Author/ Year	Study Design	Demographics	Intervention, outcome measures; instruments	Results		Methodological Comments
				Intervention group	Control group	
Blum, 2001 (abstract)	Prospective, uncontrolled, unblinded cohort Inclusion/exclusion criteria not provided	N= 10 Demographic profile not stated	4-6 chemo cycles using various regimens, then TBI + G-CSF, then interferon alfa Outcome measures: survival; hematologic response; performance status; organ involvement	Median time from diagnosis to follow-up= 9 mos 100% survival within 100 days of transplant and at 6 mos Median survival from transplant= 18.5 mos 6 of 7 patients evaluable for hematologic response had complete response At last follow-up 5/10 alive with 3 in remission and 2 stable	None	Lack of a control group and randomization permits a number of sources of bias and confounding to be introduced into the study results, thereby decreasing the strength of the results and conclusions Small sample size Abstract-only format permits presentation of only limited study details
Casserly, 2003	Prospective, non-randomized, concurrent control case series Control group= patients without end stage renal disease treated with AuSCT during the same period Inclusion: dialysis-dependent patients treated with hi dose melphalan and AuSCT Exclusion: EF<40, O2sat<95% on room air, performance status ≥3, refractory CHF or arrhythmias	N=15 cases N= 180 controls Median age (n=15): 51 (range 40-67; 2 patients 64-67 y/o) %women (n=15): 47 Demographic profile not provided for control patients	Mobilization: G-CSF alone or with GM-CSF Conditioning: melphalan (dose adjusted for age, cardiac, and performance status) Outcome measures: complete hematologic response; survival	Overall hematologic response rate at 1 yr= 53% Hematologic response at 1 yr= 8/11 (evaluable) Overall median survival= 25 mos (p=0.1 v. control) Survival (%) 1 yr ~70 2 yr ~55 5 yr ~35 Peritransplant mortality (≤90 days from start of mobilization)= 13% Status of patients >63 yrs: • the 67 y/o female had a complete hematologic response and died after 58 mos	Survival (%) 1 yr ~80 2 yr ~73 5 yr ~60	Lack of randomization, blinding. Small sample size

				post-transplant due to hemorrhagic CVA • the 64 y/o female had a complete hematologic response and is alive after 37 mos		
Dember, 2001	Prospective, uncontrolled cohort study Inclusion: renal amyloidosis—urinary protein excretion >1 g/24h; age ≥18; EF>40 Exclusion: dialysis-dependent	N= 65 Median age: 57 (range 29-77) %women: 43	Mobilization: G-CSF Conditioning: melphalan (dose adjusted for age, cardiac, renal, pulmonary, and performance status) Outcome measures: urinary protein/24h; 24h Cr clearance; hematologic response	6/65 died during peritransplantation period (5/6 had symptomatic cardiac disease) 50/65 (77%) alive at 1 yr; comparison of 1 yr survivors v. nonsurvivors: survivors younger (p=0.024), less # organs involved, received higher melphalan dose 21/50 1-yr survivors had complete hematologic response %complete hematologic responders v. nonresponders who had a renal response at 1 yr: 71% v. 11% (p<0.001)	None	Lack of a control group and randomization permits a number of sources of bias and confounding to be introduced into the study results, thereby decreasing the strength of the results and conclusions
Dispenzieri, 2001	Primary analysis: retrospective case series to determine AuSCT eligibility and other clinical parameters as a prognostic factor Patients had to be AuSCT-eligible but not transplanted Secondary analysis of survival: 2:1 case-match-control (control= patients who were transplanted;	N= 229 cases N= 39 control Median age: 56 (range 25-70); 34% were older than 60 years %women: 42	Various chemo regimens Outcome measure: survival	Median time of follow-up= 52 mos (range 0.2-186 mos); Follow-up available for 96% of patients Median survival: 42 mos (95% CI, 43-57 mos) | | Survival rate-- % (95% CI) | |---|---| | 6 mos | 83 (75-92) | | 1-yr | 74 (65-85) | | 2-yr | 61 (54-68) | | 5-yr | 36 (30-43) | | 10-yr | 15 (9-24) |	| | Survival rate--% (95% CI) | |---|---| | 6 mos | 85 (74-97) | | 1-yr | 77 (65-91) | | 2-yr | 68 (53-87) | (No statistically significant differences)	Lack of a control group and randomization permits a number of sources of bias and confounding to be introduced into the study results, thereby decreasing the strength of the results and conclusions

<table>
<tr>
<td></td>
<td>matched by age, sex, # involved organs)

Inclusion: age ≤70, ventricular septal thickness ≤15 mm, EF>55, serum Cr≤2.0 mg/dL, symptomatic, organ involvement

Exclusion: multiple myeloma</td>
<td></td>
<td></td>
<td>3 clinical parameters predictive of poor prognosis: increasing # involved organs, worsening performance status, ≥10 lb weight loss</td>
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<tr>
<td>Dispenzieri, 2003</td>
<td>Retrospective analysis of prognostic value of serum cardiac troponin levels

NOT a clinical study of autologous stem cell transplantation</td>
<td>Not relevant</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<td>Dispenzieri, 2004</td>
<td>Retrospective case-match-control

Patients who underwent transplantation were matched 1:1 to patients who did not receive transplantation

Matching based on age, gender, time to presentation, EF, serum Cr, ventricular septal thickness, nerve involvement, 24-h urine protein, serum alk phos</td>
<td>
<table>
<tr><th></th><th>Case</th><th>Control</th></tr>
<tr><td>N</td><td>63</td><td>63</td></tr>
<tr><td>Males, n (%)</td><td>36 (57%)</td><td>36 (57%)</td></tr>
<tr><td>Median Age, y (range)</td><td>53 (30-69)</td><td>53 (32-69)</td></tr>
</table>
Only variables with a statistically significant difference between groups were time from diagnosis to transplantation/treatment: 4.4 v 1.4 mos (case v control), and EF ≤50 (6 v 19% , case v control)
</td>
<td>Mobilization: cyclophosphamide + GM-CSF or G-CSF alone

Conditioning: melphalan + TBI or melphalan alone (various dose levels)

Outcome measures: mortality within 100 days of transplantation; overall survival rate</td>
<td>Mortality within 100 days of transplant was 13%

Median follow-up from diagnosis: 3.8 yrs
<table>
<tr><th></th><th>Case (n=63)</th></tr>
<tr><td># deaths</td><td>16</td></tr>
<tr><td>Overall survival rate from transplant date (%)</td><td></td></tr>
<tr><td>1 yr</td><td>82*</td></tr>
<tr><td>2 yr</td><td>81*</td></tr>
<tr><td>4 yr</td><td>70*</td></tr>
</table>
*P<0.001

4 case patients were ≥65 y/o (66-69 y)— 1 died at 6.3 mos while other 3 cases are alive after 35, 36, & 38</td>
<td>Median follow-up from diagnosis: 8.8 yrs
<table>
<tr><th></th><th>Control (n=63)</th></tr>
<tr><td># deaths</td><td>44</td></tr>
<tr><td>Overall survival rate from start of treatment (%)</td><td></td></tr>
<tr><td>1 yr</td><td>68</td></tr>
<tr><td>2 yr</td><td>53</td></tr>
<tr><td>4 yr</td><td>40</td></tr>
</table>
4 control patients were ≥65 y/o (66-69 y)— all 4 are dead (at 6.6, 6.8, 11.6, 42.6 mos)</td>
<td>Not as robust as a randomized controlled trial. Impossible to control for all potential clinically important variables however this protocol appears to control well for the most important known variables.</td>
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				mos.		
Gertz, 2000	Uncontrolled, unblinded prospective cohort Inclusion: total lifetime melphalan dose <500 mg; serum Cr <2.5 mg/dL Exclusion: multiple myeloma; moderate to severe CHF	N=23 mobilized; 20 transplanted Median age: 57 yr (range 37-70) %women: 30	Mobilization: cyclophosphamide + GM-CSF (1 patient received G-CSF alone instead) Conditioning: melphalan + TBI or melphalan alone Outcome measures: 50% decrease of 24-h urine protein excretion without increase in serum Cr; 50% decrease in serum alk phos without increase in transaminase level, bilirubin, or liver size; 2 mm decrease in ventricular septum thickness on echo	3/23 tolerated mobilization poorly and were not transplanted: 1 died of progressive cardiac amyloidosis; 1 died of progressive hepatic amyloidosis; 1 developed severe GI toxicity and end-stage renal disease requiring hemodialysis After 3-30 mos (median 16 mos) follow-up 13/20 (65%) alive and 12/20 responders (median time to response= 4 mos) 5/20 developed unexpected GI toxicity For patients >63 yrs: 1 (70 y/o man) died 2 mos after transplant from pneumonia; 1 (65 y/o man) died 2 mos post transplant from progressive autonomic failure and aspiration; 1 (65 y/o man) is alive 4 mos post transplant with a positive hematological response	Not applicable	Lack of a control group and randomization permits a number of sources of bias and confounding to be introduced into the study results, thereby decreasing the strength of the results and conclusions
Gertz, 2002	Prospective, uncontrolled, case series Inclusion: patients who received AuSCT between Mar 1996 and Jan 2001 Exclusion: asymptomatic, multiple myeloma	N= 66 Median age: 54 (range 31-70) %women: 44	Mobilization: cyclophosphamide + GM-CSF, or G-CSF alone Conditioning: melphalan + TBI, or melphalan alone Outcome measures: included complete hematologic response, and various organ-based responses	Overall treatment-related mortality= 14% 33/66 (50%) hematologic responses; 32 (48%)organ responses Serum Cr and number of involved organs found to be independently associated with mortality	None	Lack of randomization, blinding and control significantly reduces the robustness of the data.

Hayes-Lattin, 2002	Case series	N= 4 Age range= 52-65 yr All men	Mobilization: chemo + G-CSF/GM-CSF Conditioning: chemo +/- TBI	2 cases of toxic megacolon 1 case of multi-organ system failure 1 case of mucositis	None	Due to lack of randomization, blinding, and control, case reports do not provide robust evidence to support net health outcome decisions.
Kumar, 2001	Retrospective medical record review Analysis of GI bleeding after autologous stem cell transplantation	N= 45 medical records Age range: 31-61 yrs Sex: 7 women	Mobilization: cyclophosphamide + GM-CSF or G-CSF alone Conditioning: melphalan + TBI or melphalan alone	9/45 cases identified diffuse esophagitis and gastritis most common source 2 reports of upper GI bleeding 3 reports of lower GI bleeding 4 reports of both upper and lower GI bleeding median duration to onset of bleeding: 9.5 days (range: 1-48 days)	None	Case reports do not provide robust evidence to support net health outcome decisions.
Lachmann, 2002 (abstract)	Prospective, nonrandomized, unblinded, 3-arm, active control	N= 186 Median age (y): 55 (AuSCT) 98 (VAD/C-VAMP) 33 (IDM)	55 given AuSCT; 98 given VAD/ C-VAMP; 33 given IDM Outcome measures: overall mortality; median survival; complete response	Median survival (entire group)= 59 mos Overall mortality and median survival not significantly different between 3 groups %deaths: AuSCT = 44% Complete response in 62% of 154 patients who survived 6 mos	Early mortality (not defined) great in the AuSCT and IDM groups, and in patients older than 55 or who have cardiac amyloidosis %deaths: VAD/C-VAMP= 43% IDM= 39%	Lack of blinding and randomization limits the robustness of the data and any conclusions drawn from the data Abstract-only format permits presentation of only limited study details
Sanchorawala, 2003	Prospective, stratified by predominant organ involvement and time from diagnosis to referral, randomized, 2-arm	N= 100 (52 Arm 1; 48 Arm 2) Median age: 57 Arm 1; 55 Arm 2 (range not provided)	Mobilization: G-CSF Conditioning: melphalan Outcome	Patient characteristics were similar between the 2 arms except for median time from enrollment to AuSCT 9 patients did not complete treatment: 4 withdrew, 2	16 patients did not complete treatment: 1 withdrew, 2 withdrawn for unrelated disease, 6 died, 3 with disease progression, 4 too ill to proceed.	Well-controlled trial. Median age is below 65 yrs with no indication of # of patients who were 65 yr or older limits

	design comparing hi dose melphalan/AuSCT with or without prior oral chemo Arm 1: hi dose melphalan + AuSCT Arm 2: oral melphalan + prednisone, then hi dose melphalan + AuSCT Inclusion: newly diagnosed with primary amyloidosis; EF>40; no limit on renal status if other criteria were met; ≥1 organ involvement Exclusion: diagnosis of multiple myeloma	%Women: 35 Arm 1; 38 Arm 2	measures: survival; hematologic response; clinical response per organ	died, 3 too ill to proceed Arm 1 Treatment-related mortality Pre-SC collect: 0 (0%) SC mobiliz/collect: 5 (10%) Death within 90 days of AuSCT: 5 (10%) Overall Survival 1 yr: 67% 2 yr: 60% 4 yr: 51% 5 yr: 51% Median Survival @ 45 mos: Yet to be reached Complete hematologic response @ 1 yr: 32% (No statistically significant differences)	Arm 2 Treatment-related mortality Pre-SC collect: 6 (13%) SC mobiliz/collect: 7 (15%) Death within 90 days of AuSCT: 4 (8%) Overall Survival 1 yr: 56% 2 yr: 54% 4 yr: 50% 5 yr: 39% Median Survival @ 45 mos: 37 mos Complete hematologic response @ 1 yr: 30%	generalizability of results for this age range. Focus of this trial was on timing of AuSCT and not on comparing AuSCT v. non-AuSCT. Nevertheless, there was a trend toward a survival disadvantage for patients who received oral chemo first, especially in patients with cardiac disease.
Seldin, 2004	Prospective, nonrandomized, unblinded, quality-of-life assessment compared to age-matched population norms Purpose: determine if hematologic/clinical response after AuSCT accompanied by increase in QoL	N= 251 transplanted patients who completed baseline SF-36 N= 210 age-matched transplant-ineligible patients (comparator group) N=82 transplant-eligible patients not transplanted Mean age (n=251): 56±9.5 yr Mean age (n=210): not provided Mean age (n=82): not provided Men/women for subgroups: not provided	Mobilization: G-CSF Conditioning: melphalan-- dose dependent on age or clinical status Outcome measures: quality-of-life as measured by the physical and mental components of SF-36	104 AuSCT patients completed SF-36 at baseline and 1 yr; no apparent difference in clinical characteristics between this group and the group that did not complete SF-36 84 completed at baseline and 2 yr; any difference in clinical characteristics between this group and the group that did not complete SF-36 not provided Physical component score: baseline: 34.5 1-yr: 41	# transplant-ineligible who completed baseline and 1-yr or 2 yr SF-36 not provided # transplant-eligible patients who completed a baseline, 1-yr, or 2-yr post transplant SF-36 not provided Physical and mental component scores at baseline, 1-yr, or 2-yr not provided for either the transplant-ineligible group or the transplant-eligible but not transplanted group	Lack of randomization and blinding. Incorrect comparator group—should be compared to transplant-eligible patients who did not receive an AuSCT

				2-yr: 43 Mental component score: baseline: 45 1-yr: 52 2-yr: 51 QoL significantly higher for patients who had complete hematologic response at 1-yr		
Skinner, 2004	Unblinded, non-randomized, 6-protocol-sequential, prospective cohort; transplant-eligible patients were compared to transplant-ineligible patients General inclusion: ages≤80; compensated CHF; EF≥40 6 different protocols were used—protocols varied by age of patients included, melphalan dose given, degree of renal insufficiency allowed, type of cell collected, or timing of transplantation relative to chemo	Total n=701 (394 eligible; 307 ineligible) Mean±SD Age: 56.9 ±10.3 (eligible); 64.6±10.2 (ineligible) %Women: 41 (eligible); 40 (ineligible)	Mobilized with G-CSF Conditioning: melphalan-- dose dependent on age or clinical status Outcome measures: complete hematologic response at 1 yr; ≥2 mm decrease in cardiac IV septum or ≥1 class improvement in NYHA without increase in diuretic; ≥50% decrease in 24-h urine protein excretion and ≥25% decrease in serum Cr; ≥2 cm decrease in hepatomegaly on physical exam or disappearance of diarrhea and weight loss stabilized or reversed; improvement in sensory neuropathy on serial neuro exam;	Comparison of clinical features of eligible and ineligible cohorts revealed numerous statistically significant differences (e.g., age, # organ systems involved, performance status) Of 394 eligible for transplant, 312 were mobilized and 277 eventually transplanted Median survival of mobilized patients= 4.6 yrs; estimated 5-yr survival rate= 47% (95% CI, 39-54%) 60/312 (19%) mobilized patients were ≥65 y/o—median survival was 4.9 yrs 36/277 (13%) transplanted patients died within 100 days 1-yr hematologic response (in 181 evaluable patients)= 40% (8% of these patients relapsed at 2 yrs) No difference in rate of responders seen in patients ≥65 yrs compared to younger patients	Median survival= 4 mos	Ineligible cohort is not an adequate control group because by protocol design these patients are not similar to the patients who were eventually transplanted. The results from 6 separate, different protocols were pooled. The differences in patient population and treatments given (e.g., melphalan dose) are likely to be significant confounders for the pooling of these results.

			resolution of preexisting orthostatic hypotension; normalization of factor X level; ≥1 improvement in performance measure			
Versole, 2003 (abstract)	Uncontrolled, unblinded, multicenter registry	N= 114 Median age: 55 y (31-71)	Melphalan or TBI or other, then transplant Outcome measures: organ response at 100 days; 100 day mortality; overall survival at 1 yr and 3 yr	% organ response at 100 days: Hematologic= 33 Renal= 21 Hepatic= 32 Cardiac= 66 100 day mortality= 25% (95%CI, 17-33) across treatment regimens Overall survival at 1 y was 68% and at 2 yr was 57%	None	Lack of blinding and randomization limits the robustness of the data and any conclusions drawn from the data Abstract-only format permits presentation of only limited study details

Key

TBI-- total body irradiation
G-CSF—granulocyte colony stimulating factor
AuSCT—autologous stem cell transplantation
y/o—years old
mos-- months
GM-CSF—granulocyte, macrophage colony stimulating factor
EF—ejection fraction
Cr—creatinine
CHF—congestive heart failure
VAD— vincristine, Adriamycin, dexamethasone
C-VAMP—cyclophosphamide, vincristine, Adriamycin, methylprednisolone
IDM—intravenous low dose melphalan
QoL—quality of life
SF-36—short form-36
CI—confidence interval
Alk phos—serum alkaline phosphatase
SC—stem cell
NYHA—New York Heart Association