Selected Summary

Long-term Outcome of Patients with AL Amyloidosis Treated with High-dose Melphalan and Stem Cell Transplantation

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SUMMARY:

Primary systemic amyloidosis results due to deposition of clonal immunoglobulin light chains in various organs resulting in organ failure and subsequent death. Melphalan and Prednisolone has been the standard first line therapy until late 1990's when aggressive treatment with high dose chemotherapy (HDT) followed by peripheral blood stem cell transplantation (PBSCT) showed higher response rate and improved overall survival.[1] In the present study[2], authors at Boston Medical Center, USA studied the long-term outcome of HDT followed by PBSCT.

Between July 1994-July1997, 80 patients with a median age of 56 years (range, 29 to 71) diagnosed to have primary systemic amyloidosis and SWOG (South Western Oncology Group) performance status of 1 (0 to 3) entered the study. 48% had cardiac involvement and on an average two organs (range=1-5) were involved with amyloid. All patients met eligibility criteria[3]: confirmed tissue diagnosis of amyloidosis, clear evidence of clonal plasma cell dyscrasia, age > 18 years, performance status (SWOG 0-2), cardiac function >40%, pulmonary function (O_2 saturation >=95% on room air), hemodynamic stability (baseline systolic blood pressure >=90 mm Hg). Patients on peritoneal or hemodialysis for renal failure were not excluded if they met eligibility criteria. Stem cell mobilization was done with G-CSF (granulocyte colony stimulating factor) and HDT included intravenous melphalan (100-200 mg/m^2) followed by stem cell transplant 24-72 hours after completion of chemotherapy. Response evaluation included-hematological assessment and was defined as absence of monoclonal protein in serum and urine by immunofixation electrophoresis together with a bone marrow biopsy showing less than 5% plasma cells without clonal dominance of k or λ light chain isotypes and was done at end of one year. Transplant related mortality (TRM) was defined as death within 100 days of transplant including mobilization and collection days. 17 patients could not be evaluated as they died within 1st year of study (14% due to transplant related mortality and 8% due to disease per se). Statistical analysis of survival was done using Kaplan-Meier method.

Among 63 evaluable patients, 32 (51%) achieved complete hematological response (CHR) with a relapse rate of 34% within 2.5 years and survival at 10 years being 53% in this subgroup. Median survival has not reached yet. Relapses occurred in 34% within 2.5 years and were treated with second line therapy. 31 (49%) patients who did not achieve hematological CR formed the other subgroup and had median survival of 50 months and probability of survival at 10 years being 6%. The survival at 10 years in both these subgroups was statistically significant ($p<0.001$). The median survival was higher ($p=0.20$) in the patients receiving full dose melphalan (200 mg / m^2) versus modified dose.

In patients who achieved CR, 15/32 (47%) have died compared to mortality rate of 97% (30 of 31) in patients who did not achieve CR. Causes of death in the subgroup achieving CHR were progressive disease (n=6), therapy related

myelodysplastic syndrome and acute myelogenous leukemia (n=1), solid tumours (n=2) and organ dysfunction despite CHR (n=6).

Overall, the median survival for these 80 patients was 57 months and long–term survival beyond 10 years was achieved in 18 patients (23%) of which 17 belonged to group who achieved CHR and 1 belonged to the non CHR group. Thus, achievement of complete hematologic remission following high dose chemotherapy and stem cell transplantation was the most powerful predictor of long term survival.

COMMENTS:

Kyle et al[1] in a randomized study first demonstrated the superiority of melphalan (M) and prednisolone (P) in the treatment of primary systemic amyloidosis. Promising results of HDT/PBSCT in myeloma and ability to reverse the disease process formed the basis for its therapeutic option in primary systemic amyloidosis. The earliest pilot study was published in 1996[4], which included a cohort of 5 patients followed by expanded series[5] of 25 patients and since, then many more pilot and prospective studies have been published. However, many controversies have reined regarding high dose therapy (HDT) mainly because of selection bias and high transplant related mortality. Though a number of studies[3,6-15] have shown benefits but follow up was short.

PBSCT results in improved performance status and quality of life in survivors by (i) reduction in monoclonal proteins (ii) regression of amyloid deposition from organs (iii) significant symptomatic response (iv) improved overall survival. However, high transplant related mortality in SCT ranges from 6.5% to 26% mainly due to (i) poor performance status (ii) advanced cardiac involvement & poor ejection fraction (iii) more number of organs involved (iv) age more than 70 years (v) dialysis dependent renal failure (vi) history of gastrointestinal bleeding. Other issues like pretransplant chemotherapy regimens and the choice between chemotherapy versus HDT still remains unclear.

Among carefully selected patients, the results of PBSCT are encouraging. Present study in this regard confirms these observations. Patients who achieved CHR post PBSCT had higher survival at 10 years follow up. 17 out of 32 patients (53%) are alive from this subgroup. These results are consistent with a study from UK[12], which shows estimated survival of 59% for those who survived day +100 post transplant and were in CR post-PBSCT with a follow up of more than 8 years. In the present study, among patients who did not achieve CHR, estimated survival at 10 years was 6%. Table-1 describes important studies on high dose chemo and PBSCT for AL amyloidosis.

Transplant related mortality is the major complication in HDT, which is as high as 10-20% in single centre studies and more in multicentric studies. Mortality was higher in early 90's compared to late 1990's. In the present study though the patients underwent transplant in early 90's, transplant related mortality (14%) was less than contemporary candidates mainly because of adoption of more stringent eligibility criteria for selection of candidates and it being a single centre study. The causes of death for transplant related mortality include multi-organ failure, GI bleeding, hypotension, cardiac arrythmias.

Review of transplant studies supports the author's conclusion that transplant definitely induces hematological and organ response and improves overall and median survival. Long term outcome is high in patients who achieve CHR. More than 2 organs involvement with amyloid, advanced cardiac disease, non achievement of hematological remission are important factors affecting survival and outcome negatively. However, more stringent criteria need to be adopted to lessen the transplant related mortality.

Table 1: Review of Transplant studies conducted from the year 1994-2004 for the treatment of amyloidosis

Author	Period of study	N	Subgroups	100 day TRM	HR	Follow Up	Survival	Conclusion
Sanchorawala et al[3] 2001 (Boston)	1994-2000	205	CHR Non CHR	14%	47%	>1 year	76% (1y) 65% (2y) 60% (3y) 60% (4y)	HDT as first line Tx for patients with good performance status & limited cardiac involvement.
Gertz et al[6] 2002 (Mayo)	1996-2001	66	_	14%	50%	25 months	70% (2y)	More the number amyloid organs before transplant lesser is the survival post HDT
Dispenzieri et al[7] 2004 (Mayo)	1996-2001	63	Cases=HDT Controls= Non HDT	Cases-HDT =13%	-	4 years	89% vs73% (1y) 82% vs58% (2y) 75% vs43% (4y) p<0.001	First case-match-control study Superior significant overall survival in HDT
Skinner et al[8] 2004 (Boston)	1994-2002	394		13%	40%	8 years	4.6y	HDT improves survival and reversal of amyloid organ damage in eligible patients
Porrata et al[9]2005 (Mayo)	1996-2003	145	ALC≥500 ALC<500	ALC≥500 =5% ALC<500 =12% ovrall=90%	ALC≥_500 =41% ALC<500 =21% p<0.0008	22months (-87)	ALC≥500=53m P<0003 ALC<500=27m P<0.0001	Early lymphocyte recovery (ALC≥500 cells at day 15) predicts superior survival Post HDT
Leung et al[10] 2005 (Mayo)	1997-2003	126	>2Kg vs ≤2Kg (weight gain)	>2Kg=20% ≤2Kg=6.5%	>2Kg=57% ≤2Kg=74% p=0.04	>1year	mortality >2Kg=34% <=2Kg=9.8% p=0.002	Weight gain during mobilization is marker of adverse outcome post HDT
Seldin et al[11] 2006 (Boston)	1994-2002	345	>65y vs <65y (baseline age)	>65y=10% <65y=13.4% (NS)	>65y=32% <65y=43% (NS)	10years	>65y=48m <65y=58m (NS)	Eligible older should not be excluded from HDT
Goodman et al[12] 2006 (UK)	1994-2004	92		23%	83%	>8years	OS=5.3y& 8.5 y*	High TRM mandates more stringent criteria in patient selection for HDT
Perfetti et al[13] 2006 (Italy)	1995-2002	22		14%	55%	47months	68m	Risk adapted approach prolonged survival. Additional therapy needed if no HR at +3m after HDT
Perz et al[14] 2006 (London)	1996-2001	19		26%	-	-	48m OS=62% (2y)	Questioned the time interval between diagnosis and HDT
Vesole et al[15] 2006 (New York)	1995-2001	107		18%	32% (16% CR 16% PR)	40months	66% (1y) 56% (3y)	More stringent selection criteria result in less TRM and improved survival

HR=hematological response, CHR= Complete hematological remission, HDT=high dose therapy, ALC=absolute lymphocyte count, TRM=transplant related mortality, HR=hematologic response, CR=complete response, PR=partial response, OS= overall survival, m=months, y=years, * =who survived day +100, n= number of patients, NS=not significant

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