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Amyloidosis relapsing after autologous stem cell transplantation treated with bortezomib: normalization of detectable serum-free light chains and reversal of tissue damage with improved suitability for transplant

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RMBMT-08-A
A Treatment Guideline for High-Dose Melphalan with Autologous Hematopoietic Stem Cell Reconstitution for Primary Systemic Amyloidosis

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Background

Primary systemic amyloidosis (AL) is a clonal B cell disease manifested as beta-pleated sheets of immunoglobulin light chain deposition in various organs including the heart, tongue, liver, spleen, kidneys, and bone marrow. It is an incurable disease with a median survival of 12-18 months and <1 percent surviving 10 years (1). Standard treatment for patients with primary systemic amyloidosis had been alkylating agent based chemotherapy resulting in a demonstrable response rate of 20-30%. A prospective randomized study has demonstrated that chemotherapy treated patients have an improved overall median survival compared to patients who do not receive chemotherapy (2). Since most patients never demonstrate objective evidence of disease regression, they usually progress rapidly to irreversible end organ function and, ultimately, succumb to their disease. Even in responding patients, the median survival is poor the median survival is considerably shorter than that observed in multiple myeloma, another clonal B cell disease. No salvage chemotherapy program exists for patents with amyloidosis who fail to respond to alkylating agents.

The Southwest Oncology Group studied high dose dexamethasone pulsing followed by alpha interferon in the treatment of AL (3). A number of other chemotherapeutic agents alone or in combination have previously been evaluated including colchicine, vitamin E, and interferon alone, none of which have shown significant activity. VAD or intermediate dose IV melphalan (20-30 mg/m2) have been used. Thalidomide is also being studied in a phase II setting at centers such as Boston University and the Mayo Clinic. Lenidalomide is presently in trials.

The original report by Boston University describing 7 patients with AL amyloid completing high dose therapy and auto transplant (no mortality; 4 of 7 with objective responses) (4) has been extended to 25 patients (5). Predominant amyloid-related organ involvement was cardiac (n=8), renal (n=7), hepatic (n=6), neuropathic (n=3) and lymphatic (n=1). All patients were treated with melphalan 200 mg/m^2 with peripheral blood stem cell transplant. With a median follow-up of 24 months, 17 of 25 patients (68%) are alive and the median survival has not been reached. Thirteen of 21 patients (62%) evaluated at 3 months post transplant had complete responses of their clonal plasma cell disorders. Two-thirds of the surviving patients (11/17) have experienced improvements of amyloid-related organ involvement in all systems, while 4 of 17 have stable disease. Three patients have experienced relapses of the clonal plasma cell disorder at 12, 12, and 24 months. Two of 3 patients with predominantly neuropathic amyloid involvement have improved. Resolution of peripheral neuropathy is virtually never seen even in patients responsive to chemotherapy (6).

The Eastern Cooperative Oncology Group has extensive experience in the harvesting, collection, and use of autologous peripheral blood stem cells in patients with multiple myeloma, a disease very closely related to amyloidosis (7). The use of high-dose melphalan is a well-established technique in the treatment of multiple myeloma with low mortality (8). Most published reports reflect a transplant-related mortality rate in multiple myeloma of < 5%. In multiple myeloma renal insufficiency was not a contraindication to transplant (9). Furthermore, the use of peripheral blood stem cell transplantation for patients with plasma cell dyscrasias can safely be performed (10) up to age 70. Falk et al. (11) has reported complete remissions in 65% of patients with primary systemic amyloidosis. Improvement in amyloid-related organ disease was observed in over 75% of patients with liver, gastrointestinal, and neural involvement. Over 50% of patients with predominantly renal or cardiac amyloid also respond to dose-intensive therapy. The ECOG has completed a phase II study of high dose melphalan and autologous stem cell transplantation

for patients with primary systemic amyloidosis. The protocol completed accrual in May 2000. Our center participated in that trial.

At the RMBMT, approximately 10-20 new patients with amyloid are seen each year. In general, over one-half of these patients are within the age range to consider transplantation. Since not all patients will agree to the proposed treatment or will receive third party insurance coverage, it is anticipated that 2-5 patients be treated yearly. This guideline proposes to outline the role of high-dose chemotherapy and autologous stem cell transplantation in an attempt to improve the outlook for patients with this invariably fatal disease.

Since only immunoglobulin light chain amyloidosis (AL) is derived from a clonal plasma cell proliferative disorder, this is the only form that will be considered as being eligible for transplantation following this guideline. In order to ensure that a patient with biopsy-proven amyloidosis has the primary form, this protocol is limited to those patients who have a detectable monoclonal light chain in the serum or in the urine, thereby excluding patients with secondary and localized amyloidosis.

Furthermore, patients will be screened for hereditary or familial amyloidosis as well. A family history for amyloid will be obtained and if there is any question, genetic studies performed. Hereditary amyloidosis patients will be excluded as high-dose therapy is felt inappropriate. (N Engl J Med 2002:346;1786). A positive biopsy will be defined as demonstration of green birefringence when a congo red stained specimen is viewed under polarized light. A source of this specimen may be biopsies of heart, liver, kidney, sural nerve, skin, gingiva, rectum, or subcutaneous fat. For patients to be eligible for the study, they must have an overt clinical manifestation of amyloidosis, such as nephrotic syndrome, hepatomegaly, and echocardiographic evidence of cardiac amyloid, symptomatic peripheral neuropathy, or autonomic neuropathy in addition to a positive biopsy.

The presence of a monoclonal protein will be necessary to avoid entry of patients with non-AL amyloid. In addition, the monoclonal protein can serve as an ancillary criterion of response in addition to the outlined organ manifestations of response in amyloid. This will slightly reduce patient accrual, (only 11 % of patients have no light chain, fewer when one uses the serum free light chain assay) but this will ensure the homogeneity of the patient group. In this way a secondary endpoint can be complete eradication of the light chain from the serum or urine. One difficulty with this guideline will be selecting patients for whom dose-intensive chemotherapy is safe. Since amyloidosis is often manifested as diastolic dysfunction of the heart, the MUGA measurement of ejection fraction alone is not a sufficient assessment of cardiac function. Therefore, an echocardiogram and <u>not a MUGA will</u> be required in this study to ensure that marked infiltration of the myocardium has not occurred, that would increase the risk of transplantation. New data suggest that measuring the BNP and troponin can further and in perhaps a more sensitive fashion identify patients with cardiac amyloid. In the previous protocol, we suggested 15 mm of septal thickness as an upper limit reflecting moderate infiltration differentiating a poor prognosis group from a moderately poor prognosis group. With this guideline patients with a septal thickness above 15mm or a depressed left ventricular ejection fraction can be enrolled, but may only receive the lower doses of melphalan (100-140 mg/m^2). We have also built in restrictions of the serum creatinine to ensure that safe transplantation can be performed. Although the SGOT is a better indicator, the SGOT does not rise until advanced hepatic amyloid occurs, and alkaline phosphatase should be a suitable surrogate. In discussions with the amyloid group at the Mayo Clinic, they no longer use elevated liver function tests (ALT, AST, Alk Phos) alone, including an elevated alkaline phosphatase, to exclude patients and therefore this protocol will be likewise amended. Patients

with an elevated bilirubin above 2.0 who do not have documented Gilbert's will be excluded because of the risk of VOD.

1.0 INCLUSION CRITERIA

- Patients must have a histologic diagnosis of primary systemic amyloidosis.
- Presence of paraprotein determined by immunoelectrophoresis/immunofixation of the serum or urine (no minimum values required), or by the serum free light chain assay. SPEP and UPEP must be performed within 6 weeks prior to treatment. Both serum and urine studies must be evaluated at baseline and followed.
- Organ involvement

- Patients with known sensitivity to E. Coli derived proteins are excluded from this trial.
- Patients must not have primary amyloidosis manifested only by carpal tunnel syndrome or purpura.
- Patient must not have evidence of overt, symptomatic (BJH, 2003, NEJM 2004) multiple myeloma. Patients must not have a history of secondary, familial, or localized amyloidosis.
- Patients must be 18 to 70 years of age.
- ECOG performance status 0, 1, or 2
- Patients must have the following laboratory values (within $\leq$ 28 days prior to treatment):
  Granulocytes > $1000/mm^3$.
  Platelets > $100,000/mm^3$.

- If total bilirubin is > 2.0 mg/dl, then direct bilirubin must be done and it must be < 2.0 mg/dl.
- Serum creatinine < 2.0 mg/dL.
- The following demonstrated by echocardiogram (Echocardiogram must be performed within 8 weeks prior to treatment. MUGA scans are NOT acceptable):
  Ejection fraction $\geq$ 40%

2.0 EXCLUSION CRITERIA

- Patients must not have New York Heart Association classification of II-IV on appropriate therapy at the time of enrollment

- On pulmonary function tests performed within 8 weeks prior to treatment, patients must not have any of the following:
  DLCO on pulmonary function of < 50%.
  FVC < 60%.
  FEV-1 < 55%

Patients must not have had any of the following prior therapies:

- Melphalan therapy within 4 weeks prior to treatment.
- Lifetime cumulative dose of melphalan > 150 m2

- No more than 2 cycles of prior non Melphalan chemotherapy (lifetime).

Note: Prior use of dexamethasone or interferon is allowed.

- Patients must not be pregnant or breast-feeding. Female patients of childbearing potential must have a negative pregnancy test within 14 days prior to treatment. These patients are excluded because the effects of this treatment on the fetus and young children are unknown.
- Women of childbearing potential and sexually active mates must agree to use an effective method of contraception.
- Patients must not have active infection.

3.0 TREATMENT PLAN

For patients with an IVS thickness < 15mm, normal LVEF and age < 61 years, Melphalan 200 mg/m² IV into 2 split doses over two consecutive days (-3, -2), followed by stem cell infusion Day 0. At the discretion of the investigator and with the approval of the interdisciplinary committee, the melphalan dose may be decreased for very high risk patients, (advanced age, decreased creatinine clearance, multiorgan or significant cardiac involvement). Melphalan dosing is based on calculated ideal body weight.

Melphalan	**Day**			
	-3	-2	-1	0
Melphalan 100 mg/m²	X	X		
Hematopoietic stem cell infusion				X

For patients 61 years of age and older, or with a depressed LVEF, IVS thickness ≥15mm, prior melphalan exposure over 40 mg/m² or significant comorbidities, including multiorgan amyloidosis, the dose of Melphalan shall be 140 mg/m², given in one day, usually day –2. At the discretion of the investigator and with the approval of the interdisciplinary committee, the melphalan dose may be decreased to 100 mg/m2 in appropriate or very high risk patients, (advanced age, decreased creatinine clearance, multiorgan or significant cardiac involvement). **At least 18 hrs must elapse between melphalan and stem cell reinfusion.** Albumin infusions should be considered to keep the serum albumin above 2.0.

Melphalan	**Day**		
	-2	-1	0
Melphalan 140 mg/m²	X		
Hematopoietic stem cell infusion			X

Melphalan	**Day**		
	-2	-1	0
Melphalan 100 mg/m²	X		
Hematopoietic stem cell infusion			X

4.0 SUPPORTIVE CARE

Supportive care will follow Standard Operating Procedures and Institutional Guidelines.

5.0 CORRECTED IDEAL BODY WEIGHT

For patients with an actual body weight ≤ their ideal body weight, actual body weight will be used to calculate all chemotherapy doses. For patients whose actual body is > 1.1 times their ideal body weight, corrected ideal body weight will be used for the calculation of dosing weight and body surface area:

$$\text{Corrected ideal body weight} = \text{Ideal BW} + 0.25\ (\text{Actual BW} - \text{Ideal BW})$$

6.0 TRANSPLANTATION

Either bone marrow or peripheral blood may be used as the stem cell source. The minimum CD34 cell dose is > 2 x 10^6/kg. Higher doses (> 4.0 x 10^6/kg CD34+ cells/kg) are recommended for allogeneic transplants. Peripheral blood stem cells must be mobilized using hematopoietic growth factors, such as G-CSF or GM-CSF. Standard operating procedures will be followed for collection, processing and infusion of cells.

7.0 TOXICITIES

Melphalan may cause the following toxicities:

- Myelosuppression (leukopenia, thrombocytopenia), which can be cumulative; recovery can be prolonged (6-8 weeks).
- Dermatologic: Pruritus, dermatitis, rash;skin necrosis rarely requiring skin grafting, vasculitis, alopecia.
- Gastrointestinal: Nausea, vomiting, diarrhea, oral ulceration (infrequent).
- Hypersensitivity: Urticaria, pruritus, exanthema, rash, rarely anaphylaxis.
- Other: Hemolytic anemia, pulmonary fibrosis, interstitial pneumonitis; secondary AML/MDS (risk is uncommon, but may be increased when given in combination with an anthracycline, especially if one or both drugs are given at higher than standard doses); secondary tumors (rare).

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