Attachment B: Literature Review

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Buren M van , Hene R, Verdonck L, Verzijlbergen F, Lokhorst H / Clinical remission after syngeneic bone marrow transplantation in a patient with AL amyloidosis / Annals of Internal Medicine / 1995	Case study	Improved response to alternative therapy.	A 32 year old woman who was unresponsive to treatments of melphalan and prednisone received a syngeneic bone marrow transplantation with stem cells harvested from a monozygotic twin.	Gradual improvements in symptoms were observed. Monoclonal light chains disappeared from both urine and serum. Amyloid deposits decreased markedly, especially in the spleen.	Findings based on a single case study provide insufficient evidence. Authors acknowledge the need for further clinical evidence as to the utility of the treatment.
Comenzo R / Advances in the treament of plasma cell diseases / Hospital Practice / 1996	Overview	Not a clinical trial	Not a clinical trial	Not a clinical trial	This report does not provide scientific information in regards to the clinical utility of autologous stem cell transplantation (AuSCT) for AL amyloidosis.
Comenzo R, Falk R, Reisinger J, Dubrey S, Finn K, Sarnacki D, et al / AL amyloidosis frequently remits after dose-intensive melphalan with blood stem cell support: outcome in 55 patients / International Workshop on Multiple Myeloma: Poster Sessions / 1997	Case series	Assessment of remission rates, survival rates, persistence of plasma cell dyscracia, and of any worsening, stabilization, or improvement of amyloid-related organ disease.	55 AL amyloidosis patients (median age of 48) with adequate cardiac, renal, and pulmonary functions were treated. All patients were given high dose melphalan (HDM) with AuSCT. Enrollees were followed 3 months, 12 months, and annually thereafter.	There were 3 treatment-related deaths after chemotherapy. A total of 8 patients died within the first 9 months. 67% of deaths overall occurred in patients with amyloid cardiomyopathy At follow-up of 13 months: 42% (23/55) are alive in complete remission (CR) 31% (17/55) are alive with disease presistence 27% (15/55) died	The abstract does not contain sufficient evidence to thoroughly review and critique the clinical information and study protocols. Note 58% of patients did not benefit from treatment.

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Comenzo R, Sarnacki D, Finn K, Falk R, Sanchorawala V, Akpek G, et al / AL amyloidosis responds to high-dose melphalan and blood stem cells / New Approaches to Gene Therapy /	Case series	Assessment of complication and outcome rates for patients undergoing HDM and AuSCT.	21 patients were enrolled (median age of 45). Dominant organ dsyfunction were catagorized as either heart, kidneys, liver, GI tract, or lymphoid system. 19 patients received HDM & AuSCT	At follow-up of 13 months, 17 patients were alive. -- 11 patients experienced complete remission -- 6 patients experience organ improvements	The orgin of this abstract is unclear. The abstract does not contain sufficient evidence to thoroughly review and critique the clinical information and study protocols.
Comenzo R, Vosburgh E, Falk R, Fisher C, Finn K, Dember L, et al / High dose melphalan for AL amyloidosis: outcomes in 50 patients / International Amyloid Symposium / 1998	Case series	Assessment of survival, CR, change in function of major organ involvement.	50 AL amyloidosis patients (median age of 55) treated with HDM and AuSCT.	10 months after treatment, 39 of 50 patient were alive. Of those patients with major organ involvement who were alive at 12 months (n=21), 13 improved and 6 stabilized. Age and number of organ systems involved were identified as negative prognastic factors to overall survival.	Abstract suggests that AuSCT may be safe for only a subset of patients less then 55 years of age with 1 to 2 major systems involved. The abstract does not contain sufficient evidence to thoroughly review and critique the clinical information and study protocols.

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Comenzo R, Vosburgh E, Falk R, Sanchorawala V, Reisinger J, Dubrey S, et al / Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients / Blood / 1998	Case series	Response to therapy was determined by survival, improvement in performance status, CR, persistence of clonal plasma cell disorder, and change in function of involved organs	25 patients (median age 48 years) were enrolled. - 22 were SWOG performance status 1 or 2 - 16 had no prior therapy. Predominant organ involvement was cardiac (n=8), renal (n=7), hepatic (n=6), neuropathic (n=3), and lymphatic (n=1). 15 patients had 1-2 organ systems involved; 10 had three or more.	2 patients died before receiving chemotherapy. At 24 months, 17 of 25 patients were alive. Of which: -- 11 had improvements in involved organ systems -- 4 stabilized -- 13 of 15 patients with 2 or less involved organ systems survived -- 4 of 10 patients with >2 involved organ systems survived There were 3 deaths within 100 days of transplant.	The article suggests that patients with predominant cardiac involvement, particularly those with more then 2 involved organ systems, are high-risk candidates for AuSCT. Patients with 0-2 involved organ systems are considered good candidates for the procedure. However, with such small sample sizes, the data may be biased. No comparisons were made to alternative modes of treatment.

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Comenzo R, Vosburgh E, Simms R, Beregethon P, Sarnacki D, Finn K, et al / Dose-intensive melphalan with blood stem cell support for the treatment of AL amyloidosis: one-year follow-up in five patients / Blood / 1996	Case series	Provide support to the efficacy of AuSCT used with dose-intensive intravenous (IV) melphalan	5 patients were enrolled. - age range: 38-53 years - median SWOG performance status of 2 Clinical presentations included: nephrotic syndrome (n=1), symptomatic cardiomyopathy (n=1), GI involvement (n=2), hepatomegaly (n=1); Median follow up 13 months	All patients showed stable improvements post treatment. 50% reduction in daily proteinuria with no change in creatinine. Reversal of symptoms of cardiomyopathy, polyneuropathy, and gastric atony. Resolution of hepatomegaly by CT scan. At 12 months, plasma cell dyscrasias could not be detected in 3 patients.	The very small sample leads to questions in regards to the significance of the study.
Desikan KR, Dhodapkar MV, Hough A, Waldron T, Jagannath S, Siegel D, et al / Incidence and impact of light chain associated (AL) amyloidosis on the prognosis of patients with multiple myeloma treated with autologous transplantation / Leukemia and Lymphoma / 1997	Prospective cohort study	The study determines the incidence of AL amyloid in patients with multiple myeloma (MM) and its prognostic impact on treatment with HDM.	84 consecutive, previously untreated patients with MM enrolled in a phase II trial for sequential chemotherapy. Patient were evaluated for amyloid by abdominal fat pad aspirate and bone marrow biopsy.	The presence of amyloid was noted in 38% of patients. There were no characteristic difference between patients with amyloid and those with out. For MM patients who receive AuSCT, clinical outcome was not unrelated to presence of amyloid.	This study lends information on the incidence and prognostic relationship of AL amyloid for MM patients. However, there is no obvious relationship between this study and treatment outcome for AL amyloidosis patients undergoing AuSCT.

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Dubrey S, Cha K, Anderson CJ, Chamarthi B, Reisinger J, Skinner M, Falk RH / The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement / Quarterly Journal Medicine / 1998	Case series	Reviewed clinical presentation, investigations, therapy, prognosis, and outcome of 232 patients with primary (AL) cardiac amyloidosis.	Median age at presentation was 59 years. AL heart disease was unusual both in patients under the age of 40 (3.0%) and in non-Caucasians (6.5%). Fatigue and weakness were the commonest presenting symptoms. Heart involvement represents the worst prognostic indicator with a median survival from diagnosis of 1.08 years, falling to 0.75 years with the onset of heart failure.	Cardiac involvement from AL amyloidosis is rapidly fatal. It should be suspected in all patients with heart failure who have wall thickening, normal chamber sizes, low EKG voltages and evidence suggesting a multi-system disease.	The article does not provide data on the clinical utility of AuSCT on patients with AL amyloidosis.
Dubrey S, Mendes L, Skinner M, Falk R / Resolution of heart failure in patients with AL amyloidosis / Annals of Internal Medicine / 1996	Case series	Correlation between improvements in cardiac symptoms, echocardiographic features, and disease activity.	3 patients out of a study of 140 patients displayed marked resolution of congestion heart failure (CHF) and evidence of disease remission.	All 3 patients were treated with melphalan. Light chain fragments may play a toxic role in the prevalence of heart failure among patients with AL amyloidosis.	The article presents no direct evidence on the clinical utility of AuSCT.

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Falk R, Comenzo R, Skinner M / The systemic amyloidoses / New England Journal of Medicine / 1997	Overview	Not a clinical trial.	1275 to 3200 new cases of AL amyloidosis are reported annually in US. Cardiac involvement is common. Congestive heart failure, usually rapid in onset and progressive, may be preceded by symptomatic EKG abnormalities. Splenic dysfunction (hyposplenism) is a common finding, occurring in 24% of cases. Diagnosis can be established by a tissue biopsy or by Congo Red staining.	Since patients with cardiac amyloidosis have a very short survival, few receive sufficient therapy to influence survival. The article suggests that patients must live long enough to receive several cycles of melphalan before a survival benefit can occur. Increases in survival from a median of approximately 6 months to 12 months can occur on average in patients receiving chemotherapy.	This article provides background information on systemic amyloidosis. No direct evidence is presented.
Gillmore J, Apperley J, Craddock C, Madhoo S, Pepys M, Hawkins P, et al / High dose-melphalan and stem cell rescue for AL amyloidosis / International Amyloid Symposium / 1998	Case series	Evaluate AuSCTas a viable treatment option.	27 patients with AL amyloidosis underwent HDM and AuSCT.	8 treatment-related deaths occurred. Regression of amyloid was noted in 7 patients. 33 months after treatment, 17 patients were alive.	The abstract does not contain sufficient evidence to thoroughly review and critique the clinical information and study protocols. It's worth noting that the authors conclude that response rates from HDM are promising but that AuSCT carries a substantial mortality risk.

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Kyle, R / High-dose therapy in multiple myeloma and primary amyloidosis: an overview / Seminars in Oncology / 1999	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	The article presents no direct evidence on the clinical utility of AuSCT. It is important to note that the author makes the following conclusions: "confirmation of the favorable results obtained from AuSCT for primary AL is necessary". Furthermore, author goes on to say "consequently, a cohort of patients with primary AL who are eligible for transplant must be randomized to receive the best available chemotherapy regimen or AuSCT".
Majolino I, Raimondo M, Pecoraro G, Scime R, Vasta S, Liberti G, et al / High-dose therapy and autologous transplantation in amyloidosis / Haematologica / 1993	Case study	Disease course of AL amyloidosis through treatment and after.	A 53 year old woman with AL amyloidosis underwent HDM and AuSC after unsuccessful attempts at standard dose.	Two weeks after transplant, patient's marrow plasma cells were reduced in number and immunohistochemically polyclonal. However, patient died of interstitial pneumonitis 10 weeks post-transplant.	Findings based on a single case study provides insufficient evidence on clinical utility. Authors warn of possible increases in susceptibility of fatal infections in AL amyloidosis patients who receive AuSCT.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Moreau P, Leblond V, Bourquelot P, Facon T, Huynh A, Caillot D, et al / Prognostic factors for survival and response after high-dose therapy and autologous stem cell transplantation for systemic amyloidosis: a report on 22 cases / International Amyloid Symposium / 1998	Case series	Evaluate the feasibility of AuSCTas a treatment option and identify factors predictive for overall and event-free survival.	21 AL amyloidosis patients (median age 45 years) underwent 22 AuSCT combined with HDM.	Toxic death rate was a high 43% (9/21 patients died within the first month of AuSCT). 2 patients did not respond to HDM. The major prognostic factors for survival and response was the number of clinical manifestations at the time of AuSCT.	The abstract does not contain sufficient evidence to thoroughly review and critique the clinical information and study protocols. Abstract suggests AuSCT may not be safe for all AL amyloidosis patients, only for patients with less than 2 clinical manifestations.
Moreau P, Leblond V, Bourquelot P, Facon T, Huynh A, Caillot D, et al / Prognostic factors for survival and response after high-dose therapy and autologous stem cell transplantation in systemic AL amyloidosis: a report on 21 patients / British Journal of Haematology / 1998	Case Series	Response is defined to be a 50% reduction in 24h protein without an increase in serum creatine levels (nephrotic syndrome), normal creatine levels (renal insufficiency), resolution of clinical symptoms of congestive heart failure (cardiac involvement).	21 patients with confirmed AL amyloidosis underwent AuSCT with HDM. Patients with secondary, familial, senile, localized amyloidosis or overt symptomatic multiple myeloma were not included in this study. Number of patients with AL amyloidosis who could not proceed to AuSCT was not known.	There were 9 toxic deaths observed within 1 month of AuSCT (43%). 10 of 12 surviving patients experienced response with improved organ function (47% from original sample size). For the whole group of patients, actuarial 4-year event free survival was 29.9% The number of clinical manifestations at the time of AuSCT was identified as a prognostic factor.	The high toxicity rate raises safety concerns. Exclusions criteria and the inability to account for patients who were unable to tolerate AuSCT suggests possible selection biases within the results. The study does not compare AuSCT to alternative forms of treatment.

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Moreau P, Milpied N, Faucal P de, Petit T, Herbouiller P, Bataille R, Harousseau JL / Correspondence: high-dose melphalan and autologous bone marrow transplantation for systemic AL amyloidosis with cardiac involvement / Blood / 1996	Case study	Survival and symptom improvement	A 45 year old female with AL amyloidosis and congestive heart failure underwent HDM and AuSCT.	After 17 months, considerable improvements in performance status were observed, but no improvement in amyloid deposition in the left ventricle.	Findings based on a single case study provide insufficient evidence. Authors suggest HDM and AuSCT should be considered in patients with evaluative AL disease under the age of 60.
Oheson B / Lymphoid leukemias and plasma cell disorders / Scientific American Medicine / 1999	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	The article presents no direct evidence on the clinical utility of AuSCT. It is important to note that the author makes the following conclusions: "high-dose therapy with stem cell support has been reported in a small number of patients but without clear clinical benefit".
Reisinger J, Dubrey S, Falk R / Cardiac amyloidosis / Cardiology in Review / 1997	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Overview of the types of systemic amyloidoses that affect the heart. No direct evidence on clinical utility is presented.

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Sanchorawala V, Wright D, Dember L, Seldin D, Vosburgh E, Finn K, et al. / Five years experience with high dose intravenous melphalan and autologous peripheral blood stem cell transplantation for the treatment of patients with AL amyloidosis / Abstract /	Case series	HDM and AuSCT with AL amyloidosis Protocols were developed depending upon age and clinical status. Patients received either 200 mg/m2 (n=83) or 100-140 mg/m2 (n=76) of IV melphalan.	159 patients were treated (median age of 56 years).	Of 117 patients treated before July 1998, -- 88 were alive at 1 year -- 16 died within 3 months -- 13 died between 3-12 months Of 79 treated before July 1997, - 48 survived after 2 years Mean survival of patients in CR 30.4 months vs. 25.5 months for non-CR patients.	The abstract does not contain sufficient evidence to thoroughly review and critique the clinical information and study protocols.
Skinner M / Amyloidosis / Current Therapy in Allergy, Immunology, and Rheumatology / 1996	Overview	Not a clinical trial	Not a clinical trial	Not a clinical trial	Article provided an overview of AL amyloidosis. No direct clinical evidence was presented.

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Skinner M, Anderson J, Simms R, Falk R, Wang M, Libbey C, et al / Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only / American Journal of Medicine / 1996	Randomized clinical trial	Median survival between patients receiving either colchicine (C) alone or colchicine with melphalan and prednisone (MPC).	100 patients with AL amyloidosis were treated: -- seen between 1987 and 1992 -- median ages in both treatment groups were 62.7 years and 60.6 years -- no prior treatment of melphalan and prednisone -- not diagnosed with multiple myeloma Patients were randomized by sex, time from diagnosis to study entry, and dominant organ system involvement.	Overall survival for the entire group was 8.4 months: -- MPC = 12.2 months; C = 6.7 months -- 80% of patients had died after 6 years Poorest survival was in the cardiac group (4.4 months), the longest in the renal group (18.7 months). Significant differences between treatments were only observed in neurological and other groups, favoring MPC.	Study does not provide clinically relevant data on AuSCT. This study, however, demonstrates the differential effect of organ system involvement on survival and the possible delaying effect of MPC in regards to organ failure.
Skinner M, Finn K, Comenzo R, Vosburgh E, Sanchorawala V, Akpek G, et al / Four years experience with high dose IV melphalan and peripheral stem cell Rescue in AL amyloidosis / Arthritis and Rheumatism / 1998	Randomized clinical trial	CR of plasma cell dyscrasia at 3 months and survival. Protocols (with eligibility based on age, performance status, renal and cardiac function) were developed to: 1. Test efficacy, 2. Treat sicker patients, 3. Use CD 34 selected stem cell rescue (SCR) 4. Randomize patients to IV melphalan/SCR either immediately or after 2 cycles of oral melphalan.	108 patients were treated and evaluated.	11 patients were not treated for reasons of death, complications, or choosing to go elsewhere. Negative prognostic factors were involvement of more than 2 major organ systems, predominant cardiac involvement, and age greater than 55 years.	The abstract does not contain sufficient evidence to thoroughly review and critique the clinical information and study protocols.