CURRENT CLINICAL APPLICATIONS OF ADULT STEM CELLS

CANCER TREATMENTS

BRAIN TUMORS
Combination of high-dose chemotherapy with stem cell transplant from the patients themselves shows good response in treatment of brain tumors.

Reference:
“Patients with recurrent medulloblastoma had a significant improvement in long-term survival (median: 34 months) as compared with historical reports; two patients with glioblastoma survive beyond four years without progression.”

Reference:
“Review of HDCT and stem cell transplant for children with brain tumors. Studies demonstrating durable disease-free survival for a proportion of patients with recurrent malignant gliomas and medulloblastomas/PNET, as well as encouraging data in some of those patients with newly diagnosed brain tumors.”

Reference:

RETINOBLASTOMA
A localized retinoblastoma of the left eye in a 7-year-old girl, was treated by enucleation. She received no additional therapy. Four months later, metastases of retinoblastoma in the lymph nodes, bone and bone marrow were diagnosed. Relapse chemotherapy consisting of three courses of vincristine, cyclophosphamide, etoposide and carboplatin led to a second complete remission.
Subsequent high-dose chemotherapy with thiopeta, etoposide and carboplatin and autologous stem
cell transplantation with CD34-selected stem cells were successful, with no adverse effects. No radiotherapy was given and the girl remains in continuous second remission with a follow-up of more than 4 years.

Reference:
4. Hertzberg H et al.; “Recurrent disseminated retinoblastoma in a 7-year-old girl treated successfully by high-dose chemotherapy and CD34-selected autologous peripheral blood stem cell transplantation”; Bone Marrow Transplant 27(6), 653-655; March 2001

Patients with metastatic retinoblastoma have a poor prognosis with conventional treatments. This study used intensive conventional chemotherapy, high-dose chemotherapy, with autologous stem cell rescue, and radiation therapy. The treatment strategy was effective for all four patients with metastatic retinoblastoma that does not involve the central nervous system, surviving event free from 46-80 months after diagnosis.

Reference:

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OVARIAN CANCER

Report studying whether patients benefit more from autologous stem cell transplantation. “Some patients with ovarian cancer seem to have good outcomes after autotransplantation”.

Reference:

“Developing data suggest that this approach in both of these settings merit further evaluation for the treatment of epithelial ovarian carcinoma.” Used autologous, purified peripheral blood stem cells

Reference:

SOLID TUMORS

**Merkel cell carcinoma is a rare cutaneous tumor with neuroendocrine differentiation; there is no standard protocol for treatment of the metastatic disease. This study used high-dose chemotherapy and autologous peripheral blood stem cell transplantation to achieve complete remission that lasted for 6 months.

Reference:

**Patients with metastatic or locally advanced, unresectable soft tissue sarcoma are seldom curable, with 5-year survival rates of less than 10%. Used high-dose chemotherapy with autologous hematopoietic stem cell transplant; “a high survival rate was observed in HDCT-treated patients who were in complete remission after conventional chemotherapy.”

Reference:

“The prognosis of metastatic malignant mesenchymal tumors (MMT) remains poor.” Used high-dose chemotherapy with bone marrow or peripheral blood stem cell transplant. “A response exceeding 50% was observed in 6/18 patients (response rate 33%).”

Reference:
10. Lafay-Cousin L et al.; “High-dose thiotepa and hematopoietic stem cell transplantation in pediatric malignant mesenchymal tumors: a phase II study”; Bone Marrow Transplant 26, 627-632; Sept. 2000
High-dose chemotherapy followed by autologous haematopoietic rescue is widely used in the treatment of patients with paediatric malignancies. It is now well established as a major component for the treatment of children with metastatic neuroblastoma over the age of one at diagnosis. Its place for other tumours, such as metastatic Ewing and rhabdomyosarcoma, needs to be better established.”

**Reference:**


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3 Used for malignant solid tumors. Overall response rate 96%, complete clinical response rate 67%. Treatment described as safe, feasible, and active.

**Reference:**

12. Schilder, RJ et al.; “Phase I trial of multiple cycles of high-dose chemotherapy supported by autologous peripheral-blood stem cells”; J. Clin. Oncol. 17, 2198-2207; July 1999

**TESTICULAR CANCER**

“Thirty-seven (57%) of the 65 patients are continuously disease-free. Three additional patients are disease-free with subsequent surgery. High-dose chemotherapy was associated with significant morbidity but no treatment-related mortality. High-dose chemotherapy as initial salvage chemotherapy achieved impressive long-term survival with acceptable toxicity in patients with relapsed testicular cancer.”

**Reference:**


“High-dose chemotherapy with the transplantation of peripheral blood stem cells (PBSC) has been performed for the treatment of advanced testicular cancer patients.” “After mobilization of peripheral blood stem cells with G-CSF alone, sufficient amounts of MNC were obtained from testicular cancer patients who had undergone chemotherapy several times.”

**Reference:**


**MULTIPLE MYELOMA, LEUKEMIAS**

UMBILICAL CORD BLOOD EFFECTIVE AT TREATING ADULT BLOOD DISORDERS

A new report shows that umbilical cord blood can provide effective treatment of various blood disorders in adults. It had previously been assumed that there were too few stem cells in cord blood to treat adults, and only children were treated. The results of this study show that cord blood stem cells can proliferate extensively and provide sufficient numbers of cells for adult treatments.

**Reference:**


This retrospective study included 21 children with acute lymphoblastic leukaemia, 15 with acute myelogenous leukaemia and one each with chronic myelogenous leukaemia, refractory anaemia with myelodysplastic syndrome (MDS) and juvenile myelomonocytic leukaemia (JMML). These data confirm that HLA-mismatched, unrelated CBT is a feasible procedure to cure a significant proportion of children with leukaemia, especially if conducted in a favourable phase of the disease.

**Reference:**


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a lymphoproliferative disorder with abnormalities characteristic of malignant T cell lymphoma (angioimmunoblastic T cell lymphoma -- 65-year-old male patient with unusually aggressive AILD. At relapse, treatment with high dose chemotherapy shown to be successful. The patient is alive and diseaseafter APSCT. Considering the poor prognosis of the majority of patients with AILD, intensive

Reference:
17. Lindahl J; “High hemolysing AILD”; Leuk Res 25(3), 267-1
Patients given high blood stem cells rather than bone marrow results in higher rates of overall and diseaseand restores blood counts faster. Patients in whom the benefit of peripheral blood cells was most apparent were those with advanced hematologic cancer. Other studies have also shown that the use of blood cells is associated with fewer days of hospitalization and lower overall costs.

Reference:
. Bensinger WI; “Transplantation of bone marrow as compared with peripheral from HLAMedicine 344, 175-
ng stem cell transplantation. The authors note that “Stem cell transplantation has been successfully used to treat a wide variety of hematologic malignancies. New ul in overcoming tumor resistance.”

Reference:
Margolis J et al.
Semin. Oncol. 27, 524-
apapeutic approach in patients with acute myelocytic leukemia over 60 years of age.”

Reference:
Gorin NC et al.
Acut myelocytic leukaemia in patients over 60 years of age: importance of the source of stem -893; Sept 2000
“Infants with acute leukemia have a poor prognosis when treated with conventional chemotherapy.” -year overall survival 64%. “SCT is a valid option in the treatment of infants may overcome the high risk of relapse with conventional chemotherapy showing very reduced toxicity.”

Reference:
Marco F et al. -Dose -C -3261; Sept. 15 2000
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5 “Actuarial survival and disease-free survival at 34 months are 56% and 50% respectively, with 95% confidence interval (25-78%). These results suggest that nonmyeloablative conditioning significantly reduces transplant-related toxicity, thus making a second transplant feasible.”

Reference:
Review of autologous stem cell treatment strategies. “Controlled clinical trials have demonstrated a long-term disease-free survival of 40%-50% for patients treated with at least two courses of HIDAC. Other studies have demonstrated that postremission autologous bone marrow transplantation results in a disease-free survival equal to or better than conventional chemotherapy. However, autotransplantation with mobilized peripheral blood stem cells (PBSC) would now be preferred instead of autologous bone marrow, due to the shorter hematopoietic reconstitution period.”
Reference:
Study to evaluate high-dose melphalan followed by autologous stem-cell transplantation in patients with refractory multiple myeloma. High-dose therapy with melphalan 200 mg/m(2) is feasible with high response rates (58% overall) and an OS of 19 months in patients with refractory multiple myeloma.”

Reference:

BREAST CANCER
**The “data suggest that high-dose chemotherapy with hematopoietic stem cell rescue is safe and can be beneficial to patients with high-risk primary breast cancer and for those with metastatic breast cancer achieving complete response/no evidence of disease.”

Reference:
Stem cells in circulating blood can be isolated, expanded in number in culture, and provide better clinical results.

Reference:
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“The collection of small aliquots of bone marrow (BM), followed by ex vivo expansion for autologous transplantation may be less morbid, and more cost-effective, than typical BM or blood stem cell harvesting. Passive elimination of contaminating tumor cells during expansion could reduce reinoculation risks.” “It is feasible to perform autotransplants solely with BM cells grown ex vivo in perfusion bioreactors from a small aliquot.” this procedure could reduce the risk of tumor cell reinoculation with autotransplants and may be valuable in settings in which small stem cell doses are available, eg, cord blood transplants.”

Reference:
27. Stiff P et al.; “Autologous transplantation of ex vivo expanded bone marrow cells grown from small aliquots after high-dose chemotherapy for breast cancer”; Blood 95, 2169-2174; March 15, 2000
“This report is the first describing infusion of autologous MSCs with therapeutic intent. We found that autologous MSC infusion at the time of PBPC transplantation is feasible and safe. The observed rapid hematopoietic recovery suggests that MSC infusion after myeloablative therapy may have a positive impact on hematopoiesis and should be tested in randomized trials.”

Reference:

NEUROBLASTOMA
“According to initial reports, stage 4 neuroblastoma patients with amplification of the MYCN protooncogene developed progressive disease within 8 months. The prognosis for such patients, however, should now be reevaluated in light of recent results achieved with up-to-date combination chemotherapy. Not all patients with advanced neuroblastoma who have more than 10 copies of MYCN will die. The requisites for survival in such patients seem to be intensive induction
chemotherapy, effective surgery, irradiation, and the use of SCT” (stem cell transplant).

Reference:

NON-HODGKIN’S LYMPHOMA
“To determine differences in prognosis between primary progressive Hodgkin's disease (HD) and aggressive non-Hodgkin's lymphoma (NHL), we retrospectively analyzed patients with progressive lymphoma who were treated with different salvage chemotherapy regimens including high-dose chemotherapy (HDCT) followed by autologous stem-cell support (ASCT). There are striking differences in the prognosis of patients with progressive HD and aggressive NHL. The prognosis of progressive NHL patients is dismal. Most patients have rapidly progressive disease after salvage treatment and are, therefore, excluded from HDCT programs. In contrast, progressive HD patients can achieve long-term survival after HDCT.”

Reference:

“Patient achieved complete remission and has survived in continuous complete remission for more than 72 months to date. Marrow-ablative chemotherapy facilitated by PBSCT is thought to be useful as part of the primary therapy for patients with NHL who have poorer prognoses.”

Reference:
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“These results suggest first that ex vivo expansion of hematopoietic stem cells in patients with non-Hodgkin's lymphoma is feasible without incurring the parallel risk of amplifying tumor cells; second, that Flt3-L did not stimulate the growth of tumor cells while it clearly favored the growth of normal progenitors.”

Reference:

RENAAL CELL CARCINOMA
“Nonmyeloablative allogeneic stem-cell transplantation can induce sustained regression of metastatic renal-cell carcinoma in patients who have no response to conventional immunotherapy.”

Reference:

“The complete regression of metastatic disease, which has now been maintained for more than 1 year, is compatible with a graft-versus-tumor effect.”

Reference:

Updated June 25, 2001 Autoimmune Disease Treatments with Adult Stem Cells David A. Prentice 8

Autoimmune diseases
Multiple sclerosis, systemic lupus erythematosus, juvenile rheumatoid arthritis, rheumatoid arthritis

High-dose chemotherapy followed by autologous HSCT is feasible and safe, and can result in long-term improvement of disease activity in patients whose condition previously did not respond to conventional antirheumatic drugs or TNF blocking agents. The persistence of active disease in some patients may reflect the heterogeneity of the underlying disease process.

Reference:

Reference:

**Autoimmune diseases that are resistant to conventional treatment cause severe morbidity and even mortality. In the present study we demonstrate that complete remissions can be achieved in refractory polychondritis and systemic lupus erythematosus (SLE), even at advanced stage, with the use of autologous stem-cell transplantation (SCT). Remissions persisted after reconstitution of the immune system. In the treatment of advanced systemic sclerosis (SSc), stable disease may be achieved with autologous SCT.”

Reference:

Nineteen patients (14 female, 5 male) with severe autoimmune diseases were treated. Nine had a rheumatologic disorder (5 juvenile chronic arthritis, 1 rheumatoid arthritis, 1 systemic vasculitis, 1 Sjogren's syndrome, 1 Behc't disease), 4 a neurologic disorder (3 multiple sclerosis, 1 myasthenia), 3 a haematologic disease (2 pure red cell aplasia, 1 autoimmune thrombocytopenia), 2 had a gastrointestinal disease (1 Crohn's disease, 1 autoimmune enteropathy) and 1 had a multiple autoimmune disorder. There was no regimen-related toxicity and no opportunistic infections occurred. Ninety percent of the patients improved and/or had a complete remission after the procedure. Fifty percent of the subjects went into complete or partial remission after a median followup of 15 months. A non-myeloablative conditioning regimen was able to induce persistent remission in some patients with severe autoimmune diseases. There was no mortality or morbidity related to the procedure. The extent of remission remains to be established.

Reference:

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Study that supports the concept that patients with autoimmune cytopenias with severe resistant disease might be appropriate candidates for autologous stem cell transplantation.

Reference:

Patients (including several children) with severe lupus were treated with their own bone marrow stem cells, and had relief of symptoms, with little or no need for medication after treatment.

References
Numerous studies showing efficacy of adult stem cell transplants in the successful treatment of autoimmune diseases.

References:
Overview—juvenile rheumatoid arthritis; multiple sclerosis; rheumatoid arthritis; systemic lupus erythematosus.
43. Traynor A and Burt RK; “Haematopoietic stem cell transplantation for active systemic lupus erythematosus”; Rheumatology 38, 767-772; August 1999
44. Martini A et al.; “Marked and sustained improvement 2 years after autologous stem cell transplant in a girl with systemic lupus erythematosus”; Rheumatology 38, 773; August 1999

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Other Clinical Uses of Adult Stem Cells

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Stroke

A cultured stem cell line (originally derived from an adult tumor; a “teratocarcinoma”, sometimes called an “embryonal carcinoma” because it mimics some of the characteristics of embryonic cells.) The cultured and adapted cell line was used in successful treatment of several stroke patients.

Reference

Immunodeficiencies

Banked unrelated umbilical cord blood was used to reconstitute the immune system in 2 brothers with X-linked lymphoproliferative syndrome and 1 boy with X-linked hyperimmunoglobulin-M syndrome. Two years after transplantation, all 3 patients have normal immune systems. These reports support the wider use of banked partially matched cord blood for transplantation in primary immunodeficiencies.

Reference:
Eight children with severe immunodeficiencies treated by adult bone marrow stem cell transplants. Six of 8 showed relatively normal immune systems after 1 year.

Reference

Anemias

Allogeneic peripheral blood stem cell transplantation (PBSCT) is rarely applied for the treatment of severe aplastic anemia (SAA) because of questionable durability of engraftment and increased risk of graft versus host disease (GVHD). We performed allogeneic PBSCT in 3 SAA patients from their human leukocyte antigen (HLA)-identical siblings. In 2 cases, no graft failure has been observed, and a successful and complete hematological recovery was achieved and maintained for 28 and 25 months, respectively. In conclusion, PBSCT provides a quick and complete hematological recovery in SAA patients.
51. Gurman G et al.; “Allogeneic peripheral blood stem cell transplantation for severe aplastic anemia”; Ther Apher 5(1), 54-57; Feb. 2001
Results suggest that treatment can reverse progression of vasculopathy. Bone marrow transplantation may enable stenoses to heal and can substantially reduce cranial blood velocity, suggesting that allogeneic bone marrow transplantation may prevent infarction or brain damage.

Reference:
52. Steen RG et al.; “Improved cerebrovascular patency following therapy in patients with sickle cell disease: initial results in 4 patients who received HLA-identical hematopoietic stem cell allografts”; Ann Neurol 49(2), 222-229; Feb. 2001
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Able to treat severe anemias using transplants of adult bone marrow stem cells.

References
54. Kook H et al.; “Rubella-associated aplastic anemia treated by syngeneic stem cell transplantations”; Am. J. Hematol. 64, 303-305; August 2000
Possibility of using adult stem cell transplantation as cure for sickle cell anemia.

Reference
Successful treatment of a congenital thrombocytopenia using allogeneic peripheral blood stem cell transplantation.

Reference
56. Yesilipek et al.; “Peripheral stem cell transplantation in a child with amegakaryocytic thrombocytopenia”; Bone Marrow Transplant 26, 571-572; Sept. 2000

Chronic Viral Infection With Complications
57. Fujii N et al.; “Allogeneic peripheral blood stem cell transplantation for the treatment of chronic active epstein-barr virus infection”; Bone Marrow Transplant 26, 805-808; Oct. 2000

Cartilage and Bone Diseases
59. Biopsies removed from 57 patients considered for cartilage transplantation were grown. Explant cultures allowed cell number expansion. Fifty-four out of 57 biopsies grew cells. Fanning out of the cells began after 5-15 days in culture. Two passages later, cell numbers in the 10(7) range were achieved. Explants of articular chondrocytes cultured in vitro consistently yield monolayer cultures. The cells appear to revert to dedifferentiated chondrocytes, expressing a mesenchymal stem cell protein profile. Simultaneously, these cells regained their capacity to proliferate.

Reference:
60. Robinson D et al.; “Characteristics of cartilage biopsies used for autologous chondrocytes transplantation”; Cell Transplant 10(2), 203-208; 2001 Mar-Apr
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Corneal scarring
Fifteen of 16 eyes (93.7%) achieved epithelialization with a mean time to epithelial healing of 15.2
days. The only eye that failed to heal was subsequently diagnosed with total limbal stem cell deficiency. Visual acuity improved in five of nine (44%) sighted eyes. No patient experienced any major surgical or medical complication after the procedure. Amniotic membrane transplantation represents a safe and effective method to restore a stable corneal epithelium in eyes after primary surgical removal of band keratopathy arising from ocular causes.

Reference:
Amniotic membrane transplantation appears to be a safe and effective method of restoring a stable corneal epithelium for cases of partial limbal stem cell deficiency and can be considered as an alternative to limbal autograft or allograft. 17 eyes of 15 patients; All eyes exhibited a stable, intact corneal epithelial surface after a mean follow up period of 25.8 months with no eyes developing recurrent erosion or persistent epithelial defect. The mean time to re-epithelialisation was 22.8 days. Overall improvement in visual acuity was observed in 92.9% of 14 eyes with visual potential.

Reference:
An objective long term benefit from the procedure (improved Snellen acuity, reduced frequency of epithelial defects, reduced vascularisation, and scarring) was recorded for four out of five patients. Some subjective benefit was also reported. However, in no instances were donor cells recovered from the ocular surface at 3-5 years post-graft. Initial experiments to examine sensitivity indicated that any surviving donor cells must have constituted less than 2.5% of cells sampled. Limbal stem cell allotransplantation can provide long term benefits, as measured by objective criteria. However, such benefits do not necessarily correlate with survival of measurable numbers of donor cells on the ocular surface.

Reference:
**Adult stem cells from relatives used to restore vision
Nine living related donors, 8 recipients (10 eyes, various conditions). Restoration of corneal epithelium, opacification reduced, visual improvement; 2 initial failures.

Reference:
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Adult Stem Cells Used to Grow New Corneas
Researchers in the United States and Taiwan have used corneal adult stem cells to grow new corneas for patients with previously untreatable eye damage. Adult stem cells were taken from the patients themselves in 16 cases, or a family member for 4 other patients. The cells were then grown in culture before transplantation onto the damaged eyes. Sixteen of the 20 patients had improved vision. Dr. Ivan Schwab, professor of ophthalmology at the University of California at Davis Medical School, leader of the U.S. team, said “We think this is the beginning of a very exciting change in terms of how we manage surface disease of many kinds, not just in the eye.”

References
**Blood and Liver Disease**

**4-month-old girl received stem cell transplant after receiving living-related liver transplant from same donor (mother). Four months after stem cell transplant the patient was disease-free, complete donor chimerism in bone marrow and stable hepatic function without any immunosuppressive therapy.**

**Reference**

69. Matthes-Martin S et al.; “Successful stem cell transplantation following orthotopic liver transplantation from the same haploidentical family donor in a girl with hemophagocytic lymphohistiocytosis”; Blood 96, 3997-3999; Dec 1, 2000

**Primary amyloidosis is a plasma cell disorder in which deposits of amyloid protein cause progressive organ failure; most common target is the kidney, although heart, liver, and nervous tissue effects are also seen. Compared to standard treatments, high-dose chemotherapy with autologous peripheral blood stem cell transplantation is shown to be much more effective in the clinical condition of patients.**

**Reference:**

70. Sezer O et al.; “Novel approaches to the treatment of primary amyloidosis”; Exper Opin. Investig. Drugs 9, 2343-2350; Oct 2000

**Gene Therapy**

*First successful trial of human therapy, re-injecting the infants’ own bone marrow stem cells containing a normal copy of the gene that they lacked.*

**Reference:**

71. Cavazzana-Calvo M et al.; “Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease”; Science 288, 669-672; April 28, 2000

**Heart Damage**

**First successful human stem cell treatment for heart disease uses adult stem cells**

The first reports of successful treatment for heart disease using the patient’s own adult muscle stem cells are encouraging news regarding therapy after heart attack. French physicians implanted skeletal muscle stem cells back into the patient; the encouraging result after eight months’ follow-up underlines the potential of this new approach using adult stem cells. Further clinical trials are now underway in Europe and the U.S. for other patients with heart disease. No embryonic stem cells have ever been reported to be used in human trials.

A review of potential heart treatments notes that cell transplantation is a potential therapeutic approach for patients with chronic heart failure. Experimental transplantation of muscle cells showed that the grafted cells can functionally integrate with and augment the function of the recipient heart. The scientists note that skeletal stem cells are abundant and can be grafted successfully into the animal’s own heart even after genetic manipulation in vitro.

**References:**


**General References Related to Clinical Uses of Adult Stem Cells**
Cells

Recent studies have revealed that much of this remarkable developmental potential of embryonic stem cells is retained by small populations of cells within most tissues in the adult. Intercellular signals that control the proliferation, differentiation and survival of stem cells are being identified and include a diverse array of growth factors, cytokines and cell adhesion molecules. Intracellular mechanisms that regulate stem cell fate are also emerging and include established second messenger pathways, novel transcription factors and telomerase. The possibility that a decline in the numbers or plasticity of stem cell populations contributes to aging and age-related disease is suggested by recent findings. The remarkable plasticity of stem cells suggests that endogenous or transplanted stem cells can be 'tweaked' in ways that will allow them to replace lost or dysfunctional cell populations in diseases ranging from neurodegenerative and hematopoietic disorders to diabetes and cardiovascular disease.

Reference:
77. Rao MS and Mattson MP; “Stem cells and aging: expanding the possibilities”; Mech Ageing Dev 122(7), 713-734; May 31, 2001

Mesenchymal stem cells (MSCs) are the first non-hematopoietic progenitors to be isolated from the bone marrow and extensively characterized. In addition to their ability to support hematopoiesis, MSCs can differentiate into osteocytes, chondrocytes, tenocytes, adipocytes and smooth muscle cells. This article will review our current understanding of bone marrow stroma and MSCs and their potential therapeutic role in the setting of hematopoietic stem cell transplantation.

Reference:
78. Koc ON and Lazarus HM; “Mesenchymal stem cells: heading into the clinic”; Bone Marrow Transplant 27(3), 235-239; Feb. 2001

It appears that basal haematopoiesis is maintained throughout life, yet, the capacity to cope with haematological stress is decreased in advanced age. In principle, stem cells derived from aged donors can be used for autologous transplantation, when needed to recover basic haematopoiesis. Current methods for expansion and maintenance of stem cells in vitro enable examination of stem cell potential for long-term expansion and function. Understanding of the mechanisms underling these processes will enable the fidelity of stem cell expansion and maintenance of their potential for long-term function.

Reference:
79. Globerson A; “Haematopoietic stem cell ageing”; Novartis Found Symp 235, 85-96; discussion 96-100, 101-4; 2001

This study examined whether cryopreservation following expansion has a detrimental effect on the ability of cells to engraft, using the NOD-SCID mouse model. Cord blood (CB) CD34(+) cells were incubated for 7 days with stem cell factor (SCF), flt-3 ligand (FL), and megakaryocyte growth and development factor (MGDF). Expanded CD34(+) cells were transplanted into NOD-SCID mice either fresh or following cryopreservation and thawing. Thawed expanded CD34(+) cells had significantly higher SCID Engrafting Potential (SEP) than freshly expanded CD34(+) cells. Results suggest that prior cryopreservation does not prevent expanded cells engrafting in NOD-SCID mice.

Reference:
80. Rice AM et al.; “Prior cryopreservation of ex vivo-expanded cord blood cells is not detrimental to engraftment as measured in the nod-scid mouse model”; J Hematother Stem Cell Res 0(1), 157-165; Feb. 2001

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Represents the first case of successful transplantation of PBSC, cryopreserved twice and purged after cryopreservation. Indicates that purging procedures can successfully be carried out with cryopreserved cell material and that purified CD34+ cells can be cryopreserved a second time before transplantation, without affecting their hematopoietic capacity.

Reference:
81. Humpe A et al.; “Successful transplantation and engraftment of peripheral blood stem cells after cryopreservation, positive and negative purging procedures, and a second cryopreservation cycle”; Ann Hematol 80(2), 109-112; Feb. 2001

General review of growth factors using in hematopoietic stem cell transplants. Recently, EPO has been shown to significantly accelerate hematopoietic reconstitution after peripheral blood stem cell transplantation (PBSCT) resulting in reduced infection rates. Both, G-CSF and GM-CSF have been shown, in numerous trials, to shorten the period of chemotherapy-induced neutropenia, with reduction in attendant morbidity and to mobilize PBSC. In addition, administration of both cytokines after PBSCT significantly reduced the use of antibiotics and duration of hospitalization suggesting an economic benefit.

Reference:

Review of increasing use of umbilical cord blood for transplants; banking of cells, etc.

Reference:
83. Surbek DV and Holzgreve W; “Fetal cells from cord blood as stem cell source: current status and possible implications in gynaecologic oncology”; Eur J Gynaecol Oncol 22(1), 6-12; 2001

Mobilized peripheral blood progenitor cells (PBSC) are increasingly being used instead of bone marrow for allogeneic transplantation. This article gives a concise and clinically oriented overview on current results and perspectives of allogeneic peripheral blood stem cell transplantation, with particular focus on reconstitution of hematopoiesis and the immune system, graft-versus-host disease, graft-versus-leukemia effects, intensity-reduced conditioning, and graft engineering.

Reference:

**Previously reported human stem cell frequencies and their in vivo self-renewal activity have been markedly underestimated.

Reference
85. Cashman JD and Eaves CJ; “High marrow seeding efficiency of human lymphomyeloid repopulating cells in irradiated NOD/SCID mice”; Blood 96, 3979-3981; Dec. 1 2000

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**Evidence for expansion protocol to maintain cord blood stem cells for clinical applications.

Reference

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**Study notes that disease recurrence is lower after peripheral blood stem cell transplants than with bone marrow; “The general opinion is that peripheral blood grafts are indicated
for patients with advanced disease, whereas for patients with early-phase disease the two sources may give comparable results.”

Reference:
87. Bacigalupo A et al.; “Bone marrow or peripheral blood as a source of stem cells for allogeneic transplants”; Curr. Opin. Hematol. 7, 343-347; Nov 2000
**Quality of life for 415 adult patients who received hematopoietic stem cell transplants was measured; typical patients can look forward to a quality of life after transplantation that is broadly comparable to that of the normal population.

Reference:
**Review of techniques to mobilize hematopoietic bone marrow stem cells into peripheral blood.

Reference:
89. Fu S, Liesveld J; “Mobilization of hematopoietic stem cells”; Blood Rev 14, 205-218; Dec 2000
**Technique to expand numbers of human hematopoietic stem cells in culture. Cells from umbilical cord blood and adult patient peripheral blood were expanded with 2 factors, flt-3 ligand and thrombopoietin/c-mpl ligand, and maintained for prolonged periods (up to 16 weeks), and sufficient numbers were generated for adult transplantation.

Reference:
90. Gilmore GL et al.; “Ex vivo expansion of human umbilical cord blood and peripheral blood CD34(+) hematopoietic stem cells”; Exp. Hematol. 28, 1297-1305; Nov 1 2000
**Review of records for cord blood stem cell transplants. Results showed survival comparable to bone marrow transplants. “This large registry study confirms the potential benefit of using umbilical cord blood hematopoietic stem cells for allogeneic transplants.”

Reference:
Review of potentials for stem cell transplantation.

Reference
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Improved technique to quickly expand numbers of cord blood cells in culture, allowing adequate numbers for treatment of adult patients.

Reference:
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“Can expand primitive hematopoietic progenitors from Cord Blood and Peripheral Blood and expanded cells retain the capacity for myeloid and lymphoid differentiation. These findings emphasize the importance of assessing multi-lineage differentiation capacity following ex-vivo expansion.

Reference:
95. Lewis ID, Verfaillie CM; “Multi-lineage expansion potential of primitive hematopoietic progenitors. Superiority of umbilical cord blood compared to mobilized peripheral blood”; Exp. Hematol. 28, 1087-1095; Sept. 1, 2000
Generating a high frequency of clonally repopulating stem cells from blood.

Reference


Autologous (same patient) circulating blood stem cell transplants show faster recovery, less transplant problems, shorter hospital stay, and reduced cost compared to bone marrow transplants.

Reference

Allogeneic peripheral blood stem cell transplants as good or better than bone marrow

Reference

Reviews of current protocols allowing better methods for collection of stem cells from peripheral blood.

References


103. Kessinger A, Sharp JG; “Mobilization of blood stem cells”; Stem Cells 16 Suppl 1, 139-143; 1998
Review of cord blood stem cell transplants

Reference

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