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Review

Myeloablative chemotherapy with stem cell rescue for the treatment of primary systemic amyloidosis: a status report

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Summary:

Stem cell transplantation has been incorporated in the treatment of primary systemic amyloidosis for 5 years. Results reported to date suggest that the response rates are substantially better than those for patients treated with low-dose traditional melphalan and prednisone chemotherapy. Unexpectedly high mortality rates have, however, been reported with stem cell transplantation, reaching 40% in some series. This unexpectedly high mortality appears to be related to multiorgan failure of tissues infiltrated with amyloid deposits. Deaths have been reported from gastrointestinal tract hemorrhage, gastrointestinal tract perforation, sudden cardiac death, and renal failure. The best patient for transplantation appears to have single organ involvement, an age <55 years, the absence of renal insufficiency, and no symptomatic cardiac dysfunction. Patients eligible to receive stem cell transplant represent a highly selected population, and before conclusions about the efficacy of transplantation are drawn, comparison with a matched control group is necessary. Amyloidosis should be considered an indication for stem cell transplantation in the context of a clinical trial so that results can be compiled and reported for an accurate assessment of response rate, survival, relapse rates and treatment-related toxicities. *Bone Marrow Transplantation* (2000) **25,** 465–470.
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Primary systemic amyloidosis (AL) is the disease that results from the extracellular deposition of insoluble deposits composed of immunoglobulin light or heavy chains. The deposition of these amorphous deposits in the extracellular space disrupts organ function and ultimately leads to the death of the patient. Patients may present with various syndromes, but the most common are nephrotic-range proteinuria with or without renal insufficiency, congestive cardiomyopathy, unexplained hepatomegaly, or painful peripheral neuropathy. The disorder is rare, occurring in eight patients per million per year, similar to the incidence of Philadelphia chromosome-positive chronic granulocytic leukemia or agnogenic myeloid metaplasia. Amyloidosis is approximately one-fifth as common as multiple myeloma. The disorder is devastating in that the median survival of patients seen within 1 month of diagnosis is 13.2 months,[1] with a median survival of 4 months for those with congestive heart failure and only 5% surviving for 10 years or more.[2]

Because amyloid deposits are derived from a clonal population of plasma cells in the bone marrow, therapy has historically been directed at disrupting the precursor protein synthesis by these cells. Amyloidosis is not a true neoplasm. The percentage of plasma cells in the bone marrow does not increase over time, and the size of the monoclonal peak does not tend to increase over time, as it does in multiple myeloma. The treatment has been similar to that of multiple myeloma. It was not long after melphalan was introduced for the treatment of multiple myeloma[3] that the first reports documenting resolution of amyloidosis syndromes appeared after treatment with melphalan and prednisone.[4,5] Subsequently, prospective randomized studies demonstrated that the use of melphalan and prednisone prolonged the survival of patients who had the disease compared with patients treated with colchicine alone.[6,7] Unfortunately, in spite of a clear survival benefit, the reported median survivals were 12.2 and 17 months.[6,7] Better therapies are required for the management of this disease. Improving survival with melphalan is difficult, because the response rates do not exceed 30%, even in carefully selected subsets of patients.[8,9] Trials looking at other regimens known to be effective in myeloma were introduced for the treatment of AL. The use of vincristine, doxorubicin and dexamethasone is a well-established regimen for the treatment of multiple myeloma[10] and has also been introduced for the treatment of amyloidosis, with a response reported in three of four patients.[11] However, this chemotherapy is difficult to administer to many amyloid patients because patients with peripheral neuropathy should not receive vincristine, and the risk of doxorubicin in the context of amyloid cardiomyopathy is unknown.

VBMCP (vincristine, carmustine (BCNU), melphalan, cyclophosphamide and prednisone) was introduced more than 20 years ago for the treatment of multiple myeloma[12] and has been shown to produce a higher response rate than melphalan and prednisone alone.[13] We treated 101 patients

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in a prospective randomized fashion and found that there was no improvement in response rate or survival using VBMCP, with an overall response rate of only 30%.[14]

Given the poor results obtained with standard chemotherapy and recognizing the improved complete response rates and increased survival that have been demonstrated with transplantation for multiple myeloma, it was inevitable that this technique should be applied to patients with amyloidosis. The purpose of this review is to summarize the published literature on the status of transplantation for this disorder in an effort to help determine which patients should be considered candidates for the procedure.

Marrow transplantation

Most patients who come to transplantation with a hematologic malignancy have significant dysfunction of the bone marrow that frequently is manifest by multiple cytopenias or, in the case of patients with malignant lymphoma, infiltration of lymph nodes. In general, there is no visceral dysfunction present, and most programs require satisfactory cardiac and pulmonary function with an Eastern Cooperative Oncology Group performance status of 0 or 1, good synthetic function of the liver, and good nutrition. Unfortunately, many patients with amyloid present with precisely the opposite findings. Hematologically, these patients are generally normal. Anemia is uncommon unless there is renal insufficiency, and the white cell count and platelet count are generally normal. Thrombocytosis is seen occasionally in patients with hepatic involvement and hyposplenism. Amyloidosis patients regularly have cardiac, hepatic, renal, or neuropathic problems, which make this patient group distinct from other transplant candidates.

The first syngeneic transplant for amyloidosis was reported in 1995.[15] The patient was age 32 years at diagnosis and had failed to benefit from melphalan and prednisone therapy. The patient was conditioned with standard cyclophosphamide (120 mg/kg) and total body radiation (12 Gy). There was resolution of nephrotic-range proteinuria and autonomic neuropathy. A hematologic response was achieved, with the disappearance of monoclonal light chains from serum and urine. There was also improvement on a I-labeled serum amyloid P component scan, which is a good gauge of total body amyloid burden.[16]

There have been two reports of allogeneic bone marrow transplant for systemic amyloid. One patient with periorbital purpura, macroglossia, and minimal proteinuria (1.4 g/day) was treated with six cycles of C-VAMP (cyclophosphamide, vincristine, doxorubicin, methylprednisolone) and had a hematologic response. The patient's allotransplant conditioning regimen was melphalan (110 mg/m^2) and total body radiation (12 Gy). A complete hematologic response was seen at 6 months, and the patient was alive and well at 29 months.[17] A second patient received a transplant from a human leukocyte antigen-identical sister with melphalan (140 mg/m^2) and total body radiation (8 Gy) and had a reduction in 24-h urine protein from 9.15 g to 1.3 g and disappearance of monoclonal light chains from the urine. The patient had limited chronic skin and liver graft-versus-host disease. The patient was alive at 18 months post transplant.[18] Both of these patients had only a single visceral organ involved with amyloid. It is unlikely at this time that allogeneic transplant will be applicable to many patients with amyloidosis given the necessity for a human leukocyte antigen-compatible sibling, the age restrictions (amyloidosis patients have a median age of 63 years), and the need for good performance status, renal function, and cardiac function. Nonetheless, these encouraging reports suggest this treatment is an option for carefully selected patients who are younger and have only one organ involved.

A report of autologous bone marrow transplantation for AL in a 45-year-old patient with cardiac involvement has appeared.[19] This patient had infiltration of the left ventricle and endomyocardial biopsy-proven amyloid, with an ejection fraction of 52%. She was conditioned with melphalan (200 mg/m^2). With 17-month follow-up, there was objective clinical improvement and a hematologic response with disappearance of monoclonal λ light chains from the urine. The echocardiogram remained abnormal, and a repeat endomyocardial biopsy 17 months post transplant showed persistent amyloid.[19]

Peripheral blood stem cell transplant

Owing to the ease of collection, lower rate of tumor contamination, and quicker engraftment observed with blood stem cells over autologous bone marrow, most of the high-dose chemotherapy experience is with blood stem cells. Contamination with clonotypic immunoglobulin-positive plasma cells has been demonstrated in the collected apheresis products from patients with amyloidosis undergoing leukapheresis after growth factor priming alone. CD34$^+$ cell selection is possible in these patients with adequate yields for successful engraftment, but the effect of having a positively purged apheresis product on the disease course remains unknown.[20]

The group that had originally performed the syngeneic transplant for amyloid reported on two patients who had stem cell transplants for AL. At the time of the report, one patient was alive but not evaluable, and the other patient had a hematologic response with eradication of light chains from the urine and conversion of the bone marrow from monoclonal to polyclonal plasma cells. Nephrotic syndrome and orthostatic hypotension had improved, and amyloid deposits visible in the bone marrow pretransplant had cleared.[21]

The world's largest experience of stem cell transplant for AL is derived from the Boston University data set. They initially reported on five patients, aged 38 to 53 years, including one patient with cardiomyopathy. Mobilization was with growth factor only. Cells were harvested on day 5. Patients received melphalan conditioning (200 mg/m^2). With an initial median follow-up of 13 months, all five patients showed clinical remission of organ-related dysfunction, reversal of neuropathy, and resolution of hepatomegaly. In three of the five patients, clonal plasma cells could not be detected in the bone marrow.[22]

This experience was expanded to 25 patients[23] using the

same mobilization scheme of granulocyte colony-stimulating factor alone and melphalan given intravenously (200 mg/m^2). All patients were selected to have adequate cardiac, pulmonary and renal function. The median age was 48 years, with 88% having a performance status of 1 or 2. Eight of the patients had cardiac amyloidosis, but none had congestive heart failure. Ten had three or more organ systems involved. Seventeen of 25 patients (68%) were alive at 24 months. Thirteen of 21 evaluable (62%) had resolution of the clonal plasma cell disorder, and 11 of 17 (65%) experienced improvement of amyloid-related organ involvement. There were three patients who had relapsed between 12 and 24 months. There was a marked reduction of proteinuria in nine patients with renal involvement, and two of three patients with predominant neuropathic involvement had complete resolution of autonomic and peripheral neuropathy. Adverse predictors of survival included more than two major organ systems involved or predominant cardiac involvement. There was also one patient who developed acute nonlymphocytic leukemia, presumably related to prior exposure to melphalan. Two patients died after stem cell collection before receiving conditioning chemotherapy. Three of the 25 patients died within 100 days after transplantation.

Treatment-related toxicity included the development of moderate renal failure with a creatinine value of 4.9 mg/dl in one patient. Delayed platelet engraftment was seen in one patient who had received prior melphalan therapy. In patients with predominant cardiac involvement, treatment-related mortality was 38%.[23] There was a 39% incidence of bleeding, particularly gastrointestinal tract bleeding.

An abstract presented at the 1998 American Society of Hematology meeting updated the results to 102 patients receiving high-dose melphalan.[24] The median age of patients was 55 years. Patients with advanced age or reduced cardiac or renal function received 100 or 140 mg/m^2 of melphalan. Three-month treatment-related mortality was 15%. The survival in patients whose predominant organ involvement was cardiac was 33% compared with 83% survival for renal patients. The rate of complete hematologic response was 55%.[24] Following the encouraging publication of these results, the accreditation subcommittee of the European Group for Blood and Marrow Transplantation held a consensus conference and added AL to the list of indications for transplant procedures, categorizing autologous transplant for AL as a technique to be undertaken in an approved clinical research protocol and considered sibling donor allotransplant as developmental in nature.[25]

We have conducted a study of stem cell transplantation and have been impressed with the high morbidity and mortality compared with stem cell transplantation for multiple myeloma. Between January 1996 and September 1998, 22 AL patients had stem cells collected. All cells were collected after priming with cyclophosphamide (3 g/m^2) followed by granulocyte–macrophage colony-stimulating factor (5 μg/kg per day). Fifteen of the patients received melphalan (140 mg/m^2) and total body radiation (12 Gy), and four patients received melphalan alone. Three patients never had stem cells transplanted after collection owing to poor performance status. Two died of progressive amyloid at 1 and 3 months, and one patient is alive 1 year after collection and receiving hemodialysis. Nineteen had transplants at a median age of 57 years. Renal, cardiac (by echocardiography), peripheral nerve, and liver amyloidosis were present in 13, 12, three and one, respectively. The median creatinine value was 1.1 mg/dl. Seventeen of the 19 had a monoclonal protein in the serum or urine. The other two had clonal plasma cells demonstrable in the bone marrow. Six patients had an echocardiographic interventricular septal thickness $\geqslant$15 mm. The ejection fraction was $<$60% in two. Seven of the 19 patients died, four before day 100; two of pneumonia, one of multiorgan failure, and one of sudden cardiac death with autopsy evidence of severe cardiac amyloid. Two subsequently died of progressive cardiac amyloid, having failed to show a response to transplants at 7 and 9 months, respectively. One responded and subsequently progressed, dying of cardiac amyloid at 22 months.

Twelve patients are alive post transplant with a median follow-up of 13 months, and nine patients had objective responses. Six of these patients had renal amyloid only. There was one nonresponder and two were inevaluable owing to short follow-up. Three of the responses took $>$9 months, consistent with the long time required for resolution of amyloid deposits. Gastrointestinal tract bleeding was seen in two. An additional three required prolonged enteral and parenteral nutrition. Five had significant cardiac arrhythmias, either during stem cell collection or post transplantation.

Toxicity of transplantation for AL

The first multicenter survey on the outcome of transplantation was published in 1998, and the results were sobering. A retrospective survey in France found 21 patients had undergone transplantation for AL: 18 with melphalan alone and three with melphalan plus total body radiation. The death rate from toxic reactions was 43%: nine of 21 died within the first month after transplantation. Although 10 of the 12 surviving patients achieved a response, all nine deaths were due to multiorgan failure, including one patient with severe bleeding. The median time from diagnosis of AL to transplantation was 11 months, with one patient undergoing transplantation at 20 months, suggesting patient selection may have occurred. Half of patients with amyloid would be expected to have succumbed to the disease by the time they were ready for transplantation at 1 year. The number of organs clinically involved at the time of transplantation (that is, kidney, heart, liver, or nerve) was prognostic. For patients presenting with two or more clinical manifestations, the 4-year overall survival was 11.1%. The risk of death from toxic response when two or more organ dysfunctions were documented was $>$75%, reflecting the need for careful patient selection before application of this procedure.[26]

The group from Hammersmith evaluated 27 patients who received high-dose melphalan (from 100 to 200 mg/m^2). There were eight treatment-related deaths (30%) due to multiorgan failure: gastrointestinal tract hemorrhage in two and sepsis and cardiac complications in one each. A clonal

response of marrow plasma cells was seen in 64% of patients and clinical organ regression in 57%. Seventeen of the 27 patients were alive at the time of publication. This group confirmed that there was a higher response rate than traditionally seen with conventional chemotherapy, but the procedure carried a substantial mortality risk, and exclusion of high-risk patients is justified to avoid the unacceptably high treatment-related mortality.[27] Nine patients underwent transplantation and were reported by Amoura *et al.*[28] Four of nine patients died within the first year after transplantation (treatment-related mortality, 44%). Five are alive with a mean follow-up of 12.6 months. There were four responses and one progression. Three of the four patients who died had cardiac amyloid, and the fourth had renal, intestinal, and peripheral nerve amyloid.

The development of multiorgan failure and gastrointestinal tract bleeding appears to be the result of toxic responses to transplantation occurring more frequently in patients with amyloidosis than in those who receive transplants for other indications. Gastrointestinal tract bleeding is unusual after autologous transplant and appears to be specific to patients with AL. Although the group from Little Rock reported that the presence of amyloid does not influence the outcome of transplantation in patients with multiple myeloma, these patients did not actually have a true systemic amyloid syndrome.[29] These patients had a screening fat aspirate test performed during the assessment of their newly diagnosed multiple myeloma, and a positive result for the fat aspirate did not impact on outcome. These results should not be construed as indicating that amyloid does not increase the morbidity and mortality of transplantation. The majority of patients had incidental amyloid deposits. Only seven of 84 had an amyloid organ-specific syndrome. Even in this circumstance, one of the deaths reported was related to organ failure from amyloidosis. This was the only patient who had evidence of multiorgan amyloid involvement pretransplant. Responses included regression of hepatomegaly in one and improved functional status in pulmonary amyloidosis in a second.[29] Toxic reactions that have been reported include progressive impairment of renal function in a patient with renal amyloidosis associated with delayed engraftment.[30]

The first two reports of transplantation for amyloidosis appeared as correspondence in 1992 and 1993. In the first report, Mehta *et al*[31] reported on a patient who 3 days after transplantation had massive gastrointestinal tract hemorrhage and died 14 days later, and the second[32] reported on a patient who died 74 days post graft with respiratory failure. In an extensive review,[33] the British group noted that a 63-year-old patient died as a result of intestinal tract hemorrhage, having presented with gastrointestinal tract symptoms. A fatal gastrointestinal tract perforation has also been reported on day +4 after stem cell transplantation.[34]

Four amyloidosis patients were reported, of which one patient conditioned with melphalan went on to develop dialysis-dependent renal failure with subsequent catastrophic gastrointestinal tract hemorrhage and died on day 97. A second patient developed post-transplant bronchopneumonia and died on day 374.[35]

We concluded that blood cell transplants for amyloidosis have a much higher morbidity and mortality than transplants for myeloma. Patients who have clinically significant cardiac amyloid should not receive transplants because five of the six deaths observed in our program were in patients who had cardiac amyloidosis. The best results were achieved in patients with isolated renal amyloidosis as the only manifestation of their disease.[36] It does not appear that treatment-related mortality was any higher in patients conditioned with melphalan and total body radiation than in those conditioned with melphalan alone.

Conventional treatment of younger patients

Patients receiving transplants for amyloidosis are a highly selected group of patients by virtue of age, performance status, number of organs involved, and the absence of important cardiac involvement. It is difficult to know what the survival of a comparable control group would be. It would be expected to be greater than the 13 months reported for all AL patients. Dispenzieri *et al*[37] reviewed the amyloid database of the Mayo Clinic from 1983 to 1997 to select those patients who would theoretically be eligible for stem cell transplants. The liberal criteria included symptomatic disease, the absence of multiple myeloma, age $\leqslant$70 years, a ventricular septal thickness $\leqslant$15 mm, a cardiac ejection fraction $>$55%, a creatinine concentration $<$2 mg/dl, an alkaline phosphatase value $<$3 times normal, and a direct bilirubin value $<$2 mg/dl. Of the 1288 patients seen during this 14-year period, 234 met the eligibility criteria. The median age was 57 years, with 131 males and 103 females. One hundred and twenty-one had nephrotic-range proteinuria. Heart, liver and nerve involvement were present in 98 (42%), 13 (5 1/2%) and 36 (16%) patients, respectively. With a median follow-up of 44.5 months, 150 patients have died, with a median survival of 45.6 months.

The most significant prognostic factors by multivariate analysis were age, alkaline phosphatase value, and 24-h urine monoclonal protein excretion. For patients younger than age 50, age 51–60 and age 61–70 years, the median survivals were 60.6, 46.3 and 30.2 months, respectively. The survival for patients with a normal *vs* increased alkaline phosphatase value was 50.5 *vs* 17.1 months. It is clear from this cohort of patients that eligibility to receive a transplant is a favorable prognostic factor which predicts for a better outcome than unselected patients with AL. At present, the 4-year survival rate with stem cell transplant is unknown, but patients eligible for a stem cell transplant are inherently a good risk population with a superior median survival of 46 months. Therefore, it will become imperative to stratify patients receiving transplants for risk factors known to impact on survival in this disease.

Conclusion

The response rates in patients with amyloidosis who receive a stem cell transplant appear to be higher than those seen in patients treated with traditional melphalan and prednisone.[9] The morbidity and mortality associated with the procedure are clearly higher than in patients with multiple myeloma or other hematologic malignancies undergoing

stem cell transplant. There is an unusually high rate of gastrointestinal tract toxicity, with significant gastrointestinal tract hemorrhage. Cardiac complications, including arrhythmias, appear to be unexpectedly prevalent. Patients eligible for transplant have an inherently better prognosis and, therefore, outcomes must be compared with a matched control group. At present, the response duration and actuarial median survival cannot be determined with accuracy. The optimal conditioning regimen and the best priming for stem cell collection have not been tested adequately. Current protocols are focusing on melphalan doses of 80 to 140 mg/m^2 in an effort to reduce toxic responses and maintain the higher response rates.

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