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Centers for Medicare and Medicaid Services
7500 Security Boulevard
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RE: Formal Request for Reconsideration for Coverage of Autologous Stem Cell Transplantation for AL Amyloidosis, Track #1

Benefit Categories: Inpatient hospital services; Outpatient hospital services incident to a physician's service; Physicians' Services

This letter serves as a formal request to the Centers for Medicare and Medicaid Services (CMS) to reconsider coverage of high dose therapy and autologous stem cell transplantation (ASCT) for patients with AL amyloidosis. CMS posted a decision memorandum on January 14, 2000 concluding "that a sufficient body of evidence does not exist to justify a national coverage decision in favor of AuSCT for patients with AL amyloidosis."[1] The literature review used for the decision included articles published from 1993 – 1999. Several larger trials, institutional series, and prognostic models have been published in the intervening three years that provide stronger evidence for the benefit of ASCT for patients with AL amyloidosis. Unfortunately, standard therapy offers little benefit for this patient population and improved outcomes with non-transplant treatments have not been forthcoming. Median survival for patients from diagnosis is approximately 13 months. Recently published reports have demonstrated a substantial improvement in survival for patients treated with high dose therapy and ASCT. Moreover, patient selection criteria have been refined to reduce transplant related mortality. A review of the data pertinent to this reconsideration request is summarized below.

New Efficacy Data

The largest report on ASCT in AL amyloidosis to date was published this year by researchers at Boston University School of Medicine.[2] The authors reported their experience in treating 701 consecutive patients referred to their center between July 1994 and June 2002. Patients with biopsy proven AL amyloidosis were enrolled in one of six clinical trials during the study period. Fifty-six percent (394 pts.) met eligibility criteria for autologous transplant and 312 proceeded to autologous stem cell mobilization. Half of the patients had involvement of at least 3 organ systems with amyloid while an additional 30% had two organs involved. Median age of eligible patients was 56.9 years and 19% were $\geq$ 65 years of age. Thirty-five patients started stem cell mobilization but did not proceed to transplant due to death (n= 13) or mobilization related complications

(n= 22), whereas 277 patients completed high dose therapy and stem cell transplantation. Median survival for all 312 patients is 4.6 years and actuarial 5 year overall survival is 47%. In comparison, the 307 patients who were deemed ineligible for stem cell transplant had a median survival of only 4 months. Granted, many of these patients had worse prognostic features including poor performance status or inadequate organ function. Patients with cardiac involvement (defined as septal or posterior wall thickening of $\geq$ 13 mm by echocardiogram or clinical syndrome of congestive heart failure or cardiac arrhythmia without other cardiac history) fared worse with a median overall survival of 1.6 years, compared to 6.4 years if no cardiac involvement. The 100-day regimen related mortality was 13% (41.6% cardiac; 25% sepsis). At the time of the report, forty percent of patients were evaluable for response assessment at one year. Forty percent showed a hematologic complete response and 66% of these same patients had improved organ function. An additional 30% had a hematologic partial response along with organ function improvement. The authors stress that autologous transplantation can offer an improvement in overall survival with durable responses and improvement in organ dysfunction. Moreover, patients age 65 and over had comparable survival to younger patients.

Several updates to institutional series have been presented in abstract form over the past two years.

The Mayo Clinic recently reported a case control study of 63 patients undergoing autologous stem cell transplantation and 63 controls matched for age, gender, time to presentation, cardiac and renal function, nerve involvement, urinary protein excretion, and LDH.[3] Their results are as follows:

Overall Survival	**Autologous Transplantation**	**Matched Controls**	**P**
1 year	89%	81%	
2 year	81%	64%	
4 year	71%	54%	P = 0.004
# deaths at time of report	16 patients	44 patients	

This study helps control for selection bias that is problematic when reporting consecutive patients. Randomized trials could potentially strengthen the data supporting autologous transplantation in AL amyloidosis. However, the rarity of the disease and diversity of presentation poses challenges to timely completion of such a study.

Blum and others presented a “total therapy” approach tested at Washington University, St. Louis.[4] They reported on a series of 10 patients, seven of whom would be considered ineligible due to organ dysfunction (n = 6) or age (n = 1). Patients received 4 – 6 cycles of induction chemotherapy followed by an attenuated dose total body radiation (550 cGy) preparative regimen and autologous stem cell support. There were no transplant related

deaths. Complete response was seen in 50% (n = 5) and partial response in 10% (n = 1). Median survival from transplant was 18.5 months in this poor risk sample. This series proposed a transplant regimen that may be safer for patients with organ impairment.

A non-randomized open study conducted in the United Kingdom found that 186 patients with AL amyloidosis appeared to derive similar benefit with combination chemotherapy compared to ASCT.[5] Fifty-five patients undergoing ASCT were compared with 98 receiving vincristine, doxorubicin, dexamethasone (VAD)or cyclophosphamide vincristine, doxorubicin and methylprednisolone (C-VAMP), and 33 treated with intravenous low dose melphalan IDM). Treatment related mortality at 100 days after last therapy was similar in the ASCT (22%) and IDM (18%) groups and lower in VAD/C-VAMP (7%). The authors stated that no significant differences were seen in clonal response, mortality, or median survival although significance levels were not reported. They suggested that future randomized trials of ASCT might include VAD/C-VAMP or IDM as a comparison arm.

Researchers from the Autologous Blood and Marrow Transplant Registry (ABMTR) presented an analysis of 114 patients entered in the registry between 1995 and 2001.[6] Evidence of cardiac involvement, demonstrated by intraventricular septal wall thickness $\geq$ 15 mm was present in 14% while two thirds had nephrotic syndrome and 25% suffered from peripheral neuropathy. High dose melphalan based regimens were employed in 82% of transplants. Organ function response was seen in 36% of patients by day 100. Overall 100 day mortality rate was 25% in this unselected group of patients treated at 52 centers in North America. Overall survival for the entire group at one and three years was 68% and 57%, respectively. As in previous reports, patients had worse one year survival if cardiac involvement was present (54% vs. 74% if no cardiac involvement). The authors noted that organ response to high dose therapy and autologous transplantation can be gradual and 100-day response may not accurately reflect overall benefit of the procedure. They concluded that ASCT "appears to improve survival in select patients with AL."

Safety

The January 2000 CMS decision memorandum also cited safety of ASCT as further source for concern. Transplant- related mortality rates (TRM) of up to 43% were reported in earlier series. The TRM continues to exceed those seen in hematologic malignancies such as lymphoma and myeloma with many institutions continuing to report rates of approximately 14%. Patient selection criteria have evolved and new prognostic factors identified. Comenzo and Gertz have proposed a risk adapted approach to patient selection criteria in order to reduce peritransplant mortality and identify patients that are most likely to benefit from ASCT.[7] Patients are categorized according to risk and recommended Melphalan dose (for those deemed acceptable ASCT candidates) as follows:

Good Risk (any age with all criteria)	**Intermediate Risk (age < 71; either criteria)**
1 or 2 organs involved	1 or 2 organs involved (one organ must be cardiac or renal with creatinine clearance < 51 ml/min.
No cardiac involvement	Asymptomatic or compensated cardiac function
Creatinine clearance $\geq$ 51 ml/min.	
Melphalan Dose Based on Age	**Melphalan Dose Based on Age**
200 mg/m^2 if $\leq$ 60	140/mg/m^2 if $\leq$ 60
140/mg/m^2 if 61 – 70	100 mg/m^2 if 61 – 70
100 mg/m^2 if > 71	

Patients are considered poor risk for ASCT if they have three or more organs involved or if they have advanced cardiac involvement.

Dispenzeri and others have suggested that serum cardiac troponins may provide valuable data pertaining to patient selection for autologous transplantation.[8] In a study of 261 patients, a prognostic model was tested that included cardiac troponins T and I. The cardiac troponin levels were more powerful than traditional cardiac assessments, including echocardiography and physical evidence of congestive heart failure, in predicting survival.

Gastrointestinal complications from high dose Melphalan occur with greater frequency and severity in patients with AL amyloidosis than in multiple myeloma. The Mayo Clinic reported nine out of 45 patients (20%) who developed gastrointestinal bleeding during the post transplant period.[9] Oregon Health & Science University published a report of two patients (one with AL amyloidosis; one with multiple myeloma and amyloid deposition) who developed toxic megacolon as a fatal post-transplant complication.[10] In an effort to reduce serious gastrointestinal toxicities from high dose Melphalan, thorough pre-transplant gastrointestinal evaluation is recommended. In addition, proton pump inhibitors and aggressive antiemetic regimens are recommended for at least seven days post transplant.[7]

Timing

A prospective randomized trial was published in February 2004 that compared two cycles of oral melphalan and prednisone followed by ASCT to immediate ASCT in AL amyloidosis.[11] Researchers at Boston University Medical Center randomized 100 patients to the trial and evaluated survival and response. Overall survival, hematologic response, and organ system improvement did not differ between the two groups. However, more patients on the oral chemotherapy arm did not proceed to transplant due to progression of disease. The authors concluded that oral chemotherapy did not offer benefit to newly diagnosed AL amyloidosis patients that were ASCT candidates. Patients

with cardiac involvement showed a trend to worse survival if their ASCT was delayed due to treatment with oral chemotherapy.

Current clinical trials

A search of the National Cancer Institute's PDQ® Database identifies five active phase II clinical trials and one phase I trial employing high dose therapy for AL amyloidosis. There are no phase III trials listed. The Southwest Oncology Group has recently activated an NCI sponsored, multi-center phase II trial (S0115) designed to assess the overall survival, hematologic response, and toxicity of two cycles of modified high dose melphalan (100 mg/m2) in patients with AL amyloidosis and/or high risk multiple myeloma. The trial proposes to accrue 100 patients. There is no upper age limit, however, patients must have evidence of insurance coverage or ability to pay for transplantation.

Conclusions

High dose melphalan and ASCT appears to offer the best chance of improved organ function and survival for selected patients with AL amyloidosis. Oral and standard dose intravenous cytotoxic therapies offer minimal benefit and evidence is lacking for non-cytotoxic approaches. Unfortunately, high dose therapy conveys considerable risk, particularly to patients with significant cardiac or gastrointestinal involvement. Employing a risk adapted approach, as described by Comenzo and Gertz, can help guide clinicians to appropriately select patients who are most likely to benefit without excess risk of treatment related mortality. Although phase III trials would be extremely helpful in providing comparative data for transplant versus non-transplant therapy, the rarity of the disease, it's propensity to present later in life (often in Medicare-covered patients), and the heterogeneity of patient characteristics create challenges for researchers planning such a trial. Coverage of ASCT by Medicare could provide substantially more clinical trial candidates, thus making a phase III trial more feasible. In the meantime, the benefits of ASCT in AL amyloidosis are sufficiently compelling that appropriate patients covered by Medicare should have access to this promising therapeutic option.

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