

Attachment B: Literature Review

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Alegre A, Diaz-Mediavilla J, San-Miguel J, et al / Autologous peripheral blood stem cell transplantation for multiple myeloma: a report of 259 cases from the Spanish registry / Bone Marrow Transplantation / 1998	Retrospective cohort study	<p>Overall survival (OS), event-free survival (EFS), Complete response (CR), partial response (PR), treatment-related toxicity were assessed after patients were given high-dose chemotherapy (HDT) and autologous stem cell transplantation (AuSCT).</p> <p>CR was defined as disappearance of myeloma protein on electrophoresis in both serum and urine, and < 5% of bone marrow plasma cells (immunofixation was not required). PR required > 50% reduction in serum and/or urinary measurable monoclonal proteins. Nonresponders (NR) were those without CR or PR.</p>	<p>259 patients with multiple myeloma (MM) from the Spanish Registry were included in the study.</p> <p>Median Age: 52 (23-67)</p> <p>Stage at diagnosis: Stage I 22 (9%) Stage II 57 (22%) Stage III 180 (69%)</p> <p>Renal insufficiency at diagnosis (serum creatinine > 2 mg/dl) 39 (15%)</p> <p>Prior chemotherapy regimens: 1 135 (52%) 2 61 (24%) 3 55 (21%) >3 8 (2%)</p> <p>Response status prior AuSCT: CR 56 (21%) PR 153 (59%) NR 25 (10%) Progression 25 (10%)</p>	<p>11 patients (4%) died from treatment-related complications. 248 patients were evaluated post-transplant.</p> <p>Response status post AuSCT: CR 125 (51%) PR 100 (41%) NR 12 (5%) Progression 10 (4%)</p> <p>59 prior-PR patients entered into CR. Of those patients with progressive disease, 9 entered into CR and 7 into PR.</p> <p>Median duration of EFS and OS were 23 and 35 months, respectively. Analysis estimated that EFS and OS at 3 years would be 38% and 50%, respectively.</p> <p>Prognostic factors influencing OS include number of lines of prior treatment (1 vs. 2+), response status pre-transplant, and use of IFN-alpha post-transplant. Presence of renal failure had borderline influence.</p>	<p>This study failed to compare the treatment group with a control which makes it difficult to judge comparative effectiveness in treating multiple myeloma.</p> <p>In addition, the use of registry data makes it difficult to assess whether patient recruitment was influenced by selection bias. The study does highlight which prognostic factors, pre and post transplant, influence survival, and there is underpowering of prognostic results, with small groups.</p>

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Alexanian R, Dimopoulos M, Smith T, Delasalle K, Barlogie B, Champlin R / Limited value of myeloablative therapy for late multiple myeloma / Blood / 1994	Case-control study	<p>Treatment-related deaths, survival, remission and response rates were assessed after patients were either given HDT, total body irradiation (TBI), and AuSCT or given vincristine-doxorubicin pulse dexamethasone (VAD).</p> <p>Response was defined as a 75% reduction of serum myeloma protein production, disappearance of Bence Jones protein, and reduction of marrow plasma-cytosis to less than 5%. CR required disappearance of serum monoclonal globulin on immunofixation studies.</p>	<p>49 patients with MM received HDT/AuSCT of which 26 also received TBI. Age limit of 62 was chosen. Median age of group was 52. All received intensive therapy after at least 2 courses of VAD.</p> <p>Patients were classified into 3 groups: resistance relapse (myeloma relapsed despite VAD; n=23), prolonged primary resistance (resistance to primary treatment > 1 year; n=15), and late remission (successful VAD treatment of resistance disease; n=11).</p> <p>For each of the 3 groups, control patients who received VAD and met the eligibility criteria for HDT and AuSCT were also selected. These patients continued receiving VAD. A total of 79 patients were enrolled: 33 in resistance relapse, 32 primary resistance, 14 in late remission.</p>	<p>7 patients (14%) died of treatment-related complications and considered NR.</p> <p>Resistance relapse: Intensive therapy induced responses in 14 patients (61%) of AuSCT group. Treatment-related deaths occurred in 4 patients (17%). No patients achieved CR. Median survival and remission was at 8 months and 3 months respectively. Survival for treatment group was similar to control group.</p> <p>Primary Resistance: In the treatment group, there were 2 treatment-related deaths (13%). 6 patients responded but no patient achieved CR. Among the 6 patients, median remission was 17 months. Survival for treatment group was similar to control group.</p> <p>Late remission: Treatment-related deaths occurred in 1 patient. 4 patients achieved CR in treatment group compared to 1 in the control group. Median remission time was 12 months, similar to control group.</p>	<p>This compares treatment group to a control group. The findings of the study indicate that for these particular MM patient groups, HDT and AuSCT result in similar remission and survival outcomes as in the control group. However the study does not fully explain the variation within the treatment and control groups. In addition, outcomes data resulting from the various regimens used (TBI vs. no TBI) was not teased out of the aggregate data. Finally, although the control group was eligible for AuSCT, these patients were selected as controls because they were unable to obtain the treatment because of economic or insurance coverage. All these factors can introduce important selection bias, which can significantly affect results.</p>

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Anderson K, Andersen J, Soiffer R, et al / Monoclonal antibody-purged bone marrow transplantation therapy for multiple myeloma / Blood / 1993	Cohort study	<p>OS, EFS, CR, PR, treatment-related toxicity were assessed after patients were given HDT followed by either AuSCT or allogeneic stem cell transplantation (AlloSCT).</p> <p>Criteria for CR include, for at least 3 months, both (1) absence of serum paraprotein and Bence Jones proteinuria by immuno-electrophoresis and immunofixation; and (2) fewer than 5% polyclonal plasma cells. A 50% decrease in measurable protein sustained for at least 1 month was considered PR.</p>	<p>Patients were eligible for AuSCT if they < 60. Patients underwent AlloSCT if < 55 and had a histo-compatible sibling. Additional criteria include absence of a comorbid organ disease. Patient with prior radiotherapy were given only HDT and did not receive TBI. Where possible, AlloSCT had preference over AuSCT.</p> <p>AuSCT group (n=26): ---Median Age: 47 (35-59) ---Stage at diagnosis: Stage I 2 Stage II 4 Stage III 19 ---Prior chemotherapy regiments: 2 7 3 11 >3 8 ---Prior radiotherapy: 14</p> <p>AlloSCT group (n=13): ---Median Age: 43 (37-52) ---Stage at diagnosis: Stage I 2 Stage II 3 Stage III 8 ---Prior chemotherapy regiments: 1 1 2 7 3 3 >3 2 ---Prior radiotherapy: 3</p>	<p>25 patients with MM and 1 patients with recurrent extramedullary plasmacytomas underwent AuSCT. There was 1 treatment-related death. There were 11 CRs and 14 PRs post treatment. With 24 months median follow-up, 21 of 26 were alive at 2+ to 68+ months post-transplant and 16 remained alive progression-free at 2+ to 55+ months post-transplant. Of these, 5 patients remained in CR at 6+ to 55+ months post-transplant. 3 patients died from disease progression and 7 patients relapsed. Median EFS was 36 months.</p> <p>7 patients achieved CR, 4 achieved PR, and 1 was NR after undergoing AlloSCT. 1 patient underwent syngeneic grafting. There were 2 treatment-related deaths. With 24 months median follow-up, 9 of the 14 patients who received either AlloSCT or syngeneic grafting are alive. 8 patients remain alive free some progression at 8+ to 34+ months post transplant. Of these 5 remain in CR. 4 patients relapsed. 1 patient remains alive post transplant at 24 months.</p>	<p>This article does not comment on the differences in effectiveness regarding the use of AlloSCT or AuSCT. In fact, the purpose of the study was not the compare the two treatments. Rather the authors concluded from their results that these treatments strategies should be use earlier in the disease course. The potential for selection bias in this study is significant. Patients were not randomized to the treatment groups. They were allocated based on the availability of histo-compatible siblings. There is very little evidence that compares the effectiveness of AuSCT to standard chemotherapy.</p>

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Anderson K, Hamblin T, Traynor A / Management of multiple myeloma today / Seminars in Hematology / 1999	Review	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This article reviews the current outstanding issues in the management of multiple myeloma. Discussions include (but are not limited to) conventional vs. combination chemotherapy, the use of alpha-interferon, and high-dose chemotherapy vs. standard dose. No direct evidence is presented, however.
Atkins C / High-dose chemotherapy in multiple myeloma: letters to the editor / New England Journal of Medicine / 1996	Editorial	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Author offers a dissenting opinion contrary to the conclusions made in Attal, et al. (1996). No direct evidence is presented, however.

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Attal M / Unpublished data / Located at: Intergroupe Francais du Myeloma / 1999	Update	See Attal et al, 1996.	See Attal et al, 1996.	<p data-bbox="1423 272 1675 383">New analysis (using a 70 months median follow-up) projects overall survival estimates to 7 years:</p> <p data-bbox="1423 412 1688 493">CC Group n=100: Median OS: 42 months at 7 yrs. post-diagnosis</p> <p data-bbox="1423 522 1688 604">HDC Group n=100: Median OS 57 months at 7 yrs. post-diagnosis</p> <p data-bbox="1423 633 1688 743">Percent of patients projected to be alive: (p<0.05): CC Group: 15% HDC Group: 40%</p>	<p data-bbox="1717 272 1978 578">Graphs continue to project survival data based on n=100 patients receiving HDC in combination with ABMT. However, the original published article indicates n=26 patients in HDC arm were excluded from ABMT. Therefore, n=74 patients actually received HDT & ABMT.</p> <p data-bbox="1717 607 1978 688">Because of this discrepancy, one questions the basis of the OS statistical projections.</p> <p data-bbox="1717 717 1978 799">No other data or information, no explanation is provided.</p> <p data-bbox="1717 828 1919 854">See Attal et al, 1996.</p>

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Attal M, Harousseau J / Standard therapy versus autologous transplantation in multiple myeloma / Hematology/Oncology Clinics of North America / 1997	Update	See Attal et al, 1996.	See Attal et al, 1996.	<p data-bbox="1425 274 1703 521">Author postulates that further improvements of HDC vs. CC can be expected in terms of feasibility (HDC combined with hematopoietic growth factors and peripheral blood stem cells) and in terms of response rates (using tandem transplants).</p> <p data-bbox="1425 553 1703 769">Author concludes that a substantial improvement in long-term survival, however will require the development of effective maintenance therapy to control the minimal residual disease present after transplant.</p>	<p data-bbox="1719 274 1976 412">This article summarizes the results of the IFM90 trial and discusses future developments of high-dose therapy in myeloma.</p> <p data-bbox="1719 444 1976 493">No additional evidence is presented.</p>
Attal M, Harousseau J, Bataille R / High-dose chemotherapy in multiple myeloma / New England Journal of Medicine / 1996	Editorial	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	<p data-bbox="1719 829 1976 984">Authors respond to dissenting opinions made regarding their clinical trial reported in Attal, et al. (1996). No direct evidence is presented, however.</p>

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Attal M, Harousseau J, Stoppa A, et al / A prospective randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma / New England Journal of Medicine / 1996	Randomized, prospective clinical trial	<p>OS, EFS, CR, Very good partial response (VGPR), PR, Minimal Response (MR), and Progressive disease (PD) were assessed after treatment with either conventional dose (CC) or HDT with AuSCT.</p> <p>CR= absence of a paraprotein on electrophoresis of serum & urine, and 5% or fewer plasma cells with normal morphologic features in a bone marrow aspirate. VGPR= 90% decrease in serum paraprotein level. PR= 50% decrease in serum paraprotein levels and 90% decrease in Bence Jones proteins. MR= 25% decrease in serum paraprotein levels. PD=25% increase in serum paraprotein levels.</p>	<p>200 patients less than 65 years of age, with multiple myeloma Durie-Salmon Stage II/III were eligible.</p> <p>Exclusion Criteria: prior treatment, other cancer, abnormal cardiac function, chronic respiratory disease, abnormal liver function, and psychiatric disease.</p> <p>Randomization: n=100 assigned at time of diagnosis to two treatment groups, CC and HDT with AuSCT.</p> <p>CC group: Age: 58 yrs. (+- 5.2) Stage (II/III): 23/77 LDH (IU): 230 (+- 131) Creatinine (mg/dL): 1.3 (+- 0.9) B2 Microglobulin (mg/L): 5 (+- 4.4)</p> <p>HDT Group: Age: 57 (+- 6.4) Stage (II/III): 28/72 LDH (IU): 264 (+- 155) Creatinine (mg/dL) 1.3 (+- 0.9) B2 Microglobulin (mg/L): 4.5 (+- 4)</p> <p>Treatment Regimen: CC Group: 18 cycles alt. VMCP & BVAP, every 3 wks. for 12 months for a total of 18 cycles. Recombinant interferon</p>	<p>74 patients in the HDT group underwent AuSCT.</p> <p>Among the 26 patients in the HDT group who did not undergo AuSCT, 5 died, 6 had poor performance status, 5 had abnormal renal function, and 10 had insufficient bone marrow cellularity.</p> <p>This article does not discuss the disposition of the remaining 21 patients.</p> <p>AuSCT exclusions were related to age: 12/67 (18%) patients <60 yrs. did not undergo AuSCT vs. 14/33 (42 %) patients >60, P=0.01.</p> <p>Response Rates: CC Group (n=100) CR 5 VGPR 9 PR 43 MR 18 PD 25</p> <p>HDT Group (n=100) CR 22 VGPR 16 PR 43 MR 7 PD 12</p> <p>HDT/AuSCT Group (n=74)* CR 22 VGPR 16 PR 32</p>	<p>This study did not enroll patients over age 65 which makes it difficult to assess the extent of age as a prognostic factor for patients with multiple myeloma.</p> <p>However, this study stratified survival of patients into above age 60 and below age 60 groups.</p> <p>Without additional data on patients 65 or older, it is difficult to estimate the extent of age related comorbidities that affect response to treatment, treatment toxicity and bone marrow stem cell reserve capacity.</p> <p>In addition, Kaplan-Meier graphs appear to project survival data based on n=100 patients receiving HDT in combination with AuSCT. However, n=26 patients in HDT & AuSCT treatment arm were excluded from AuSCT. Therefore, only n=74 patients actually received the intended HDT & AuSCT, thus raising questions about the robustness of the survival projections.</p> <p>Low p-value does not</p>

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			<p>alpha was administered 3x/wk until the occurrence of any relapse.</p> <p>HDT Group: After 4-6 cycles alt. VMCP & BVAP, patients with a performance status below WHO criteria grade 3 (creatinine <1.7 mg/dL & bone marrow >200 million nucleated cells/kg of body weight) underwent unpurged AuSCT after preparation with melphalan and TBI. Interferon alpha was started after hematologic reconstitution following AuSCT.</p>	<p>MR -- PD --</p> <p>*A low level of B2 Microglobulin was the only significant predictor of a complete or a very good partial response (p<0.001)</p> <p>Survival estimates (median): CC Group: OS - 37.4 mo. (12% prob.) EFS - 18 mo. (10% prob.) 52 patients died (47 due to disease progression, 5 due to treatment toxicity).</p> <p>HDT/AuSCT Group: OS - Not reached as of this writing (52% prob.) EFS - 27 mo. (28% prob.) 37 patients in the high dose group died (30 due to disease progression, 7 due to treatment toxicity - including 2 transplantation-related deaths).</p>	<p>enable one to determine whether patients with low beta-2-microglobulin will better respond to a given therapy.</p>

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Attal M, Harousseau J, Stoppa A, et al / High dose therapy in multiple myeloma: an update analysis of the IFM 90 protocol / Blood / 1997	Update	See Attal et al, 1996.	See Attal et al, 1996.	<p>New analysis with 60 months median follow-up:</p> <p>Conventional chemotherapy (CC) group: --6-year post-diagnosis: probability of EFS and OS 15% (median 18 months) EFS, 21% (median 42 months) OS</p> <p>High dose therapy (HT) group: --6-year post-diagnosis: probability of EFS and OS 24% (median 28 months) EFS, 43% (median 57 months) OS</p>	See Attal et al, 1996.
Attal M, Payen C, Facon T, et al / High dose therapy in multiple myeloma: the experience of the "intergroupe francais du myelome" (IFM) / Cancer Research Therapy and Control / 1998	Review	Not a clinical trial.	Not a clinical trial.	<p>Report describes the conclusions of the IFM90 and IFM94 protocols.</p> <p>Report concludes that recent analysis of the IFM90 protocol confirms HDC improves survival.</p> <p>Preliminary analysis of the IFM94 protocol suggests that unselected peripheral blood stem cells (PBSC) could be a recommended source for BMT.</p>	<p>Report states that further improvement in long term survival require the development of effective maintenance strategies to control for residual disease present after single, and double bone marrow transplantation.</p> <p>No direct evidence is presented.</p>

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Barlogie B / Autologous hematopoietic cell treatment for multiple myeloma / Hematopoietic Cell Transplantation / 1998	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This article provides background information on AuSCT for multiple myeloma. Information presented includes disease etiology, review of clinical trials assessing the effectiveness of AuSCT, and outstanding issues currently being investigated. No direct evidence is presented, however.
Barlogie B / Unpublished data / Located at: University of Arkansas for medical sciences / 1999	Unknown	EFS and OS.	1004 patients enrolled in tandem high-dose therapy program. No other characteristics reported.	Results were consolidated into the following graphs: ----survival by age group (>65 vs. <65), ----survival by age group and <12 months of prior therapy (>65 vs. <65), ----overall survival in low, intermediate, and high risk groups (>65 vs. <65). Actual numbers were not easily abstracted.	Data provided has not been published. Treatment protocols and patient characteristics were not included, thus making a proper evaluation difficult.

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Barlogie B, Jagannath S, Vesole D, et al. / Superiority of tandem autologous transplantation over standard therapy for previously treated multiple myeloma / Blood / 1997	Cross-study/Case-control study	<p>Patients were assessed on EFS, OS, and response rates after receiving total therapy (TT). TT involves VAD regimens followed by high-dose cyclophosphamide (HDCTX). Etoposide, dexamethasone, cytarabine, and cisplatin (EDAP) were used to target immature tumor cells. In the absence of tumor progression, patients proceed through the induction phase followed by the first AuSCT. In case of PR or CR, a second AuSCT was performed. Those without PR or CR were treated with melphalan and TBI or HDT. TT was followed by interferon-alpha therapy (IFN)</p> <p>CR criteria required the disappearance of monoclonal gammopathy in serum and urine on immunofixation analysis, and attainment of normal marrow aspirate and biopsy with less than 1% light chain-restricted plasma cells on flow cytometry. PR required 75% or more tumor mass reduction, including a normal marrow aspirate and biopsy and a reduction of Bence Jones proteinuria to less than 100 mg per day.</p>	<p>Eligibility criteria for TT included symptomatic MM, and upper age limit of 70 years, and adequate cardiopulmonary function. Patients with renal failure secondary to MM could also be eligible. Patients were assessed using an intent-to-treat approach.</p> <p>134 previously untreated patients were registered at least 15 months before analysis. 3 were denied insurance coverage and 8 opted for AlloSCT for their second transplant. Of the remaining 123 patients in the analysis, 50% of TT patients were over 50 years. 11% of the patients had creatinine levels 2 mg/dL or greater. 54% of patients had beta-2 microglobulin levels 3 mg/L or greater.</p> <p>For comparison with TT, 116 patients with MM on standard therapy (ST) were selected from the Southwest Oncology Group (SWOG) trials and matched for age, beta-2 microglobulin levels, and serum creatinine.</p>	<p>Of the 123 patients who were in the TT group, 107 patients (87%) completed 1 AuSCT and 94 (76%) completed 2. 82 started IFN after TT.</p> <p>The following are the response rates after each step in the TT sequence: of note "PR+" signifies "at least PR"</p> <table border="1"> <thead> <tr> <th></th> <th>PR+</th> <th>CR</th> </tr> </thead> <tbody> <tr> <td>VAD</td> <td>41%</td> <td>5%</td> </tr> <tr> <td>HDCTX</td> <td>61%</td> <td>9%</td> </tr> <tr> <td>EDAP</td> <td>69%</td> <td>16%</td> </tr> <tr> <td>1 AuSCT @Time of</td> <td>78%</td> <td>25%</td> </tr> <tr> <td>2 AuSCT</td> <td>85%</td> <td>40%</td> </tr> <tr> <td>2 AuSCT</td> <td>92%</td> <td>48%</td> </tr> </tbody> </table> <p>Cumulative treatment-related mortality during the first 12 months was 4%.</p> <p>Comparing the TT group to the ST group with an intent-to-treat approach:</p> <table border="1"> <thead> <tr> <th></th> <th>TT</th> <th>ST</th> <th>p-val.</th> </tr> </thead> <tbody> <tr> <td>PR+</td> <td>86%</td> <td>52%</td> <td>.0001</td> </tr> <tr> <td>CR</td> <td>N/A</td> <td>N/A</td> <td></td> </tr> <tr> <td>EFS</td> <td>42</td> <td>22</td> <td>.0001</td> </tr> <tr> <td>OS</td> <td>62+</td> <td>48</td> <td>.01</td> </tr> <tr> <td>5yr EFS</td> <td>36%</td> <td>19%</td> <td>.0001</td> </tr> <tr> <td>5yr OS</td> <td>61%</td> <td>39%</td> <td>.01</td> </tr> </tbody> </table>		PR+	CR	VAD	41%	5%	HDCTX	61%	9%	EDAP	69%	16%	1 AuSCT @Time of	78%	25%	2 AuSCT	85%	40%	2 AuSCT	92%	48%		TT	ST	p-val.	PR+	86%	52%	.0001	CR	N/A	N/A		EFS	42	22	.0001	OS	62+	48	.01	5yr EFS	36%	19%	.0001	5yr OS	61%	39%	.01	<p>The study does not include an age range in order to determine the age of the oldest patients enrolled in the trial. It is important to note that nearly a quarter of the patients enrolled did not complete the fully prescribed regimens. In fact, only 83 of the original 123 completed and survived the entire treatment regimens. Having results lumped into aggregate numbers does not enable the reader to tease out the important characteristics of patients who either died, suffered disease progression, or benefited from the treatment. The potential for selection bias is significant. The healthiest and most resilient patients may have been the only ones to survive the treatment, leading to overly positive outcome results. This may have been remedied by the intent-to-treat analysis. Only a prospective randomized trial could lessen the impact of selection bias on the results.</p>
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Barlogie B, Shaughnessy J, Munshi N, Epstein J / Plasma cell myeloma / William's Hematology (ed 6) / 1999	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This article provides background information on multiple myeloma. Information presented includes disease etiology, biology, clinical features, and treatment options. No direct evidence is presented, however.
Bataille R, Harousseau J / Multiple myeloma / New England Journal of Medicine / 1997	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This article provides background information on multiple myeloma. Information presented includes biology and clinical features of multiple myeloma. Authors discuss current and investigational treatment options available. No direct evidence is presented, however.
Blue Cross Blue Shield Association / High dose chemotherapy with autologous stem cell support for multiple myeloma / TEC Assessment Program / 1996	Technology assessment	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This assessment provides a structured critique of the available medical literature regarding the effectiveness of HDT and AuSCT for patients with MM. No direct evidence is presented, however.

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Blue Cross Blue Shield Association / High-dose chemotherapy with autologous stem-cell support for treatment of multiple myeloma in older patients / TEC Assessment Program / 2000	Technology assessment	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This assessment provides a structured critique of the available medical literature regarding the effectiveness of HDT and AuSCT for patients with MM. No direct evidence is presented, however.
Burke H, Henson D / Evaluating prognostic factors / CME Journal of Gynecologic Oncology / 1999	Review	Not a clinical trial	Not a clinical trial	Not a clinical trial	<p>Supports discussion on the methodological steps needed to transform any putative oncologic prognostic factor into one which can be used for clinical management:</p> <ol style="list-style-type: none"> 1. Discovery and characterization of the factor 2. Replication 3. Validation

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Cunningham D, Paz-Ares L, Milan S, et al / High-dose melphalan and autologous bone marrow transplantation as consolidation in previously untreated myeloma / Journal of Clinical Oncology / 1994	Retrospective cohort study	<p>Patients were assessed for response rates, OS, and EFS after they received induction therapy (VAMP -- vincristine, doxorubicin, and methylprednisolone) followed by high-dose melphalan (HDM) and AuSCT.</p> <p>CR was defined as no measurable serum or urine paraprotein as measured by scanning densitometry and 5% or fewer plasma cells of normal morphology in bone marrow aspirate for at least 3 months. PR was defined as more than 50% decrease in measurable paraprotein or bone marrow infiltration sustained for 1 month or more.</p>	<p>53 previously untreated patients with MM were considered eligible for HDM and AuSCT and were enrolled. These patients were selected from a group of 105 MM patients. The following are the inclusion criteria for this group of patients: (1) < 65 years, (2) no prior chemotherapy, (3) no previous ischemic heart disease, (4) glomerular filtration rate < 30 ml/min, and (5) less than 30% bone marrow infiltration in response to induction therapy. 32 of the 126 patients did not proceed to HDM due to disease progression or death. 20 patients received only HDM because of failure to reach myeloma infiltration of 30% or less. Another 21 patients were excluded because they received post-HDM IFN.</p> <p>The following are characteristics for the 53 patients: ---Median Age: 52 (30-69) ---Stage at diagnosis: Stage I 10 Stage II 2 Stage III 41 ---Beta-2 microglobulin median 3.1 range 1.2 - 1.7</p>	<p>52 of the 53 patients (98%) had a response to HDM. 40 patients (75%) achieved a CR, including 27 of 38 patients who had a PR after induction chemotherapy and 4 of 6 who showed NR.</p> <p>At the time of evaluation 24 patients had relapsed, 28 remained in remission, and 1 died of treatment-related toxicity. The estimated median duration of response is 23 months with 30% of patients free from progression at 36 months. Probability of survival at 54 months was 63%.</p> <p>An evaluation of prognostic factors in predicting response to treatment indicated that CR following HDM was associated with a longer EFS (p < .025).</p>	<p>This study does not compare outcomes to a control group. It is unclear whether the original patient population in which the 53 patients were derived totaled 126 or 105. Article mentions both numbers. Furthermore, in reviewing the patient selection method, it becomes clear that these 53 patients have been selected out of the original patient population. 73 patients were excluded either for disease progression, death, failure to respond, and use of IFN. Though the exclusion for IFN use may not effect the results, the other exclusions can significantly skew outcomes data. It seems that the healthiest patients were the ones that were included in the analysis, which could possibly lead to overly positive outcome results.</p>

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Ferland J, Ravaud P, Chevet S, et al / High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up front or rescue treatment? Results of a multi-center sequential randomized clinical trial / Blood / 1998	Randomized clinical trial	<p>Primary endpoints for study were OS, EFS, response status, and time without symptoms, treatment, and treatment toxicity (TWiSTT). Comparisons were made on an intent-to-treat basis.</p> <p>After stem cell collection, patients were randomized between two treatment arms: late HDT and early HDT. Early HDT group received 3 or 4 courses of VAMP as induction therapy followed by HDT and AuSCT. Late HDT group received vincristine, melphalan, and prednisone (VMCP). In patients with at least a PR, VMCP courses were pursued until a stable plateau phase was reached. HDT and AuSCT was used as rescue treatment in patients with disease progression on VMCP or disease resistance or relapse.</p> <p>CR = 5% or fewer plasma cells of normal morphology and absence of monoclonal Ig. PR = greater than 50% decrease in serum Mlg and/or greater than 75% decrease in urinary Bence Jones protein levels. MRD = 5% or fewer plasma cells and decrease of Ig levels of at least 90%.</p>	<p>202 patients were enrolled. Eligibility criteria include age less than 56 years with symptomatic MM. Patients were excluded if they had the following: (1) stage 1 MM, (2) prior chemotherapy or radiotherapy, (3) severe abnormalities of cardiac, pulmonary, and hepatic functions, (4) serum creatinine level > 300 micromoles per liter.</p> <p>17 patients did not proceed to randomization because of death (n=4), severe infection (n=2), renal failure (n=2), insufficient stem cell quantities (n=7), and protocol violation (n=2).</p> <p>Patients characteristics are as follows:</p> <table border="1"> <thead> <tr> <th></th> <th>Early</th> <th>Late</th> </tr> </thead> <tbody> <tr> <td>-- n</td> <td>91</td> <td>94</td> </tr> <tr> <td>-- Age</td> <td>48</td> <td>47</td> </tr> <tr> <td>-- Stage</td> <td></td> <td></td> </tr> <tr> <td> I</td> <td>3</td> <td>2</td> </tr> <tr> <td> II</td> <td>9</td> <td>10</td> </tr> <tr> <td> III</td> <td>79</td> <td>76</td> </tr> <tr> <td>-- Creatinine (micromoles/L)</td> <td>112</td> <td>128</td> </tr> <tr> <td>-- beta-2 microglobulin</td> <td>3.8</td> <td>3.7</td> </tr> </tbody> </table>		Early	Late	-- n	91	94	-- Age	48	47	-- Stage			I	3	2	II	9	10	III	79	76	-- Creatinine (micromoles/L)	112	128	-- beta-2 microglobulin	3.8	3.7	<p>In the early group, 89 of the 91 patients eligible received HDT. In the late group, 81 of the 94 reached requirements for HDT, of whom 73 were transplanted.</p> <p>The median OS of the 202 enrolled patients was 64 months from the time of stem cell collection. 41 and 42 patients died in the early and late groups, respectively. There were no significant differences in survival between the two groups.</p> <p>Median EFS for the early group was 39 months with relapse or death occurring in 58 patients. In the late group, median interval between randomization and death or VMCP failure was 13 months. Median time between randomization and relapse or death after HDT (post-HDT EFS) was 50 months.</p> <p>Average TWiSTT results were 27.8 months and 22.3 months in the early and late groups, respectively (no significant difference).</p> <p>At 6 months, 17 patients in the early group were in CR, 40 in MRD, and 21 in PR. In the late group, 5 achieved CR in response to VMCP, 15</p>	<p>The main issue addressed by this study is the optimal timing of AuSCT during the course of MM. The study does neither address the effectiveness of the treatment nor does it investigate its use in the Medicare population. The age cut-off for this study is 56 years. The authors conclude that, although there is no significant improvement in survival, early treatment may be preferred because it is associated with short periods of chemotherapy. The study results seem to provide persuasive evidence that there may be little difference between use of AuSCT as first-line treatment or as a rescue therapy.</p>
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				<p>in MRD, and 38 in PR. After HDT, 8 patients were in CR, 21 in MRD, and 6 had resistant disease. Among the 81 patients who met requirements for HDT, 45 were responders to VMPC whereas 36 had progressive or resistant disease.</p> <p>Treatment-related mortality for the early group was 10% and 14% for the late group.</p> <p>Analysis showed beta-2 microglobulin, hemoglobin, calcium, and creatinine levels affected OS.</p>	
Gahrton G / Treatment of multiple myeloma / Lancet / 1999	Review	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Author discussed current treatments options for patients with multiple myeloma. No direct evidence is presented, however.
Gahrton G / Blood stem cell transplantation / New England Journal of Medicine / 1999	Book review	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Author reviews medical text books on autologous stem cell transplantation. No direct evidence is presented, however.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Gore M, Selby P, Viner C, et al / Intensive treatment of multiple myeloma and criteria for complete remission / Lancet / 1989	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	<p data-bbox="1719 272 1986 354">Selected to provide working definitions of response (remission):</p> <p data-bbox="1719 386 1864 410">COMPLETE =</p> <ol data-bbox="1719 443 1986 768" style="list-style-type: none"> <li data-bbox="1719 443 1986 524">1. Absence of serum paraprotein on electrophoresis. <li data-bbox="1719 524 1986 605">2. No detectable Bence-Jones proteinuria on electrophoresis. <li data-bbox="1719 605 1986 686">3. 5% or fewer plasma cells of normal morphology on bone marrow aspiration. <li data-bbox="1719 686 1986 768">4. Above three criteria fulfilled for at least 3 months. <p data-bbox="1719 800 1839 824">PARTIAL =</p> <ol data-bbox="1719 857 1986 1019" style="list-style-type: none"> <li data-bbox="1719 857 1986 963">1. 50% decrease in measurable paraprotein (serum and/or urine) or bone marrow infiltration. <li data-bbox="1719 963 1986 1019">2. Above criterion sustained for one month or more.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Jagannath S, Vesole D, Zhang M, et al / Feasibility and cost-effectiveness of outpatient autotransplants in multiple myeloma / Bone Marrow Transplantation / 1997	Cost analysis	Days from transplant, cost, toxicity, and supportive care of inpatient vs. outpatient services are compared.	336 ABMT procedures in 251 consecutive multiple myeloma patients.	Not a clinical trial.	This article discusses the feasibility and cost effectiveness of a tandem ABMT program. 336 ABMT procedures in 251 consecutive multiple myeloma patients in an outpatient setting vs. hospitalization were compared. No patient outcome parameters (overall survival, etc.) were reported.
Kusnierz-Glaz C, Schlegel P, Wong R, et al / Influence of age on the outcome of 500 autologous bone marrow transplant procedures for hematologic malignancies / Journal of Clinical Oncology / 1997	Retrospective cohort study	To determine the effect of age on the outcome of ABMT and/or peripheral blood progenitor cell (PBPC) transplantation in Non-Hodgkin's Lymphoma (NHL), Hodgkin's Disease (HD), Multiple Myeloma (MM), or Acute Myelogenous Leukemia (AML). EFS, OS, Relapse rate (RR) and Regimen related mortality (RRM) rates. RRM: non-relapse mortality within 100 days of graft infusion.	500 consecutive patients with the following hematologic malignancies underwent ABMT: NHL=246, HD=126, MM=54, AML=74. MM patient characteristics: Disease status: Minimal 20* Advanced 34 *Minimal disease status defined as B2 Microglobulin < 3.0 g/L and paraprotein spike less than 25% of original. Age Distribution: Age/yrs. # Patients 20-29 yrs. 1 30-39 yrs. 2 40-49 yrs. 24 50-65 yrs. 27	For MM patients, distribution of RRM: Age Distribution: Age/yrs. # Patients 20-29 yrs. 0 30-39 yrs. 0 40-49 yrs. 1 50-65 yrs. 3 For MM patients, RR: 1.1 No other data reported for MM.	This study did not enroll multiple myeloma patients over age 65 which makes it difficult to assess the extent of age as a prognostic factor for patients with multiple myeloma in the Medicare population. Low MM enrollment numbers and lack of specific patient characteristics preclude proper evaluation of whether age influences outcome for MM.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Kyle R / High-dose therapy in multiple myeloma and primary amyloidosis: an overview / Seminars in Hematology / 1999	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This article reviews the diagnosis and treatment of multiple myeloma and primary amyloidosis. The authors highlight the status and conclusions of a number of research studies investigating high-dose therapy and stem cell transplantation for multiple myeloma and primary amyloidosis. No direct evidence is presented, however.

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Lenhoff S, Hjorth M, Holmberg E, et al / Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study / Blood / 2000	Case control, with historical controls	OS, EFS, response rate, treatment toxicity, and quality of life were assessed after patients were given HDT and AuSCT.	14 participating centers in Denmark, Norway, and Sweden registered all newly-diagnosed, symptomatic myeloma patients < 60 years old. 348 patients were registered. 274 patients (labeled the intensive therapy group) were actually treated. Patients with contraindications to phase 2 & 3 (n=74) were taken off the protocol.	HDT with AuSCT was performed in 214 patients (78%). 4 patients underwent AlloSCT and 1 had syngeneic transplantation. 55 patients (20%) did not undergo treatment because of death (n=12), progression (n=11), no CR or PR after phase 1 (n=12), contraindication to HDT (n=16), or patients' refusal (n=4).	This study did not enroll multiple myeloma patients over age 65 which makes it difficult to assess the extent of age as a prognostic factor for patients with multiple myeloma in the Medicare population. Furthermore, the use of historical controls carries the risk of selection bias affecting the results. It is important to note that nearly 22% of the HDT group did not receive the treatment protocols. These patients groups were selected out of the treatment protocols, yet little explanation is made as to who these patients are. Authors do not make conclusions as to which population groups HDT and AuSCT can be effective treatment options.																																			
		The treatment protocol followed sequentially in 4 phases: (1) induction therapy with VAD, (2) stem cell harvest, (3) high-dose melphalan (HDM) followed by AuSCT, (4) maintenance therapy with IFN.	This group was compared to a historic control population that were identified from 5 previous studies. 313 patients < 60 were registered. 39 did not fulfill entry criteria for intensive therapy and were thus excluded from the analysis. Characteristics of the groups are as follows:	There was a toxic rate of 4% for HDT. Of those who actually underwent HDT, 41% had a CR and 48% had a PR. EFS at 3 years was 39% and median EFS was 27 months. For patients who actually underwent HDT, EFS at 3 years was 45% and median EFS was 32 months.																																				
		CR was defined as the disappearance of M-protein from serum and urine and < 5% plasma cells in bone marrow aspirate. PR was defined by at least a 50% reduction of Bence-Jones proteinuria to < 0.2 g/24h.	<table border="1"> <thead> <tr> <th></th> <th>Cases</th> <th>Controls</th> </tr> </thead> <tbody> <tr> <td>Med. Age</td> <td>51</td> <td>54</td> </tr> <tr> <td>Stage</td> <td></td> <td></td> </tr> <tr> <td>I</td> <td>2%</td> <td>6%</td> </tr> <tr> <td>II</td> <td>28%</td> <td>38%</td> </tr> <tr> <td>III</td> <td>70%</td> <td>56%</td> </tr> <tr> <td>creatinine</td> <td></td> <td></td> </tr> <tr> <td>>200</td> <td>9%</td> <td>13%</td> </tr> <tr> <td>beta-2</td> <td></td> <td></td> </tr> <tr> <td><4</td> <td>58%</td> <td>44%</td> </tr> <tr> <td>4-6</td> <td>26%</td> <td>36%</td> </tr> <tr> <td>> 6</td> <td>16%</td> <td>20%</td> </tr> </tbody> </table>		Cases	Controls	Med. Age	51	54	Stage			I	2%	6%	II	28%	38%	III	70%	56%	creatinine			>200	9%	13%	beta-2			<4	58%	44%	4-6	26%	36%	> 6	16%	20%	The survival for HDT group was prolonged compared to the controls with a risk ratio of 1.62. Median OS for the control group was 44 months and was not reached for the HDT group.
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Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Lokhorst H, Sonneveld P, Verdonck L / Intensive treatment for multiple myeloma: where do we stand? / British Journal of Haematology / 1999	Review	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This article reviews the current issues in treating multiple myeloma. The authors highlight the status and conclusions of a number of research studies investigating intensive treatments for multiple myeloma. No direct evidence is presented, however.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Marit G, Faberes C, Pico J, et al / Autologous peripheral-blood progenitor-cell support following high-dose chemotherapy or chemoradiotherapy in patients with high-risk multiple myeloma / Journal of Clinical Oncology / 1996	Retrospective cohort study	<p>EFS, OS, and response rates analysis was performed on an intent-to-treat basis.</p> <p>Under the treatment protocols, patients received a double HDT. 1st, patients received HDCTX followed by stem cell collection. Then, patients underwent HDM + TBI followed by AuSCT.</p> <p>CR was defined by the disappearance of the monoclonal component from the serum and the concentrated urine and 5% or less plasma cells in the bone marrow. PR was defined when decrease of 50% or more was observed in measurable paraprotein and bone marrow infiltration.</p>	<p>73 patients with high-risk MM were entered into the study. Inclusion criteria for the study included (1) age < 65 years, and (2) high-risk MM designation. High risk was defined as the following: (1) stage II or III MM at diagnosis, (2) plasmocytoma or stage I MM at diagnosis with no response to treatment or relapse after a previous response to treatment, and (3) plasma-cell leukemia.</p> <p>Median Age: 54 (32 - 63)</p> <p>Stage at diagnosis: Stage I 10 (13%) Stage II 11 (15%) Stage III 52 (72%)</p> <p>1 year from diagnosis: 31 (42%)</p> <p>Prior alkylating agent-containing regimens: 32 (44%)</p> <p>Number of prior regimens: 1 45 (62%) 2 28 (38%)</p> <p>Response status prior HDCTX: Sensitive 49 Nonresponsive 24</p>	<p>1 of the 73 patients died of infection during the recovery phase post-HDCTX. Among the 72 patients who underwent AuSCT, 1 patient died of acute cardiac failure after reinfusion of stem cells.</p> <p>After HDCTX, 13 (56%) of 23 assessable resistant patients achieved PR. Of the 49 sensitive patients, 4 had a decrease in tumor burden (8%). Overall, 3 patients failed to respond, 36 achieved PR, and 32 achieved CR post-AuSCT.</p> <p>36 patients relapsed after a median response duration of 14.5 months after AuSCT, of which 19 died. The remaining 28 patients remained alive with 13 in CR and 15 in PR. Of the 73 patients, median EFS from AuSCT was 23 months. 5-year probability of OS from AuSCT and diagnosis was 66% and 77%, respectively.</p> <p>Significant prognostic variables affecting EFS include age < 60 years and sensitivity to treatment prior AuSCT. Age < 60 and type of gammopathy influenced OS.</p>	<p>This study did not compare HDM+AuSCT with a control group of high-risk MM patients making it difficult to assess whether HDM+AuSCT provides an added health benefit. In addition, no mention is made as to how the patients were selected. Randomized treatment protocols could significantly reduce the selection biases that might have influenced results. The population size of the enrolled group may be too small to guard against the influence of selection bias.</p>

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Mehta J, Singhal S, Desikan K, et al / High-dose therapy and stem-cell support in myeloma / Principles and Practice of Oncology / 1999	Review	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This article reviews the current issues in treating multiple myeloma. The authors highlight the status and conclusions of a number of research studies investigating high-dose therapy and stem cell transplantation for multiple myeloma. No direct evidence is presented, however.
National Comprehensive Cancer Network / NCCN practice guidelines for multiple myeloma / Oncology / 1998	Practice guidelines	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provides background material and guidelines on the management of multiple myeloma.
Oivanen T, Palva I / High-dose chemotherapy in multiple myeloma: letters to the editor / New England Journal of Medicine / 1996	Editorial	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Authors offer a dissenting opinion contrary to the conclusions made in Attal, et al. (1996). No direct evidence is presented, however.

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Palumbo A, Triolo S, Argentino C, et al / Dose-intensive melphalan with stem cell support is superior to standard treatment in elderly myeloma patients / Blood / 1999	Retrospective case-control study	<p>EFS, OS, toxicity rates, and response rates were assessed after patients received a reduced dose of 100 mg/m² of melphalan (MEL100) rather than the standard 200 followed by AuSCT.</p> <p>PR was defined as a 50% reduction of serum myeloma protein, 90% decrease of Bence Jones proteinuria, and 50% reduction of bone marrow infiltration. CR required a disappearance of serum or urine myeloma protein and marrow plasmacytosis less than 1% for at least 2 months.</p>	<p>71 patients (median age 64) at diagnosis were entered into the protocols. Patients were eligible if they were between 55 and 75 years of age and had normal organ function (cardiac, renal, pulmonary, and hepatic).</p> <p>To compare outcomes, 71 patients were selected among 161 untreated MM patients who were treated at diagnosis with oral melphalan and prednisone (MP). Patients met the same eligibility criteria as the MEL100 group and were matched for age, and beta-2 microglobulin levels.</p> <p>Patients characteristics are as follows:</p> <table border="1"> <thead> <tr> <th></th> <th>MEL100</th> <th>MP</th> </tr> </thead> <tbody> <tr> <td>-- n</td> <td>71</td> <td>71</td> </tr> <tr> <td>-- Age >60</td> <td>53</td> <td>53</td> </tr> <tr> <td>-- Stage</td> <td></td> <td></td> </tr> <tr> <td> II</td> <td>25</td> <td>28</td> </tr> <tr> <td> III</td> <td>75</td> <td>72</td> </tr> <tr> <td>-- Creatinine >2 mg/dL</td> <td>6</td> <td>11</td> </tr> <tr> <td>-- beta-2 microglobulin <3 mg/L</td> <td>19</td> <td>19</td> </tr> <tr> <td> >3 mg/L</td> <td>52</td> <td>52</td> </tr> </tbody> </table>		MEL100	MP	-- n	71	71	-- Age >60	53	53	-- Stage			II	25	28	III	75	72	-- Creatinine >2 mg/dL	6	11	-- beta-2 microglobulin <3 mg/L	19	19	>3 mg/L	52	52	<p>On an intent-to-treat basis, 89% of patients completed the entire treatment protocol (71 received 1st MEL100, 68 reached the 2nd, 63 were eligible for the 3rd, 39 patients received the 3rd).</p> <p>On an intent-to-treat basis, frequency of PR and CR was 77% and 19% after 1st MEL100, 86% and 34% after 2nd, and 88% and 47% after 3rd, respectively. No toxic deaths occurred. After a median follow-up of 30 months, 55% were alive in remission, 13% had died after relapse, 17% were alive after relapse, 4% were alive with progression, and 11% were alive but registered as failures due to adverse events.</p> <p>68 patients in the MP group completed 3 courses and 66 received 6 courses. 3 patients died after the 2nd or 3rd course of MP. After median follow-up of 39.4 months, 15% were alive in remission, 20% were alive after relapse or with progression, and 65% had died.</p> <p>Comparison:</p> <table border="1"> <thead> <tr> <th></th> <th>MEL100</th> <th>MP</th> </tr> </thead> <tbody> <tr> <td>PR</td> <td>88%</td> <td>49% *</td> </tr> <tr> <td>CR</td> <td>47%</td> <td>5% *</td> </tr> <tr> <td>EFS</td> <td>34 mon</td> <td>17.7 mon*</td> </tr> </tbody> </table>		MEL100	MP	PR	88%	49% *	CR	47%	5% *	EFS	34 mon	17.7 mon*	<p>The relevancy of this study to the Medicare population is unclear since the analysis of patients was only done between patients <60 and patients >60 years. In addition, the use of a reduced dose of melphalan does not address the issue of safety regarding the use of higher (standard) doses of melphalan which could be toxic to Medicare beneficiaries. The trial was not randomized, therefore there may be a risk of selection bias affecting the results.</p> <p>Low p-value does not enable one to determine whether patients with low beta-2-microglobulins will better respond to a given therapy.</p>
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				<p>OS 56+ mon 48 mon* EFS@4yrs 33% 14% OS@4yrs 71% 52% * statistically significant</p> <p>The presence of beta-2 microglobulin levels less than 4 mg/L at diagnosis influenced OS and EFS (p=0.04). CR was significant in univariate analysis, but not in multivariate analysis. Age > 60 was not found to be significant.</p>	

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Powles R, Raje N, Milan S, et al / Outcome assessment of a population-based group of 195 unselected myeloma patients under 70 years of age offered intensive treatment / Bone Marrow Transplantation / 1997	Retrospective cohort study	<p>Overall survival (OS), Progression-free survival (PFS).</p> <p>CR: 1) no measurable serum paraprotein, 2) no detectable Bence-Jones proteinuria, 3) 5% or fewer plasma cells with normal morphology on bone marrow aspirate, 4) criteria 1-3 had to be fulfilled for at least 3 months duration.</p> <p>PR: 50% decrease in paraproteins or bone marrow infiltration which was sustained for > 1 month.</p> <p>Relapse: reappearance of paraprotein or bone marrow infiltration of more than 5% for patients in CR and 25% increase in paraprotein on 2 samples 1 month apart for patient in PR.</p> <p>NR: patient failed to achieve a CR or a PR.</p>	<p>195 previously untreated patients with multiple myeloma under age 70.</p> <p>Median Age = 52 (range 31-70)</p> <p>Stage (# of patients): IA: 31 IB: 2 IIA: 8 IIIA: 114 IIIB: 40</p> <p>Creatinine (mg/dL)= > 2.3 mg/dL: 28/195</p> <p>B2 Microglobulin (g/L)= > 3.0: 96/150 > 2.7: 103/150</p> <p>Treatment: all 195 were able to start initial cytoreductive infusional chemotherapy (CIC): VAMP 67 pts C-VAMP 90 pts Verapamil + C-VAMP 38 pts</p> <p>Following CIC: 54 patients (28%) were unable to continue treatment: 8 treatment-related deaths, 9 other deaths, 37 had poor performance or refused further treatment.</p> <p>The remaining 141/195 went on to receive some form of High Dose</p>	<p>Response rates for all 195 patients (at the end of CIC): CR 36 pts PR 103 pts NR 39 pts Deaths 17 pts OS median: 4.5 yrs. PFS median: 25 months</p> <p>Response rates for HDC + ABMT, 112 patients: CR 83 pts PR 24 pts NR 4 pts Deaths 1 pt OS median: 6.6 yrs. PFS median 27 months</p> <p>Response rates for Other HD, 29 patients: CR 10 PR 7 NR 6 Deaths 6</p>	<p>This study did not enroll patients over age 70. Age information given classifies age into <50, 50-60, and >60 groups. Authors state that older patients (>60), as well as those with poor renal function were significantly more likely to belong to the group which did not receive HDM plus autologous rescue.</p> <p>This study does not compare outcomes to a control group; however represents a series of referral patients seen from 1986 to 1994.</p> <p>The authors indicate that planned treatment was not complete; only 72.3% were able to receive high dose treatment and only 57.4% with high dose plus autologous rescue.</p>

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
			<p>Treatment with 112/195 receiving HD and 29/195 receiving Other HD:</p> <p>melphalan + ABMT: 90 melphalan + PBSCT: 22 busulphan + ABMT: 3 busulphan + PBSCT: 3 melphalan alone: 23</p>		
			<p>Older patients (>60), as well as those with poor renal function were significantly more likely to belong to the group which did not receive HDM plus autologous rescue.</p>		
			<p>Patients who received only melphalan was associated with increasing age (P=0.001), increased serum creatinine (value not stated), and >30% infiltration on bone marrow aspirate.</p>		

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Rajkumar S, Fonseca R, Lacy M, et al / Plasmablastic morphology is an independent predictor of poor survival after autologous stem-cell transplantation for multiple myeloma / Journal of Clinical Oncology / 1999	Retrospective cohort study	<p>OS, EFS, and response rates were assessed.</p> <p>CR: lack of detectable monoclonal serum or urine protein.</p> <p>PR: 50% reduction of serum and urine light chain proteins accompanied by a similar reduction of soft tissue plasmacytomas if present.</p> <p>Disease progression: 50% with increased serum protein or urinary protein over the lowest remission level.</p> <p>EFS: time from AuSCT to disease progression or death.</p>	<p>75 patients underwent HDT and AuSCT for refractory or relapsed multiple myeloma. 19 were in the plasmablastic (PB) groups and 50 were in the non-plasmablastic (NPB) group. Group status was determined by blinded examination of bone marrow aspirates. Stem cells were harvested after treatment with VAD. 1 patient died before stem cell reinfusion.</p> <p>Age median: 53 yrs. (33-68)</p> <p>B2M: >2.7 mg/L 47 (63%)</p> <p>Prior chemotherapy regimens: 1 10 (13%) 2 52 (69%) 3+ 13 (17%)</p> <p>Disease status @ AuSCT: -Relapsed on chemotherapy 33 (44%) -Relapsed off chemotherapy 30 (40%) -Primary chemorefractory 12 (16%)</p>	<p>There was no significant difference in overall rates (92% vs. 89%) or CR rates (21% vs. 35%) between the PB group and the NPB group, respectively.</p> <p>Median OS for the entire group (time after transplant) was 18 months. There was a significant difference between the two groups with NPB group having a greater median OS (24 months) than PB group (5 months).</p> <p>Median EFS for the entire group was 9 months. There was a significant difference between the two groups with NPB group having a greater median OS (12 months) than PB group (4 months).</p> <p>B2M was not a significant predictor for OS or EFS. Plasmablastic morphology was prognostic for both EFS and OS in both a univariate analysis and a multivariate analysis.</p>	<p>Study does not speak to the effectiveness of AuSCT compared to CC. Analysis is largely focused on the predictive value of plasmablastic morphology in patients treated with HDT and AuSCT. The usefulness of this study is that it helps target which patient populations may or may not benefit from the treatment of AuSCT in MM. However, there is cause for concern regarding the small sample sizes used. The PB group contained only 19 patients. In addition, even though reviewers may be blinded to the clinical nature of the test-slides, there still may be a problem with observer variation.</p>

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Schlossman R, Anderson K / Bone marrow transplantation in multiple myeloma / Current Opinion in Oncology / 1999	Review	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This article reviews a number of research studies investigating high-dose therapy and stem cell transplantation for multiple myeloma. No direct evidence is presented, however.																												
Siegel D, Desikan K, Mehta J, et al / Age is not a prognostic variable with autotransplants for multiple myeloma / Blood / 1999	Retrospective case-control study	<p>Clinical endpoints included treatment-related mortality, EFS, OS, and response rates. Patients had received HDM followed by tandem AuSCT.</p> <p>Patients were identified from a group of 550 MM patients who were enrolled in tandem AuSCT trials using 200 mg/m² melphalan (MEL200) for the 1st cycle. A 2nd cycle consisting of MEL200 was administered in case PR was sustained. Patient with less than PR were offered 140 mg/m² of melphalan + TBI or MEL200 + HDCTX.</p> <p>CR was defined as the absence of serum and urine monoclonal proteins in the presence of normal morphologic examination of bone marrow aspirate and biopsy with < 1% of tumor cells identified.</p>	<p>49 patients who were 65+ years and had a minimum of 18 months follow-up post-transplant years were identified from group. These patients were matched with 49 patients < 65 years. Patients were matched on B2M, albumin, creatinine, c-reactive protein, and presence or absence of unfavorable chromosomal abnormalities.</p> <p>Patient characteristics are as follows:</p> <table border="1"> <thead> <tr> <th></th> <th><65</th> <th>65-69</th> <th>70+</th> </tr> </thead> <tbody> <tr> <td>-- n</td> <td>49</td> <td>39</td> <td>10</td> </tr> <tr> <td>-- Stage <III</td> <td>49%</td> <td>58%</td> <td>60%</td> </tr> <tr> <td>-- Creatinine <2</td> <td>96%</td> <td>95%</td> <td>100%</td> </tr> <tr> <td>-- B2M <2.5</td> <td>51%</td> <td>33%</td> <td>40%</td> </tr> <tr> <td>-- AuSCT 2</td> <td>76%</td> <td>69%</td> <td>50%</td> </tr> <tr> <td>-- <12 mo of prior therapy</td> <td>55%</td> <td>54%</td> <td>70%</td> </tr> </tbody> </table>		<65	65-69	70+	-- n	49	39	10	-- Stage <III	49%	58%	60%	-- Creatinine <2	96%	95%	100%	-- B2M <2.5	51%	33%	40%	-- AuSCT 2	76%	69%	50%	-- <12 mo of prior therapy	55%	54%	70%	<p>With regard to regimens, all patients received MEL200 and the 1st AuSCT. The 2nd AuSCT consisted of MEL200 in 18 of 37 (49%) among those <65, 11 of 27 (41%) in the middle-age group, and 4 of 5 (80%) in the old age group.</p> <p>Frequency of toxicities were similar in the three groups.</p> <p>Incidence of CR was lower in older patients compared to younger patients (20 vs. 43%, p = .02). EFS, CR, and OS durations were comparable. Favorable prognostic factors that influenced EFS and OS included low B2M. Months of prior therapy was also important for EFS. Age was not a significant risk factor for either EFS or OS.</p>	<p>The method to select patients were not identified in the treatment protocol. At first, patients seemed to have been selected from a pool of 900. However, the 49 matched-pairs appear to have been selected from a group of 550. The original age breakdown of the original population was not mentioned either. This is important when trying to assess the impact of selection bias. There is no way to determine whether the 49 patients 65+ years were randomly selected from the original population. In addition, PR was not defined in the study but was used as an outcomes measure. This study does not speak to the effectiveness of HDT + AuSCT in comparison to standard therapy in the elderly population.</p>
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Southwest Oncology Group / Unpublished data / Located at: Seattle, Washington / 1999	Unknown	Overall survival.	2000 patients registered in the Southwest Oncology Group standard chemotherapy trials. No other characteristics reported.	Survival decreased as age increased: <65 years : 37 months 65-74 years : 30 months >75 years : 19 months	Data provided has not been published. Treatment protocols and patient characteristics were not included, thus making a proper evaluation difficult.																				
Trippoli S, Messori A, Becagli P, et al / Treatments for newly diagnosed multiple myeloma: analysis of survival data and cost effectiveness evaluation / Oncology Reports / 1998	Meta-analysis	Analysis evaluated survival and cost-effectiveness of several treatments for multiple myeloma.	Only large scale clinical trials with at least 100 patients per treatment modality were included. 5 clinical trials were identified: 4 evaluated melphalan (MP) at conventional dosing without IFN, 3 evaluated melphalan at conventional dosing with IFN, and 1 provided data on AuSCT.	<p>Mean lifetime Survival</p> <table> <tr><td>MP-1</td><td>3.83</td></tr> <tr><td>MP-2</td><td>3.01</td></tr> <tr><td>MP-3</td><td>3.23</td></tr> <tr><td>MP-4</td><td>3.56</td></tr> <tr><td>Pooled</td><td>3.47</td></tr> <tr><td>MP+IFN-1</td><td>3.90</td></tr> <tr><td>MP+IFN-2</td><td>3.75</td></tr> <tr><td>MP+IFN-3</td><td>3.46</td></tr> <tr><td>Pooled</td><td>3.74</td></tr> <tr><td>AuSCT</td><td>7.28</td></tr> </table> <p>The marginal cost-effectiveness ratio was about \$26,000 per life year gained.</p>	MP-1	3.83	MP-2	3.01	MP-3	3.23	MP-4	3.56	Pooled	3.47	MP+IFN-1	3.90	MP+IFN-2	3.75	MP+IFN-3	3.46	Pooled	3.74	AuSCT	7.28	This study does provide direct evidence regarding the safety and effectiveness of AuSCT. In addition, it does not provide an analysis of more than one study regarding AuSCT. However, it does provide a useful cost-effectiveness analysis of AuSCT.
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Vesole D, Crowley J, Catchatourian R, et al / High-dose melphalan with autotransplantation for refractory multiple myeloma: results of a Southwest Oncology Group phase II trial / Journal of Clinical Oncology / 1999	Prospective cohort study	<p>EFS, OS, toxicity, and response rates were assessed on an intent-to-treat basis.</p> <p>Refractory MM patients were treated first with HDCTX. Patients were then given MEL100 followed by AuSCT. Patients were then administered IFN.</p> <p>Refractory was defined as persistent or progressive disease while receiving myelosuppressive doses of either alkylating agents, dexamethasone, or VAD; or had primary drug resistance for at least 4 months.</p> <p>PR was defined as more than 50% reduction in production rate of monoclonal serum protein and reduction in Bence Jones protein to < 0.2 g/d. CR was defined as 75% or more reduction in production rate of monoclonal serum protein and a 90% or more reduction in urine paraprotein to < 0.2 g/d.</p>	<p>Patients were eligible if they had measurable myeloma paraprotein in the blood and/or urine, age less than 70 years, SWOG performance status of 0 to 2, and adequate renal, hepatic, pulmonary, and cardiac function.</p> <p>72 patients were enrolled into the SWOG 8993 phase II trial of HDM with AuSCT in refractory MM. Of the 72, 67 were eligible, 66 were assessable, and 56 completed the planned treatment protocol.</p> <p>At least 1 month elapsed since the last chemotherapy treatment.</p> <p>Patients characteristics are as follows: -- Stage III 52% -- B2M > 3 mg/dl 48% -- 2+ prior therapies 84% -- Age median 55 years, range (34-69)</p>	<p>Response: ----HDCTX: 37 patients received HDCTX. Overall response was 22%, 8 patients achieved at least a PR (including 3 CRs). ----HDM+AuSCT: 56 patients received HDM + AuSCT, of which 54 were assessable. Overall response was 65%, 35 patients achieved at least a PR (including 16 CRs). ----Overall response for all 66 eligible patients was 58%, 38 patients achieved at least a PR (including 19 CRs).</p> <p>Survival: Median EFS and OS durations for the 66 patients were 11 months and 19 months, respectively. 3-year EFS and OS rates were 25% and 31%, respectively.</p> <p>Prognostic Factors: No significant differences were found among the various factors; however, small number of patients in the study limited analysis.</p> <p>Toxicity: Treatment-related deaths occurred in 2 patients during HDCTX. 4 patients died from infectious complications after AuSCT.</p>	<p>This study did not compare HDM+AuSCT with a control group of refractory MM patients. Thus, it is difficult to assess whether HDM+AuSCT provides added benefit. In addition, it was not documented how patients were selected. Randomized treatment protocols could significantly reduce the selection biases that might have influenced results. Furthermore, the outcomes reported do not overwhelmingly support the authors conclusions that AuSCT is an effective treatment. Less than one-third of patients are projected to survive for 3 years. Median OS is less than 20 months.</p>