those undergoing HSCT in the second and third remission, respectively. For Ph+ ALL, the current recommendation is to give induction chemotherapy with imatinib followed by allogeneic SCT if an HLA-identical match is available. Dhedin et al have reported results of an individual data based overview of three trials from the LALA Group. With intent to treat analysis, investigators compared 175 patients (age 15 to 50 years old without HLA identical sibling or 15-55 years age group with high-risk ALL) from the ASCT arm with 174 patients in the chemotherapy arm. ASCT was associated with a lower cumulative incidence of relapse (66% vs 78% at 10 years, $p<.05$) without significant gain in disease-free or overall survival.[16] A recent study by the PETHEMA group has compared the outcome of intensive chemotherapy, allogeneic or autologous SCT as post-remission treatment for 106 children with very high-risk ALL (age < 1 year, WBC $\geq 30 \times 10^9$/l in B lineage ALL, $\geq 100 \times 10^9$/L in T lineage ALL or t (9;22), t (4;11) or other 11q23 rearrangements and patients without these criteria but slow (> 25% blasts in bone marrow at day 35) response to induction therapy. Overall 100 (94%) patients achieved CR. Intention to treat analysis showed no difference in disease-free survival (DFS): Donor vs no donor, (45% vs 45%) and overall survival (48% vs 51%). Between autologous vs chemotherapy — DFS 44% vs 60% and OS-45% vs 57%. This study failed

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to prove better outcome with allogeneic SCT compared to autologous SCT and intensive chemotherapy.[17]

Myelodysplastic Syndrome (MDS)

Allogeneic HSCT is the treatment of choice for patients with International Prognostic Scoring System (IPSS) intermediate-2 and high-risk MDS. However, its use is limited because of the higher median age of patients at the time of diagnosis (70 years). For the small number of eligible patients, myeloablative allogeneic HSCT results in long-term EFS in 32-54%. Experience with reduced intensity conditioning HSCT in patients > 50 years of age is encouraging. In the CIBMTR study, in 384 patients > 50 years of age who received an HLA-identical sibling HSCT, the 3-year probabilities of survival were 32% and 39% with myeloablative and reduced intensity conditioning, respectively.[15] Autologous HSCT can be considered in selected patients who achieve CR following induction chemotherapy and do not have an HLA-identical donor. In a prospective study by de Witte et al 36 of 59 patients (61%) without a donor received autologous HSCT in their first CR. The 4-year DFS rates in patients with or without a donor were 31% and 27%, respectively.[18]

Chronic Myeloid Leukemia (CML)

Imatinib mesylate is now the treatment of choice for all newly diagnosed CML patients. It achieves complete cytogenetic response (Ph–metaphases) in 50-75% of patients at 12 months. Currently, allogeneic HSCT is considered for patients (i) who fail to achieve complete hematological remission after 3 months of imatinib therapy, (ii) who fail to achieve complete cytogenetic response after 12-18 months of imatinib therapy, (iii) who relapse after an initial response, and (iv) with advanced disease (accelerated phase/ blast crisis). Many investigators also prefer to transplant younger patients (< 20-30 years of age), if an HLA-identical sibling is available. For CML patients in the chronic phase, following allogeneic HSCT, the 5-year LFS is > 50%.[15] Similar results have been reported from India.[19] In patients with accelerated phase and blast crisis, allogeneic HSCT results in DFS rates of 15-25% and <15% respectively.[15] CML appears to be most susceptible to the GVL effect. Patients who relapse after allogeneic HSCT can be treated successfully using donor lymphocyte infusion (DLI) without pretransplant conditioning. For patients with molecular or cytogenetic relapse of CML, the CR rate is 85-90%. These observations have led to the use of nonmyeloablative or less intensive allotransplants, especially for patients > 45 years of age. Patients may engraft with mixed chimerism which gradually converts to full donor chimerism with the use of DLI.

Chronic Lymphocytic Leukemia (CLL)

The median age at presentation of CLL patients is 65 years, 40% are < 60 years of age and 12% are < 50 years of age. A number of single

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center studies have reported the results of autologous SCT in younger patients with high-risk CLL. Treatment-related mortality is low (1-5%) with CR in 12-67% of patients. Allogeneic HSCT in CLL is associated with significant morbidity and mortality due to regimen-related toxicity, GVHD and Infection.[20] Recently, HSCT with reduced intensity conditioning has also been performed. In the CIBMTR study, among 949 patients who underwent HSCT for CLL, the 3-year probabilities of survival were 77% after autologous HSCT, 50% after allogeneic HSCT with myeloablative conditioning and 53% after HLA-identical Sibling SCT with reduced intensity conditioning.[15] At present, the experience with HSCT is small but it appears that allogeneic SCT could be considered in selected young patients using reduced intensity conditioning.[21]

Hodgkin Lymphoma (HL)

HDCT supported with autologous SCT is currently considered the standard of care for relapsed HL or HL refractory to primary chemotherapy. In the CIBMTR study, among the 5,219 patients receiving autotransplants for HD between 1998 and 2006, the 3-year probabilities of survival were 78% ± 1%, 69% ± 1%, and 49% ± 3% for patients in complete remission, in partial remission, and with chemoresistant disease, respectively.[15]

Currently, there is no evidence to suggest that autologous SCT is superior to conventional chemotherapy for patients with advanced HL responding to frontline therapy.

Allogeneic SCT for HD is generally performed in patients who experience disease relapse after receiving multiple lines of therapy or who have refractory disease and an available HLA-matched donor. The use of reduced-intensity conditioning regimens in these heavily pretreated patients allows for a graft-versus lymphoma effect with less regimen-related toxicity. Among 297 patients receiving HLA-matched SCT for HD between 1998 and 2006, the 3-year probabilities of survival were 39% ± 5% with myeloablative conditioning regimens and 38% ± 5% with reduced-intensity conditioning regimens. The corresponding probabilities of survival in the 138 recipients of unrelated donor HCT were 35% ± 7% and 46% ± 8%[15].

The EBMT collected data on 94 patients who received reduced intensity allogeneic SCT for HL. Nearly 50% had a failed previous autologous SCT. The 3-year overall, progression-free survival and transplant-related mortality rates were 45%, 35% and 18%, respectively. There appears to be evidence for a GVL effect in these studies[22] however, at present, allogeneic SCT for HL must be considered experimental.

Non-Hodgkin Lymphoma

Autologous SCT is currently recommended for the treatment of patients with diffuse large B cell who have relapsed and have achieved a second

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CR or good partial response following salvage chemotherapy. Lazarus et al for the Center for International Blood and Marrow Transplant Research (CIBMTR) has analyzed the results of patients reported to CIBMTR between 1990 and 2000. They compared autologous HCT (Bone marrow/ peripheral blood) outcome in 805 NHL patients aged ≥ 55 years to 1949 NHL patients < 55 years according to histology (indolent vs aggressive (follicular grade III, DLBC, immunoblastic lymphoma). For indolent histology, DFS and OS rates at 5 years favored younger patients, 37% vs 29% and 60% vs 54%, respectively. Transplant related mortality (TRM) was 8% vs 7% (p = ns). Similarly, for aggressive histology corresponding DFS and OS rates at 5 years were superior in younger patients 32% vs 19% and 47% vs 30%, respectively. TRM rates were significantly lower in younger patients (9% vs 15%). In aggressive histology group, apart from age, poor performance status, pretransplant chemoresistant disease, > 12 months interval between diagnosis and transplant and use of purging were associated with higher TRM. For the indolent histology patients significant co-variates for increased TRM included-use of BM rather than PB as the graft source, and TBI containing regimen.[23] Higher TRM has also been reported for patients > 55 years with aggressive histology in the European Group for Blood and Marrow transplantation (EBMT) data.[24]

Mantle cell NHL is an incurable B cell NHL with a median survival of 3 to 5 years. Results of CHOP (cyclophosphamide, adriamycin, vincristine and prednisolone) or similar regimens as front line therapy are poor, with a complete remission rates being achieved in < 25% of patients and responses lasting a median of 1 to 2 years. Recently with use of front line Rituximab (anti CD 20 monoclonal antibody) and hyper CVAD (hypercyclophosphamide, vincristine, adriamycin and dexamethasone) chemotherapy regimen higher CR rates were obtained. Use of ASCT in first remission resulted in the actuarial PFS and OS rates of 39% and 61%, respectively at median follow-up of six years in a recent study from MD Anderson Cancer Center. [25] Similar results have been reported by the Nordic lymphoma group (Geisler et al 2008); In this study, following rituximab based induction therapy and ASCT, among 60 patients at a median follow-up of 3.8 years, estimated overall, event-free and progression-free survival rates at six years were 70%, 56%, and 66%, respectively.[26] These results suggest that rituximab may be included both in induction therapy and in the preparatory regimens during the front line ASCT for mantle cell NHL.

Role of rituximab has also been demonstrated in relapsed/progressive aggressive CD20 + ve NHL by the Dutch-Belgium Hematology – Oncology Cooperative Group (HOVON) in a prospective randomized trial. In this study, patients were randomized to receive DHAP (dexamethasone, Ara-C and cisplatin)—VIM (etoposide, ifosfamide and methotrexate)—DHAP chemotherapy with or without rituximab. This was followed by ASCT. At a median follow-up of 24 months, there was a significant difference in failure free survival (50% vs 24%, p < .001), and progression-free survival (52% vs 31%, p <. 002) in favor of rituximab arm.[27]

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