LATE COMPLICATIONS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

COMPLICAÇÕES TARDIAS DO TRANSPLANTE DE CÉLULAS-TRONCO HEMATOPOÉTICAS

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ABSTRACT: Significant advances in hematopoietic stem cell transplantation (HSCT) has resulted in a large cohort of patients surviving more than 20 years after transplantation for hematological and malignant disorders. The increased number of long-term survivors has provided an unique opportunity to study the late effects of the HSCT. This review describes the late complications of HSCT related to the conditioning regimen, recurrence of primary malignancy and transplant-related toxicity with an emphasis on diagnosis and treatment of chronic graft-versus-host disease.

UNITERMS: Hematopoietic Stem Cell Transplantation. Bone Marrow Transplantation. Graft VS Host Disease. Toxicity. Follow-Up Studies.

Hematopoietic stem cell transplantation (HSCT) has evolved into a modern therapeutic modality for a variety of life-threatening hematologic, neoplastic, immunologic and genetic diseases. Around the world thousands of patients are surviving more than five years after HSCT resulting in an increase interest in long-term outcome and late transplant complications[(1)].

Late complications after HSCT include **transplant-related toxicity** (i.e., chronic graft-versus host disease occuring after allogeneic HSCT and immunodeficiency); **conditioning-related toxicity** (several organ toxicity and secondary malignancy) and **relapse of primary malignancy** (Table I). The time to develop these late complications in relation to the transplant is shown in Figure 1 and the interactions of these complications and their therapies is displayed in Figure 2.

1. CHRONIC GRAFT-VERSUS-HOST DISEASE (cGVHD)

Chronic graft-versus-host disease (cGVHD) is an immunologic disorder initiated by immunocompetent donor lymphocytes recognizing and reacting against recipient (patient=host) antigens on a variety of tissues. Chronic GVHD is a clinical-pathological entity with features similar to autoimmune diseases such as scleroderma, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis and primary biliary cirrhosis[(2,3)]. During the early phase of the disease, dermal and gastrointestinal manifestations are similar to acute GVHD. Chronic GVHD is usually diagnosed after 3 months of HSCT, and may involve several organs. HLA-disparity, history for acute GVHD and older patient age are factors associated with an

Table I - Classification of late complications of hematopoietic stem cell transplantation (HSCT)

Transplant-related:
Chronic graft-versus-host disease (GVHD)
– Limited
– Extensive
Immunodeficiency and infections
Regimen-related
– Cataracts
– Neurological complications
– Endocrine and growth abnormalities
– Gonadal dysfunction
– Gynecologic and obstetric complications
– Secondary malignancies
Others
– Avascular necrosis
– Osteoporosis/osteopenia
Relapse of malignancy

increased risk for the development of cGVHD[4-6]. Extensive cGVHD was observed in 33% of HLA-identical sibling transplantation and in 80% of unrelated or mismatched transplant recipients[6]. Platelets below 100,000/cu.mm at diagnosis of cGVHD and progressive onset (acute GVHD evolving to cGVHD) are factors associated with poor survival.

Shullman and Sullivan defined the clinical-pathological classification of cGVHD in two forms: **limited and extensive** (Table II)[2,3]. **Limited disease** was defined as signs and symptoms involving one organ with biopsy revealing characteristic histopathological findings. **Extensive disease** was defined as signs and symptoms involving more than one organ with at least one biopsy showing characteristics of either generalized or localized skin involvement and/or 1) hepatic dysfunction due to cGVHD plus liver histology with chronic aggressive hepatitis, 2) eye involvement with decreased Schirmer's test (less than 5 mm), or 3) involvement of minor salivary glands with Sjogren's syndrome and 4) involvement of any other target organ[3,7].

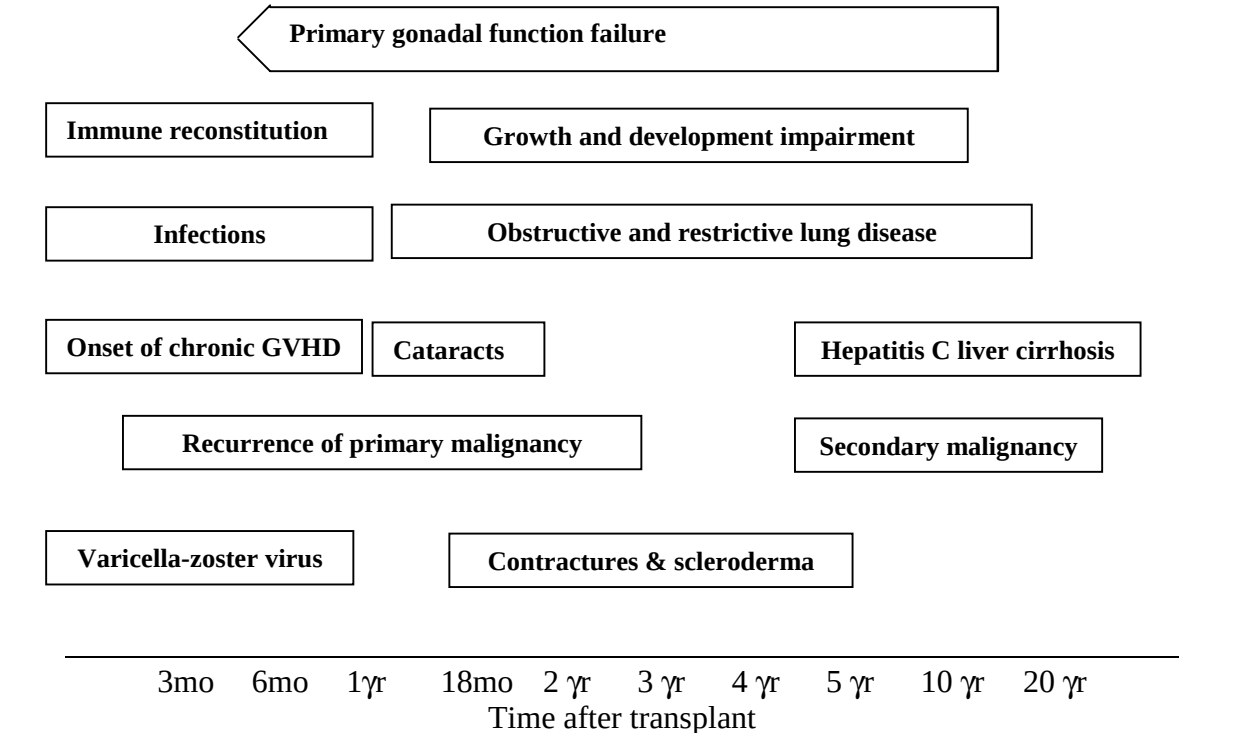

Figure 1: Chronology of late complications after hematopoietic stem cell transplantation (HSCT). mo - months. γr year

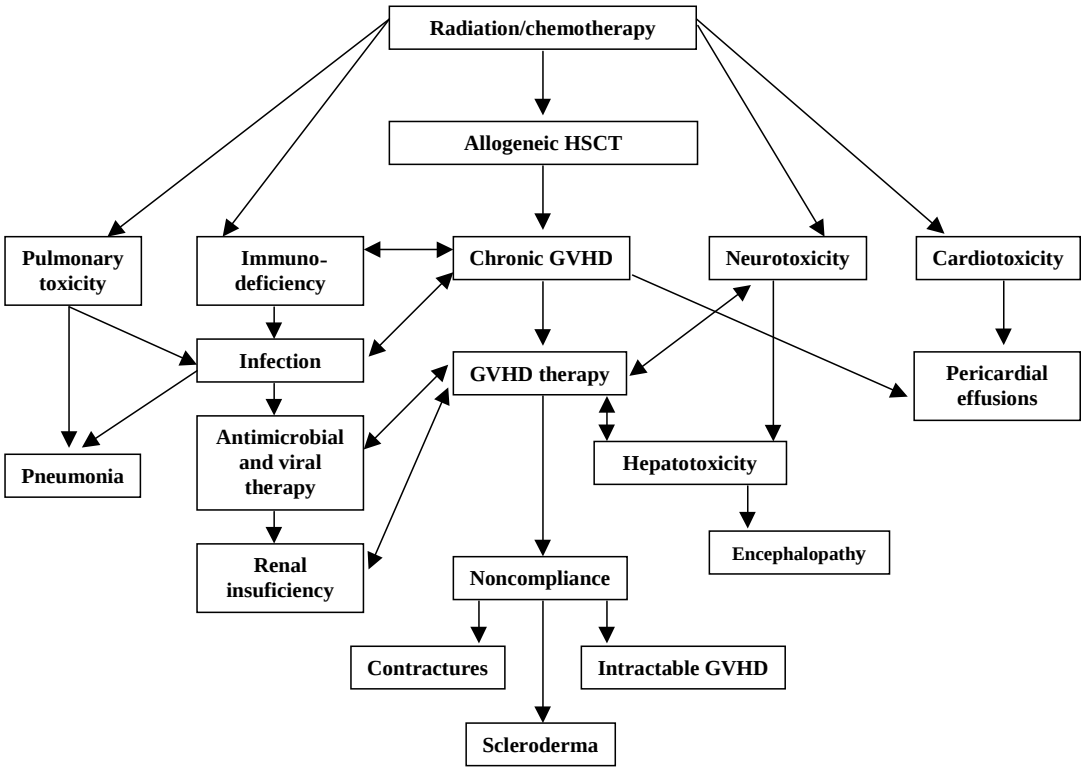

Figure 2: Interactions of late complications of HSCT and therapies.

In addition to clinical performance score (Table III), weight loss (≥15%) is also a feature of clinical extensive cGVHD even when only one organ is affected by the disease. Early detection and aggressive treatment of cGHVD (see below) appears to have decreased the incidence of contractures and other manifestation of cGVHD after bone marrow transplantation. The nature and course of cGVHD after periphearal blood stem cell transplant is still early to assess.

As shown in Table IV, cGVHD is classified in three subgroups according to the type of onset: **Progressive onset** of cGVHD emerges as a direct continuation of acute GVHD and it is associated with high mortality rate; **quiescent onset** of cGVHD occurs after complete resolution of the manifestation of acute GVHD and it is associated with an intermediate prognosis; **de novo** onset of cGVHD occurs in patients without a prior history of acute GVHD and it is associated with a better prognosis compared to progressive onset and *de novo* onset of extensive cGVHD[3,4,7,8].

Manifestations of cGVHD varies according to the organ involved by the disease (Figure 3). Signs and symptoms of cGVHD are described in details below.

1.1. Organ involvement in chronic GVHD

1.1.1. Skin

Skin manifestations include erythema, dryness, pruritis, pigmentary changes, mottling, plaques, exfoliation (ichtiosis), maculo-papular or urticarial rash. In some patients clinical features may resemble morphea and occasional nodules can be seen. In others, scleroderma (indurated or hide-bound) may lead to decreased range of motion and joint contractures. Skin biopsy shows characteristic pathological findings[9].

1.1.2. Nails/Hair

Patients may have ridging, onichodistrophy and onycholysis in nails. Partial or scarring alopecia and premature graying may be observed on scalp hair.

Table II - Classification of chronic GVHD

Limited
Signs or symptoms involving one organ system with at least one biopsy showing characteristic pathological findings of GVHD (may be in the same or in a different organ system) Either or both – Localized skin involvement by histology – Hepatic dysfunction due to chronic GVHD
Extensive
Signs or symptoms of cGVHD involving more than one organ systems with at least one biopsy showing characteristic pathological findings of GVHD Either – Generalized skin involvement by histology – Localized skin involvement by histology and/or hepatic dysfunction due to chronic GVHD Plus – Liver biopsy showing chronic aggressive hepatitis, bridging necrosis or cirrhosis, or – Involvement of eye (Schirmer's test with less than 5 mm wetting), or – Involvement of minor salivary glands or oral mucosa by labial biopsy, or – Involvement of any other target organ
NOTE: Patients with poor clinical performance (<60% Karnofsky score) and at least one organ involvement are classified as clinical extensive cGVHD .

1.1.3. Mouth

The development of new oral pain or dryness after day 80 post-transplant should alert the physician for the development of cGVHD because by that time, chemo-radiotherapy-induced oral mucositis should have resolved. Signs and symptoms of oral involvement by cGVHD include dryness, burning, gingivitis, mucositis, striae, atrophy, erythema, mucose atrophy, lichenoid changes and ulcers. Atrophy, pigmentary and mottled changes on the lip are also manifestation of cGVHD. Tooth decay and tooth loss usually signs of ongoing cGVHD. Lip biopsy shows characteristic pathological findings[10].

1.1.4. Eyes

Ocular symptoms are the results of ocular sicca and include: dryness, burning, blurring, gritty eyes, photophobia and pain. Schirmer's test shows a mean value in both eyes of <5 mm at 5 minutes or <10 mm with signs of keratitis at slit light exam[11]. Minimal edema and erythema of eyelids, decrease or premature eyelashes are also manifestation of ocular cGVHD.

1.1.5. Vagina/Vulva

Vaginal dryness, dyspareunia, stricture formation, stenosis, erythema, atrophy and/or lichenoid changes not secondary to ovarian failure are also present in patients with cGVHD involving the vulvar and vagina[12]. Vagina or vulvar biopsy to confirm the diagnosis of cGVHD and cultures to rule out infection are necessary. Follicular stimulant hormone and stradiol levels are necessary to rule out gonadal failure as the cause of the gynecological findings.

1.1.6. Liver

Abnormal liver function tests mainly show cholestatic features. Other causes of elevated liver function tests must be ruled out. Usually alkaline phosphatase is >3x upper normal limits with/without elevation of SGOT >4x upper normal values and/or elevated total serum bilirubin >2.5 mg/dl. In the absence of cGVHD involving other organs, liver biopsy is required to confirm the diagnosis[13,14].

1.1.7. Lungs

Obstructive lung defect with forced expired volume (FEV1)/forced vital capacity (FVC) <70% or an FEV1 <80% of predicted or a decrease of FEV1/FVC by >15% from previous pulmonary tests indicates bronchiolitis obliterans. High resolution CAT scan usually shows air trapping. Suspected bronchiolitis obliterans requires negative microbiological tests in bronchoalveolar lavage. Transbronchial biopsy is required to confirm the diagnosis of bronchiolitis obliterans in the absence of cGVHD involving other organs[15-17].

1.1.8. Gastrointestinal System

Patients may develop dysphagia or odynophagia with radiological evidence of esophageal stenosis (on barium swallow) or web formation on endoscopy and occasional dysmotility[18,19]. Anorexia, nausea, vomiting, weight loss and diarrhea could be the presenting symptoms. Endoscopic biopsy showing characteristic pathological findings are necessary to confirm the diagnosis of cGVHD. Weight loss of more than 15% body weight not related to other causes is usually a sign of extensive chronic GVHD but it is not always associated with GI involvement . Malabsorption syndrome is usually present in these patients[20].

Table III - Performance scores and scales used to evaluate complications of HSCT

KARNOFSKY SCORE SYSTEM (adults)	
100%	Normal; no symptoms or signs of active disease
90%	Able to carry on normal activity; minor signs or symptoms of active disease
80%	Normal activity with effort
70%	Unable to do active work; cares for self
60%	Requires occasional assistance
50%	Requires considerable assistance and frequent medical care
40%	Disabled; needs special care
30%	Hospitalized; death not imminent
20%	Hospitalized; critical condition
10%	Moribund
0%	Dead
LANSKY PLAY-PERFORMANCE SCALE (children)	
The Play-Performance Scale for children is designed to provide a standardized measure of the performance status of the child with cancer and is appropriate for use with children aged 1 to 16. Have parent select description which best describes child's play during the past week (average of good and bad days)	
100%	Fully active, normal
90%	Minor restrictions in physically strenuous activity
80%	Active, but tires more quickly
70%	Both greater restriction of and less time spent in play activity
60%	Up and around, but minimal active play; keeps busy with quieter activities
50%	Gets dressed but lies around much of the day, no active play, able to participate in all play and activities
40%	Mostly in bed; participates in quiet activities
30%	In bed; needs assistance even for quiet play
20%	Often sleeping; play entirely limited to very passive activities
10%	No play; does not get out of bed
0%	Unresponsive

1.1.9. Musculoskeletal

Patients may have arthralgias involving the large proximal girdle joints although smaller joints may also be affected. Contractures are usually secondary to scleroderma or fasciitis. Proximal muscle weakness with occasional cramping and elevation of CPK and/or aldolase can be seen. Electromyographic findings are consistent with myositis[21,22]. Biopsy is needed to confirm diagnosis if other organs are not involved. Histological findings include necrotic fibers, interstitial inflammation and IgG deposits on immunoflurescence staining. Myasthenia gravis has been reported in few cases[23].

1.1.10. Fasciae

Eosinophilic or sclerosing fasciitis characterized by stiffness with restriction of movement due to in-

Table IV - Classification of chronic GVHD according to the type of onset of the disease
Progressive*   – Onset of cGVHD as a direct continuation of acute GVHD (i.e., persistent signs and symptoms of acute GVHD at 3 months after HSCT)
Quiescent   – Onset of cGVHD after complete resolution of acute GVHD manifestation (requiring <1.0 mg/kg of steroids)
De novo*   – Onset of cGVHD with no prior history of acute GVHD
*Worst prognosis. **Best prognosis

flammation and fibrosis involving the sheaths of tendons can be seen in cGVHD[24]. Occasionally, swelling, erythema and pain may affect the wrists, forearms and hands, followed by ankles, legs and feet in a decreasing order. Induration may be present on palpation and cramping is frequent. Patients are unable to extend the wrists without flexing the fingers or the elbows.

1.1.11 Hematological Findings

Thrombocytopenia (usually >20.000/cu.mm) is more often seen in patients with progressive onset of cGVHD. Thrombocytopenia is a poor prognosis factor if present at the time of diagnosis of extensive cGVHD[25-27]. Eosinophilia is also present in some patients with cGVHD.

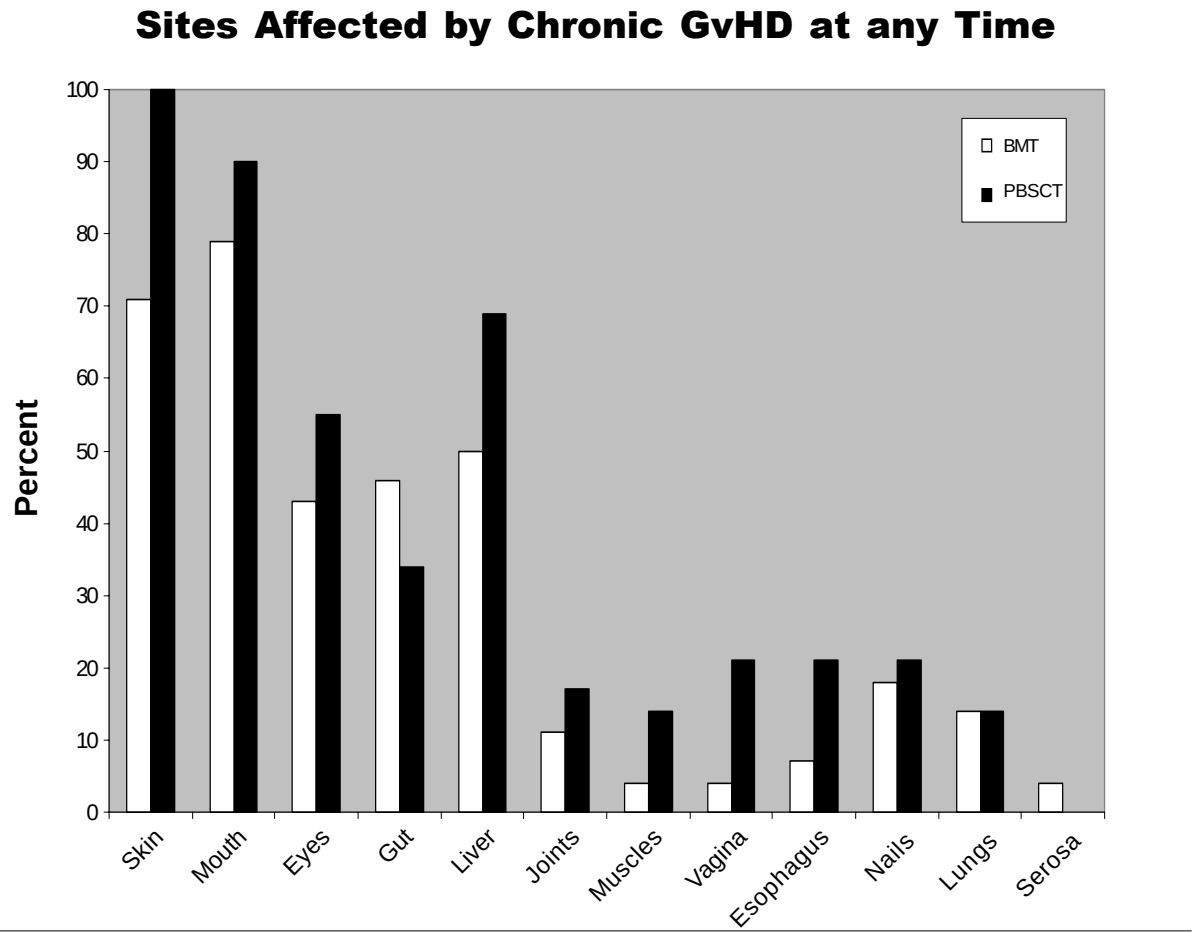

Figure 3: Sites involved by chronic graft-versus-host-disease (cGVHD) after either peripheral blood stem cell transplant (PBSCT) or bone marrow transplant (BMT) in a prospective randomized phase III study, in patients transplanted in Seattle.

1.1.12 Immunodeficiency

Recurrent infections, especially sinusitis, are often manifestation of ongoing extensive cGVHD [28]. Hypogammaglobulinemia is usually present involving IgG2 and IgG4 subclasses and IgA, including salivary IgA. Occasionally hypergammaglobulinemia is present and in few cases M-spike has been reported. Patients with cGVHD with a history of recurrent sinusitis benefit from surgical drainage and windows placement to prevent subsequent and more serious infections.

1.2. Screening Studies for cGVHD

The median day of diagnosis of cGVHD in HLA-identical sibling recipients is 201 days after transplant; in contrast, HLA–non identical related and unrelated donor marrow recipients have earlier diagnosis and onset of cGVHD. Fewer patients may develop cGVHD after day +500. Screening test to detect early cGVHD between 80-100 days after allogeneic HSCT has been used for monitoring patients in long-term follow-up[29]. Screening studies for cGVHD are summarized in Table V.

Table V - Screening tests for chronic GVHD

– Skin and oral examination
– Skin biopsy
– Lip biopsy (if clinically indicated)
– Schirmer's tear test and slit lamp examination of eyes
– Liver function tests
– Pulmonary function tests
– Gynecological evaluation
– Weight, muscle/fat store measurement
– Karnofsky score or Lansky play index (Table III)

1.3. Diagnosis of cGVHD

Concomitant pathologies including infections and drug reactions need to be ruled out in patients suspected to have manifestations of cGVHD. Histological documentation of cGVHD by skin or other tissue biopsy is necessary for diagnosis[2,30]. Pathologic findings in the skin include localized epidermal atrophy and dense focal dermal fibrosis in the absence of significant inflammation. In other patients, more generalized histological manifestations are seen with inflammation in eccrine coils and pilar units which leads to fibrosis throughout the dermis. Liver biopsy reveals bile duct damage similar to the histopathologic findings of primary biliary cirrhosis[32].

1.4. Prevention of cGVHD

Although treatment with cyclosporine (CSP) significantly reduces the incidence of acute GVHD, the rate of cGVHD has remained unchanged in the last two decades. No difference was observed in the cumulative incidence of cGVHD in transplant recipients receiving FK506/methotrexate (MTX) prophylaxis compared to those given CSP/MTX prophylaxis (reviewed in 7a). Results of a phase III double-blind randomized trial with thalidomide for prophylaxis of high-risk cGVHD were disappointing[66]. In another recent prospective randomized phase III study for prophylaxis of extensive cGVHD in Seattle, CSP given for 24 months after transplant did not reduce the rate of cGVHD compared to patients receiving CSP prophylaxis for 6 months.

1.5. Treatment of cGVHD

1.5.1 Primary Treatment

Initial attempts of treating cGVHD were largely unsuccessful. In a prospective placebo-controlled study, prednisone and azathioprine treatment improved response and decreased disability of cGVHD compared to prednisone alone[26]. However, due to an increased number of infectious complications in patients treated with prednisone and azathioprine, survival was as low as 47% compared to 61% in patients treated with prednisone alone. This analysis included only patients with platelet counts greater than 100.000/cu.mm. Thirty-eight "high-risk" patients were placed on prednisone alone.The non-relapse mortality for these patients was 26% and the survival rate was 58%[26].

Oral CSP in patients with cGVHD with thrombocytopenia was also studied[31]. Renal toxicity was modest and survival improved while infections decreased with this clinical trial. Average duration of therapy was 1 to 2 years. Again, in these high risk group of patients, infection remained a frequent cause of morbidity and contributed to transplant-related mortality in patients with high-risk cGVHD[31].

In a prospective randomized study, alternating day CSP and prednisone therapy for high-risk cGVHD (platelets less than 100.000/cu.mm) appeared to produce a higher response rate compared to CSP

alone[31-33]. However, the 3-year actuarial survival for this group of patients remained low at 48% and the non-relapse mortality rate was 35% with the combination therapy[32]. The survival and the non-relapse mortality rates were not significantly different between the two arms of the study (CSP/PRED versus CSP). The 3-year survival was 48% in patients who received primary therapy and infections appeared to be reduced in the long-term survivors[32].

In another a prospective, randomized placebo-control trial, comparing thalidomide or placebo in combination with PRED/CSP (or FK-506) for treatment of high risk cGVHD (i.e., progressive onset or platelets less than 100.000/cu.mm) the 3-year survival was similar at approximately 50% in the two arms of the study. Thalidomide intolerance was high in this study leading to premature discontinuation of the drug in the majority of the patients. There was a suggestion that thalidomide in combination with PDN/CSA (or FK-506) might induce more tolerance [64].

1.5.2 Secondary Treatment

Corticosteroid dependent or resistant cGVHD is extremely difficult to manage and is associated with high morbidity and mortality. Criteria of response to therapy and definition of failure are summarized below (Section 1.5.4., Table VII). Numerous small series and case reports describing the results of different therapies in cGVHD have been reported or are under investigation including azathioprine, alternating-day steroids with CSA or FK-506 (tacrolimus, Prograf), psoralem and ultraviolet light (PUVA), thalidomide, clofazimine, retinoic acid derivatives, ursodeoxycholic acid, mycophelolic mofetil (MMF), rapamycin, monoclonal antibodies and, more recently, extracorporeal photoimmunotherapy (ECP) and receptor antagonist agents against tumor necrosis factor-alpha (Table VI) [32-42,63].

Azathioprine, alternating CSP/prednisone and thalidomide given as secondary therapy in patients with

Table VI - Medications used in chronic graft-versus-host disease

Generic Name	Brand name in USA	Dose			Major Side Effects
		Oral		I.V.	
Cyclosporine	Sandimmune	6.25 mg/kg	BID	1.5 mg /kg BID	Nephrotoxicity (creatinine & BUN elevation), hypomagnesemia, hepatotoxicity (rise in bilirubin, ALT/AST); neurotoxicity (tremor, paresthesias, headache, seizures), hirsutism, hemolytic uremic syndrome, hypertension, hyperglycemia, gum hyperthrophy, anxiety, depression, fatigue.
	Neoral	5.0 mg/kg	BID	Not available	
Tacrolimus (FK-506)	Prograf	0.15-0.30 mg/kg/day	BID	0.05-0.10 mg/kg/day (continuous infusion)	Nephrotoxicity (creatinine & BUN elevation), hepatotoxicity (rise in ALT/AST and in bilirubin); neurotoxicity (seizures, agitation neuropathy, paresthesias), headache, nausea, vomiting, skin rash, hyperkalemia, hyperglycemia.
Mycophenolate Mofetil (MMF)	Cell Cept	1 gm	BID	Not available	Vomiting, diarrhea, neutropenia, anemia.
Rapamycin	Rapamune Sirolimus	2 mg/day		Not available	Neutropenia, thrombocytopenia, rise in cholesterol & triglycerides.
Thalidomide	Thalidomid	200 - 400 mg/day		Not available	Birth defects, sedation, constipation, neutropenia, peripheral neuropathy, weakness, dysesthesias, clumsiness, sleepiness

BUN: bound urea nitrogen, AST: aspartate transaminase, ALT: alanine transaminase

cGVHD have resulted in similar survival rates [34-35]. A larger thalidomide clinical trial for salvage therapy of cGVHD has been reported [34]. Response has been observed in 20% of patients treated with thalidomide[35,36]. Use of PUVA (psoralen plus UV light) has been shown to be beneficial in patients with refractory cutaneous cGVHD[40-42]. In patients with isolated skin involvement without scleroderma PUVA may be considered as the first line therapy. Some patients with morphea have been reported to benefit from PUVA alone. Randomized prospective trials with PUVA for cGVHD have not been reported.

In spite of several numbers of therapies reported as phase I-II studies, little advances have been made in the last decade for patients with high-risk cGVHD[32,37-39]. Challenges in clinical trials of cGVHD include the poorly understood pathophysiology of the disease, absence of a validated staging system, difficulty in measuring changes, indirect management of patient care, insurance coverage, and low enrollment in phase III clinical trials. Collaborative efforts are under way to validate a new staging system for assessing cGVHD response and outcome.

1.5.3 Supportive Care

Supportive or adjuvant therapy of cGVHD*:* Topical steroids can be successful for treatment of oral, vaginal/vulvar, or penile lesions secondary to cGVHD. Patients with ocular sicca may respond to retinoic acid and oral sicca may respond to pilocarpine. In addition to artificial tears, patients with severe ocular sicca requires ligation of lacrimal puncti. Muscular cramps and carpal spasm may be relieved by clonazepam, klonipin or beclofen. In patients with liver function abnormalities and refractory hepatic chronic GVHD, bile acid replacement therapy with ursodeoxycholic acid (UDCA or Ursodiol) has been shown to be beneficial.

Osteoporosis or osteopenia prevention: To decrease some of the toxicity of long-term corticosteroids treatment, patients are recommended to receive estrogen replacement (women), meet the daily requirements of calcium (1500 mg/d in diet or supplement) and daily vitamin-D requirments(800 IU/d in diet or supplement), weight bearing exercise; bisphosfonates should be considered or studied. A baseline and annually bone density studies to assess bone mass loss are also important[55].

Gonadal failure: Pre-menopausal females prior to transplantation should receive gonadal replacement therapy following transplant. Women who decline estrogen therapy or for whom replacement is inappropriate (patients with a history or high risk of breast cancer), should be treated with calcitonin. Males with low free testosterone levels should receive testosterone replacement. Baseline prostate examination, PSA, lipid profile and liver function tests should be monitored in patients treated with testosterone.

1.5.4 Definition of Response

No response or progression (failure): Deterioration of cGVHD in at least one organ after 9-12 months of therapy without improvement in other organs. This category also includes patients with stable cGVHD but who have persisting Karnofsky or Lansky scores less than 50 %.

Partial response: After 9-12 months of therapy cGVHD is clinically stable or improved in at least one evaluable organ without deterioration in others. If there is still a partial response after 18 to 24 months, cGVHD is considered to have failed treatment. Patients with improvement of skin and other organs involved by cGVHD, but persistent oral involvement, are considered partial responders.

Complete Response: After 9-12 months of therapy the patient is well and has resolution of all symptoms and signs of active cGVHD. Patients with complete response in all organs, but with persistent ocular sicca, will be considered complete responders. Clinical responders should be divided into two categories: (A) clinical and histologically complete responses, and (B) complete clinical response but persistent histological involvement.

Exacerbation/flare: When treatment is reduced or stopped after achieving a complete or partial response, patients develop exacerbation of cGVHD manifestation requiring systemic immunosuppressive therapy.

Patients needs to be followed by their primary physician at monthly intervals. Physical examinations, weight, liver function tests, complete blood cell counts, renal function tests, and drug leves should be carefully monitored.

1.5.5 Measurement of Response

Involvement of the skin (surface area, hair and nails), oral cavity, eyes (Schirmer's test), liver (serum bilirubin and alkaline phosphatase), gut (weight loss, malabsorption, volume of diarrhea, cramps or bleeding), musculoskeletal (range of motion, CPK, aldolase) is evaluated.

Table VII summarizes the criteria used to assess treatment response in patients with cGVHD.

Table VII - Evaluation of response to tratment in cGVHD

DEFINITION OF RESPONSE (after 9-12 months of therapy):

No response or failure: deterioration in at least one evaluable organ w/o improvement in others or stable organ involvement w/ persisting performance score <50% or partial response after 18-24 months of treatment

Partial response: stabilization or improvement in at least one evaluable organ w/o deterioration in others or improvement of skin or other organs w/ active oral involvement

Complete response: resolution of all symptoms and signs of active cGVHD w/ or w/o persistent ocular sicca syndrome. Histological involvement may persist in spite of clinical response

Exacerbation: manifestation of cGVHD returns after stopping or reducing treatment.

MEASUREMENT OF RESPONSE IN DIFFERENT ORGANS:

Skin: use the "Grid" approach (Fig. 4), comparative photographs or the Rodnan skin score for escleroderma (Table VIII). Improvement is a) decrease by ≥ 25% of involved areas, b) increase in range of motion by ≥25% in one or more joints w/o deterioration in others.

Liver: Improvement defined by decrease in serum bilirrubin or in alkaline phosphatase by ≥25%

Gastrointestinal tract: a) cessation of weight loss or weight gain, b) resolution of diarrhea or decrease by >500 ml in the 3 day average stool volume, c) resolution of cramps and bleeding

1.5.5.1 Skin

To evaluate treatment response in cutaneous cGVHD, a "Grid" approach should be used (Figure 4), complemented by comparative photographs and by the modified Rodnam skin score when scleroderma is present (Table VIII). Skin is considered to be improved if there is a 25% decrease of the surface areas involved by rash, sclerosis, lichenoid or dyspigmentation; regrowth of hair in previous sclerotic areas; softening of the skin in ≥25% of previous involved areas, or increased range of motions by ≥ 25% in one or more joints without deteriorations in others.

1.5.5.2 Liver

Liver disease is considered improved if there is a) a decrease in serum bilirubin to less than 2 mg/dl for patients with baseline values of 2 to 4 mg/dl, or b) a decrease of >2 mg%/dl for patients with baseline values of 4 to 8 mg/dl, or c) ≥25% decrease in serum bilirubin for patients with baseline values >8 mg/dl, or d) if alkaline phosphatase decreases to < 200 mg/dl for patients with baseline values of 250 to 300 mg/dl, or e) ≥25% decrease in alkaline phosphatase for patients with baseline values >300 mg/dl.

1.5.5.3 Gastro-intestinal tract (GI)

GI disease is considered improved if there is a cessation of weight loss or weight gain (i.e. >1 Kg in a 3 month interval), or resolution of diarrhea, or a decrease in the three day average stool volume by >500 ml with clearing of cramps and bleeding, if present.

2. REGIMEN-RELATED TOXICITIES

Late complications after allogeneic and autologous hematopoietic stem cell transplantation may arise from chemotherapy and/or radiotherapy associated organ toxicity[2]. These potential late effects of myeloablative conditioning regimens include cataracts, neurological problems, gonadal failure, endocrine problems, growth and development impairments (Table I, Figs. 1 and 2). These regimen - related complications are briefly reviewed below.

2.1. Cataracts

Cataract formation after transplant is due to corticosteroid and total body irradiation (TBI). In the analysis of 492 adults followed for a median of 6 years after bone marrow transplantation, cataracts developed in 159 patients (32%). The probability of cataract formation at 11 years after transplantation was 85% for patients receiving 10 Gy single dose TBI, 50% for patients receiving more than 12 Gy and 19% for patients who were not conditioned with TBI[43]. Steroids administered after Day +100 also appeared to increase

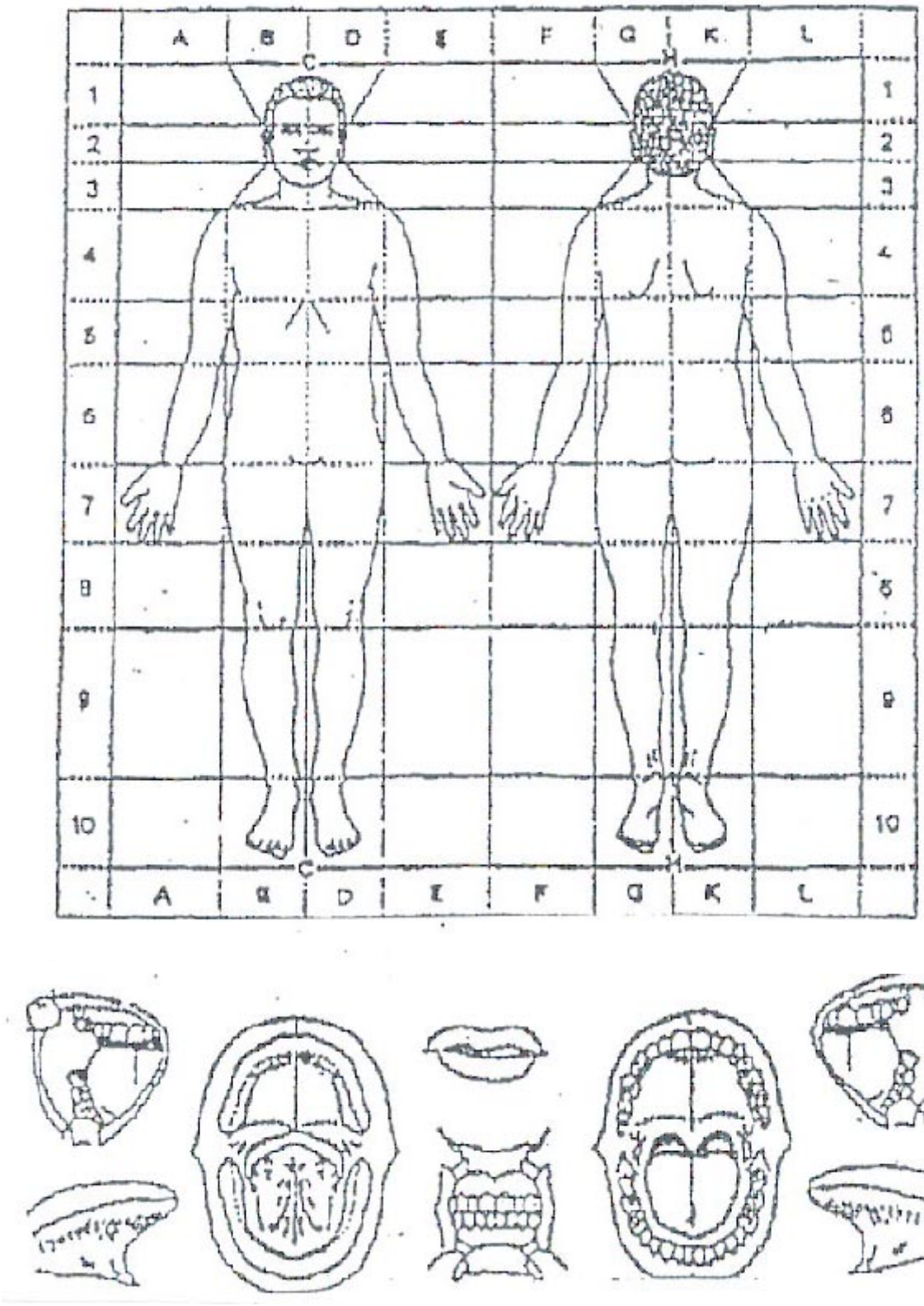

Figure 4: The “GRID” approach to assess cutaneous involvement in cGVHD. Each involved area is shaded by the examiner and the nature of the lesion (scleroderma, lichen, dyspigmentation, papules, ulcers, rash or other) is identified.

Table VIII - Modified Rodnan Skin Score for Assessment of Sclerodermic Involvement

The modified Rodnan skin score is calculated by summing the scores from all evaluated anatomic areas

A. Evaluation of skin thickness rated by clinical palpation
0= Normal, 1= Mild, 2= Moderate,
3= Severe (Inability to pinch skin into a fold)

B. Surface of anatomic areas evaluated (N= 17)

Face		0-3
Anterior chest		0-3
Abdomen		0-3
Fingers	Right	0-3
	Left	0-3
Dorsum of hands	Right	0-3
	Left	0-3
Forearms	Right	0-3
	Left	0-3
Upper arms	Right	0-3
	Left	0-3
Thighs	Right	0-3
	Left	0-3
Lower legs	Right	0-3
	Left	0-3
Dorsum of feet	Right	0-3
	Left	0-3
TOTAL		0-51

Ref: J. Rheumatol 1993, 20 (11): 1892-1896.

the risk of cataracts seen after TBI. Patients who were treated with steroids post-transplantation had a significantly higher probability of cataracts (45%) than those who did not receive steroids (38%).

2.2. Neurological Complications

Late neurological complications may result from previous cranial radiation, recurrence of the primary disease, drug toxicities (CSP, FK-506, etc) and infections (HHV-6, HSV, VZV, fungal, bacterial and protozoa). Leukoencephalopathy may develop in patients who receive intrathecal methotrexate or other chemotherapic agents and cranial irradiation and the risk may increase in young patients who receive more than six doses of intrathecal methotrexate after the transplant[44]. Late neurologic abnormalities may also be seen in patients receiving nitrogen mustard as part of the preparative conditioning regimen.

2.3. Endocrine and Growth Abnormalities

Myeloablative conditioning regimens may also affect the endocrine system, growth and development. In adult bone marrow transplant patients, two thirds of the recipients may have elevated TSH with normal blood T4 and T3 levels[45]. In the same study, it was also shown that 20 % to 25% of the patients will develop definite hypothroidism. Thyroid deficiency was reported in 31% to 43% of patients after single fraction of TBI. Thyroid hormone replacement should be administered if the diagnosis of hypothyroidism has been confirmed. In view of the clinical studies mentioned, thyroid function studies must be done annually in all bone marrow transplant recipients. Growth hormone deficiency has also been reported following TBI[46]. It may be higher than 90% in the pediatric patients conditioned with TBI who also had a history of cranial irradiation for CNS leukemia [46]. In some children who were treated with corticosteroids for chronic graft-versus-host disease (cGVHD), growth rate may be lower compared to the period during which steroids are discontinued. Concurrent drug therapies such as prednisone may cause emotional problems, rarely psychosis, and cyclosporine may cause tremors, seizures, muscle cramps and lethargy.

2.4. Gonadal Dysfunction

Gonadal function abnormalities are quite frequently observed as a result of myeloablative chemotherapy and radiotherapy. Gonadal dysfunction has been closely associated with alkylating agents, may be related to patient's age and the intensity of the chemotherapy regimen. Female patients may have anovulation, low estrogen levels and elevation of serum gonadotropins[47]. Patients who were conditioned with TBI containing preparative regimens rarely have return of their fertility[47,48].

Hormone replacement with cyclic estrogen/ progesterone therapy is employed to prevent osteoporosis and its complications of early menopause. Most women prefer Premarin 0.625 mg to 1.25 mg per day (P.O) and Provera 2.5 to 5.0 mg on days 1-14 of the menstrual cycle (P.O.). Both of these medications are well-tolerated. Provera is not indicated in women who had hysterectomy.

2.5. Gynecologic and Obstetric Complications

Post-pubertal female patients who received TBI containing regimes have been shown to have climacteric abnormalities[48]. Appropriate and early hormone

replacement with estrogen and progestrone may reduce the risk of osteoporosis and eliminate unnecessary discomfort. Although pre-term delivery and low-birth weight children were reported to be higher than expected in the bone marrow recipients, the incidence of congenital abnormalities did not appear to be different than the rates observed in the general population.

3. IMMUNODEFICIENCY AND INFECTIONS

Both allogeneic and autologous hematopoietic stem cell recipients experience impaired immunological changes for 6 to 12 months post-transplant [49]. HLA-disparity of the allogeneic donor and presence of chronic GVHD is associated with both cellular and humoral immunodeficiency[50]. Levels of CD4+ T-helper lymphocytes may stay low within the first six months after transplantation while normal numbers of peripheral blood B-cells can be found one to two months after BMT. In general, the patients are expected to reach normal levels of serum IgG within 2-3 months posttransplantation, of serum IgM in 9-12 months and of IgA in 2 to 3 years. Normalization of the serum immunoglobulin levels is delayed in patients with chronic GVHD. For the first year after transplantation patients with hypogammaglobulinemia (serum IgG levels less than 400 mg/dl) should receive I.V. immunoglobulin therapy to reduce the risk of infections[51, 52].

All marrow transplant recipients undergo a state of immune deficiency which is most severe in the first 6-12 months post-transplant. It is during this time that most bacterial, fungal and viral infections occur. After 12 months post-transplant most patients will achieve adequate immune reconstitution unless they develop cGVHD.

3.1. Antimicrobial Prophylaxis

Pneumocystis carinii (PCP*)* prophilaxis is recommended until six months posttransplant or until all immunosuppressive therapy is discontinued. Patients not able to receive trimethoprim-sulfamethoxazole should receive PCP prophylaxis with dapsone (50-100 mg PO daily). Patients receiving treatment for cGVHD need to receive prophylaxis against encapsulated bacterial infections such as *H.influenzae* and *S. pneumoniae.* Daily trimethoprim-sulfamethoxazole (double-strength, one tablet PO daily) are an adequate regimen for prophylaxis of both PCP and encapsulated bacterial infections. If twice-weekly trimethoprim-sulfamethoxazole is choosed for PCP prophylaxis, Penicillin-V (500 mg TID) must be added for encapsulated infection prophylaxis in patients receiving systemic immunosuppressive treatment for cGVHD.

3.2. Immunizations

After the first year post-transplant booster vaccination is recommended for optimal antibody response. Booster immunization is recommended against pneumococcus, hemophilus, hepatitis B, diphteria, pertussis (only for patients <7 years old), tetanus and inactivated polio. Whether patients with cGVHD will develop an antibody response is not known in all cases. Antibody titers can be helpful if drawn before vaccinations. If pre-immunization titers are low or unknown, repeat vaccinations up to 2 times in 2 month intervals, except for *Pneumococcus*. Influenza vaccination is recommended (yearly).

Should the oral polio vaccine (OPV) be given to family infants or others in close contact with the patient within the first year after transplantation or while on immunosuppressive therapy, the patient should be isolated from the person vaccinated for 8 to 12 weeks which is the period of potential live virus shedding. Immunization schedule post-HSCT is summarized in Table IX.

Antibody titers should be tested before the first vaccination and may also be tested 4 weeks afterwards to help evaluate the antibody response. Patients with unknown pre-vaccination antibody titers should complete the entire series of vaccinations listed above, unless contraindicated. The 2nd and the 3rd doses of DPT, HiB and Salk poliovirus are recommended for patients who have nonprotective antibody titers. Patients who continue to have nonprotective titers after administration of Pneumovax at one year after transplantation should receive a second dose at two years, unless there is a history of severe local reaction or other contraindication.

4. BONE DISEASE

Bone loss is a well-recognized complication of glucocorticoid therapy in doses as low as 7.5 mg daily. In hematopoietic stem cell transplant patients, other factors such as electrolyte imbalances, inactivity, significant weight loss and endocrine deficiencies may also contribute to bone loss. Management for prevention of bone loss includes minimizing glucocorticoid dose, optimizing calcium and vitamin-D intake, stimulating weight-bearing exercise and providing hormone replacement therapy for gonadal failure[53-55].

Table IX - Recommended vaccinations after hematopoietic cell transplantation

Time After Transplant	Vaccines
≥ 1 year[¶]	Diphtheria-Pertussis*-Tetanus (DPT) Haemophilus influenzae type B (HiB) Hepatitis B Salk poliovirus (inactivated vaccine) Pneumococcal vaccine (Pneumovax) Influenza (every fall /winter) Hepatitis A (only patients at risk) [†]
1 - 2 months after initial dose[¶]	Diphtheria-Pertussis*-Tetanus (DPT) Haemophilus influenzae type B (HiB) Hepatitis B Salk poliovirus (inactivated vaccine) Hepatitis A (only patients at risk)[†]
4 - 6 months after initial dose[¶]	Diphtheria-Pertussis*-Tetanus (DPT) Haemophilus influenzae type B (HiB) Hepatitis BSalk poliovirus (inactivated vaccine)
≥ 2 years after transplant and > 1 year without immunosuppressive therapy	Measles, Mumps, Rubella (MMR)[‡] Varicella-Zoster Virus (VZV)[‡]

[¶] Antibody titers should be tested before the first vaccination and may also be tested 4 weeks afterwards to help evaluate the antibody response. Patients with unknown pre-vaccination antibody titers should complete the entire series of vaccinations listed above, unless contraindicated. The 2nd and the 3rd doses of DPT, HiB and Salk poliovirus are recommended for patients who have nonprotective antibody titers. Patients who continue to have nonprotective titers after administration of Pneumovax at one year after transplantation should receive a second dose at two years, unless there is a history of severe local reaction or other contraindication.

* Pertussis vaccine should be administered only to children less than 7 years of age.

[†] Hepatitis A vaccine should be given only to patients with a history of hepatitis B or C, liver GVHD, other chronic liver disease, or increased risk because of travel or residence in an underdeveloped region.

[‡] MMR and attenuated VZV vaccines should not be given until 2 years after the transplant or at least 1 year after discontinuation of all treatment with IV Ig and immunosuppressive medications, whichever occurs later. Varicella vaccine may be given only to VZV-seronegative patients. Vaccination should be deferred until at least 5 months after the administration of IV Ig or VZ Ig or the most recent blood or plasma transfusion. No IV Ig should be given for at least 2 months after vaccination, unless the need outweighs the benefit of vaccination. Varicella vaccine can be given concurrently with MMR vaccine. The second dose of Varicella-Zoster vaccine should be administered 1 month after the first dose. Other live virus vaccines (oral polio, yellow fever and smallpox) may carry risk in immunocompromised patients and should be avoided.

4.1. Avascular Necrosis (AVN)

Approximately 10% of all allogeneic bone marrow transplant recipients may develop AVN and its incidence is more than 3 folds in patients with chronic GVHD, with an odds ratio of 19.1 in patients on steroids. Five year estimated cumulative incidence of osteonecrosis is 4 to 11 % depending upon risk factors. Patients without history of cGVHD have the lowest risk of AVN compared to those with extensive cGVHD. For these reasons, currently, patients having hip or bone pains should be evaluated with MRI of the hips and knees or other joints as clinically indicated. Approximately 40% of patients will require hip replacement between 2 to 42 months after diagnosis. Core decompression of the femoral head can benefit some patients with early osteonecrosis.

5. RELAPSE OF MALIGNANCY

The risk of relapse following transplant for hematologic malignancies is greatest in patients transplanted during relapse. Most recurrences occur within 1-2 years posttransplant and few relapses have been seen after three years. If the hematologic counts or peripheral smear examination change, the marrow exam and cytogenetics should be repeated. In Seattle, we routinely perform a marrow aspirate around day 80 posttransplant, but we do not recommend routine marrow exams again until the one-year visit to the clinic. For all patients with CML Ph1+ or ALL Ph1+ we recommend blood and marrow collections for cytogenetic and molecular studies every 6 months for 2 years after transplant and then annually[(56)]. Although some patients may be placed into a subsequent

remission with chemotherapy reinduction, its duration is usually short. Other approaches would include biologic response modifiers[57], donor lymphocyte (DLI) infusions[58,59] or a second transplant.

6. SECONDARY MALIGNANCIES

Malignant tumors following TBI have been observed in several animal studies. In human recipients of marrow transplants followed since 1970, non-Hodgkin's lymphomas, leukemias and solid tumors have been identified in a small proportion of patients (35 of 2,246 transplants, 1.5 %). The risk of developing a secondary malignancy is highest in the first year after transplant at which time it is 1.2 events/100 patient-years of exposure. The risk falls in the second year after transplant to 0.4 events/100 patient-years and remains at that level thereafter. These statistics are based on the observation of our patient population for the past 17 years[60,61]. In a multi-institutional data base, 19,229 recipients of allogeneic marrow transplants were analyzed to determine the risk of developing late solid cancers[62]. The risk of new solid cancers was 8.3 times higher than expected for the general population among those who survived 10 or more years after transplantation[62]. In this study, the risk of developing new solid cancers was also found to be higher for recipients who were younger at the time of transplantation.

FLOWERS MED & KANSU E. Complicações tardias do transplante de células-tronco hematopoéticas. **Medicina, Ribeirão Preto, 33:** 415-432, out./dez. 2000.

RESUMO: Com os avanços significativos no transplante de células-tronco hematopoéticas, (TCTH) nas duas últimas décadas, um grande grupo de pacientes sobreviveu mais de vinte anos após o transplante para doenças hematológicas e oncológicas. O grande número de sobreviventes de longo prazo propiciou uma oportunidade única de se estudar a evolução desses transplantes a longo prazo. Esta revisão descreve as complicações tardias dos TCTH relacionadas ao regime de condicionamento, a recidiva da neoplasia primária e a toxicidade relacionada ao transplante, com ênfase no diagnóstico e tratamento da doença enxerto-contra-hospedeiro crônica.

UNITERMOS: Transplante de Células Hematopoéticas. Transplante de Medula Óssea. Doença Enxerto-Hospedeiro. Toxicidade. Seguimento.

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