

Autotransplant for patients with Advanced Amyloidosis

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Amyloidosis: A changing clinical perspective

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Abstract

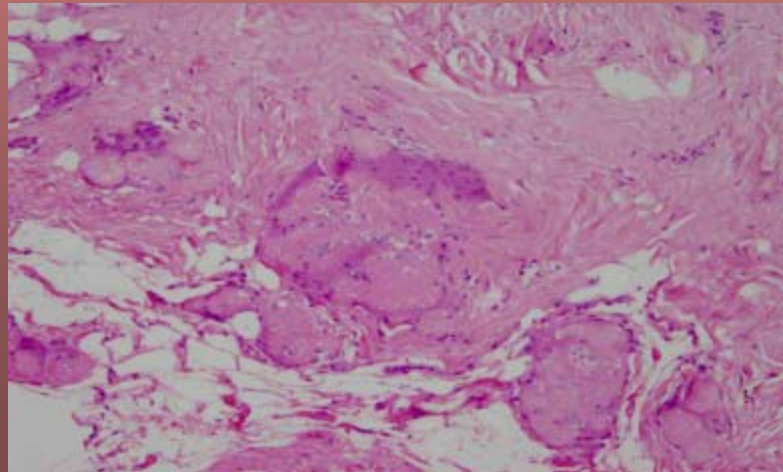
Primary amyloidosis is a plasma cell dyscrasia characterised by excess production of abnormal immunoglobulin light chains with their subsequent accumulation in kidneys, heart, liver as well as gastrointestinal tract and bone marrow [1–2]. These tissue deposits take the form of a fibrillar protein which damages the involved organ in proportion to the extent of the infiltration and roughly parallels the duration of the disease. Most cases have evidence of the underlying lymphoplasmacytoid neoplasm recognisable in two ways. Firstly, the monoclonal appears in the serum [2]. Secondly is a morphologically and immunohistochemically distinctive cellular infiltrate in the bone marrow [3] that has a specific microscopic and ultrastructural pattern [4–5]. Interestingly occasional patients, who survive long enough, may progress to multiple myeloma [6] but the correlation is variable [7].

Amyloid

- Protein conformational disorder & clonal plasma cell dyscrasia
- Amorphous extra cellular material deposition-kidneys (Nephrotic Syndrome)
heart (Congestive CMO)
liver (Hepatomegaly)
nervous system (Neuropathy)

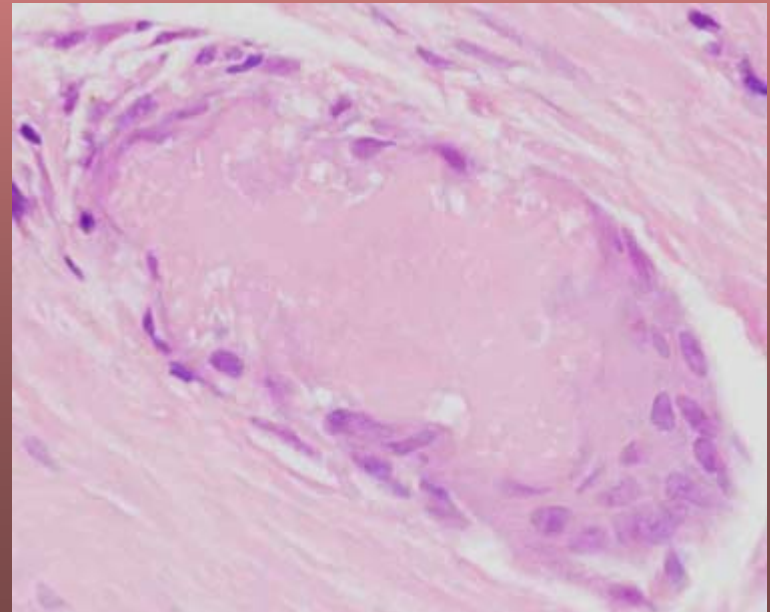
Amyloid

- Median survival at diagnosis 13.2 months
- One fifth the incidence of Myeloma
- CMO median survival 4 months
- <5% AL survive >10 years post diagnosis



Amyloid

- Halt production of deposits
- Amyloid resorbed
- PS & QOL can improve



Transplant Patient selection

- All patients considered
- Monoclonal protein does not increase with time-cannot observe patient for increasing M protein
- No evidence for cytoreductive benefit prior to transplant

Stem cell transplantation results in AL amyloidosis

Reference	Patients enrolled	Deaths at SC collection	Treated	Deaths at SC infusion	TRM	Responders
Single Centre Experience						
10	25	1	23	0	3	12
27	23	0	20	0	4	12
28	30	1	28	1	5	7
29	9	3	6	2	4	2
Total	87	5	77	3	16 (21%)	33 (62%)
Multi Centre Clinical Trials						
26	40	0	40	0	15	11
30	21	0	21	0	9	10
Total	61	0	61	0	24 (39%)	21 (62%)

TRM indicates transplantation-related mortality.

Mortality

- 4-8 times higher than for myeloma despite careful selection
- Cardiac involvement under estimated
- Melphalan related toxicities need to be looked for – GUT

Toxicities (grade 2 or higher)

Toxicity	200 mg/m ² (n = 23) Frequency, % (n)	100 mg/m ² (n = 27) Frequency, % (n)
Nausea/vomiting	83 (19)	52 (14)
Diarrhea	65 (15)	48 (13)
Mucositis	91 (21)	37 (10)
Pulmonary edema	35 (8)	26 (7)
Peripheral edema	48 (11)	15 (4)
Non-GI bleeding	71 (4)	0 (0)
GI bleeding	22 (5)	7 (2)
Hepatic	13 (3)	22 (6)
Renal	35 (8)	19 (5)
Metabolic	35 (8)	7 (2)
Sepsis	26 (6)	11 (3)

Risk Adapted Approach

Good Risk

- 1 or 2 organs involved
- No cardiac involvement
- Creatinine clearance ≥ 51 ml/min

Intermediate Risk

- 1 or 2 organs involved (Cardiac + Renal)
- Asymptomatic or compensated Cardiac dysfunction

Poor Risk

- 3 organ involvement
- Advanced cardiac disease

Risk Adapted Approach

Melphalan dosing
based on risk group
and age

Good Risk

$200\text{mg}/\text{m}^2 \leq 60$
 $140\text{mg}/\text{m}^2$ 62-70
 $100\text{mg}/\text{m}^2 \geq 71$

Intermediate Risk

$140\text{mg}/\text{m}^2 \leq 60$
 $100\text{mg}/\text{m}^2$ 61-70

Poor Risk

Standard Therapy
Clinical Trials

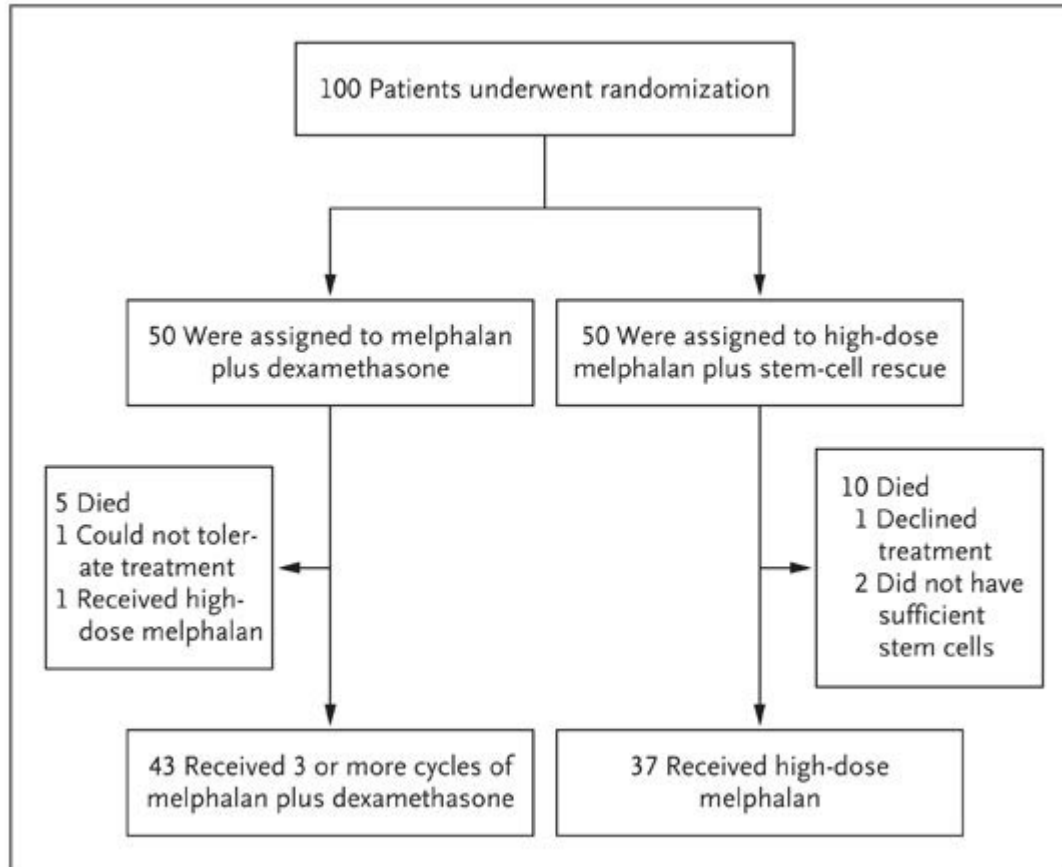
Summary

- Only applicable to a minority of patients
- Limited organ involvement
- No significant cardiac disease
- High risk of GIT haemorrhage and cardiac problems

2004



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Baseline Characteristics of the Patients

Table 2. Baseline Characteristics of the Patients.^a

Characteristic	Group Assigned to Melphalan plus Decamethasone	Group Assigned to High-Dose Melphalan	P Value
Time from diagnosis to randomization (days)			
Median	41	50	0.28
Range	9–287	8–1194	
Male sex (no.)	30	27	0.37
Age			
Mean (yr)	59.1±6.9	56.8±7.6	0.10
≥55 yr (no.)	10	8	0.27
High-risk disease (no.)	20	21	0.84
ECOG performance-status score (no.)			0.48
0	9	11	
1	25	19	
2	16	20	
NYHA category (no.)			0.87
1	9	8	
2	7	10	
3	4	3	
4	3	3	
Organs involved (no.)			0.98
1	16	17	
2	16	15	
3	13	12	
≥4	5	6	
Heart involvement (no.)	23	24	0.84
Left ventricular ejection fraction			
Mean (%)	61.3±15.4	54.9±13.0	0.21
30–50% (no.)	4	6	0.88
Interventricular septum			
Mean (mm)	17.4±2.9	16.8±2.9	0.48
>13 mm (no.)	13	15	0.63
Kidney involvement (no.)	34	35	0.83
Serum creatinine (mg/dL)	121.4±111.7	118.0±65.1	0.88
24-hr urinary protein			
Mean (g/24 hr)	6.7±5.1	7.71±5.3	0.41
>3 g/24 hr (no.)	26	28	0.55
Serum albumin (g/dL)	24.0±6.9	22.2±10.8	0.43
Liver involvement (no.)	10	16	0.17
Serum alkaline phosphatase			
Mean (IU/liter)	735.3±669.3	489.6±317.0	0.36
>2× ULN (no.)	5	8	0.99
Nerve involvement (no.)	10	12	0.63
Serum monoclonal immunoglobulin (g/dL)	10.4±7.1	10.4±7.9	0.99
Monoclonal FLC (mg/liter)			
Median	250	173.0	0.49
Range	6–1290	13.9–5460.0	
Bone marrow plasma cells			
Median (%)	7.3	6.5	0.29
Range (%)	0.0–79.0	1.0–90.0	
≥30% (no.)	2	0	0.54

^a Plus-minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group, NYHA New York Heart Association, ULN upper limit of the normal range, and FLC free light chain.

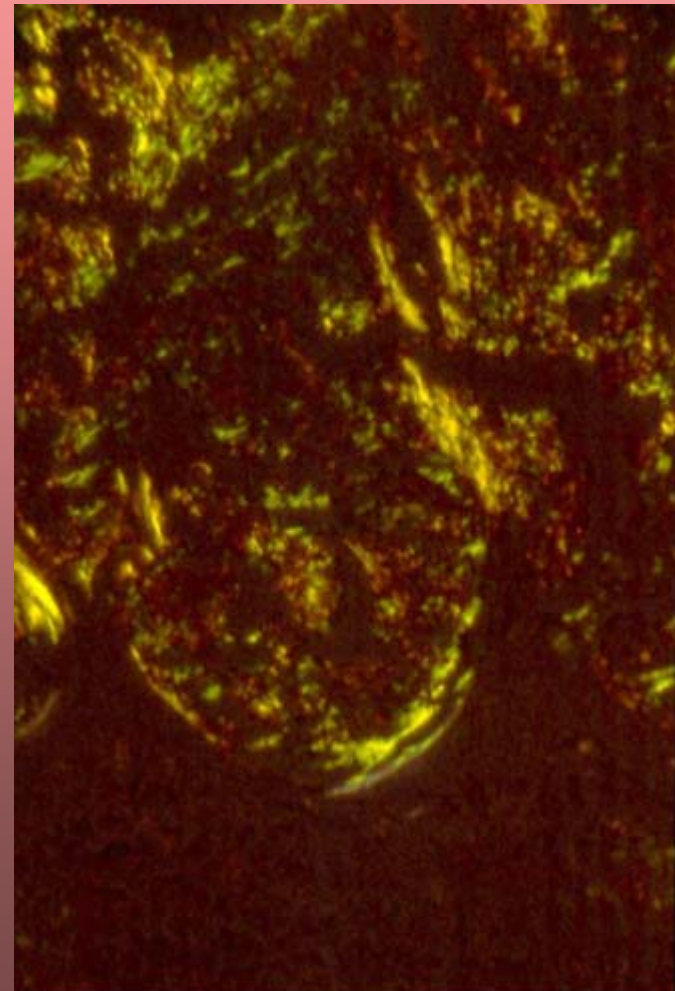


Table 1. Criteria for Organ Involvement, Organ Response, and Hematologic (Immunochemical) Response.*

Organ involvement

Kidney: 24-hr urinary protein >0.5 g/day, predominantly albumin

Heart: Mean wall thickness >12 mm on echocardiogram, no other cardiac disease responsible for the increase in wall thickness

Liver: Total liver span >15 cm in the absence of heart failure, or alkaline phosphatase level >1.5 times upper limit of normal

Nerve: Symmetric sensorimotor peripheral neuropathy in the legs, gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration

Gastrointestinal tract: Symptoms and verification by means of biopsy

Lung: Symptoms and verification by means of biopsy, interstitial radiographic pattern

Soft tissue: Tongue enlargement, arthropathy, skin purpura, myopathy (pseudohypertrophy or detected by means of biopsy), lymph node involvement, carpal tunnel syndrome

Organ response

Heart: Mean interventricular septal thickness decreased by 2 mm, 20% improvement in ejection fraction, improvement by two New York Heart Association classes without an increase in diuretic use, and no increase in wall thickness

Kidney: 50% decrease (a decrease of at least 0.5 g/day) in 24-hr urinary protein (must be >0.5 g/day before treatment), creatinine and creatinine clearance must not worsen by 25% over baseline level

Liver: 50% decrease in abnormal alkaline phosphatase value, at least 2-cm decrease in liver size on radiographic imaging

Nerve: Improvement in nerve conduction velocity on electromyogram (rare)

Hematologic (immunochemical) response

Complete response: Serum and urine negative for a monoclonal protein by means of immunofixation, normal kappa:lambda free light-chain ratio, and normal absolute value of the involved serum free light-chain (in patients without renal insufficiency)

Partial response: Serum M component >0.5 g/dl and 50% reduction; light chain in the urine with a visible peak >100 mg/day and 50% reduction; or free light chain >10 mg/dl and 50% reduction

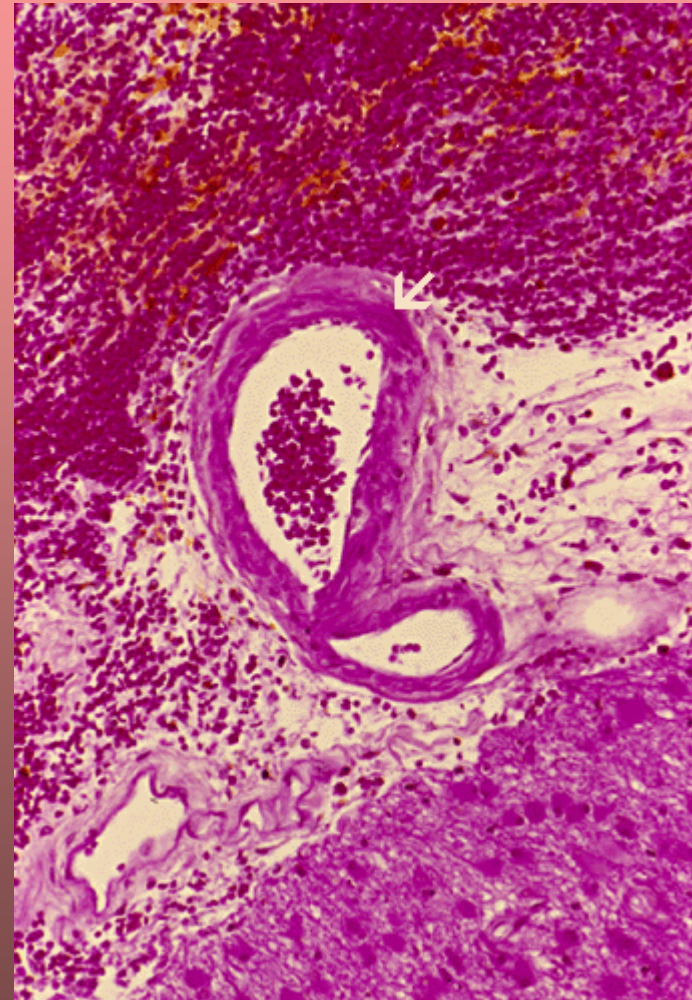
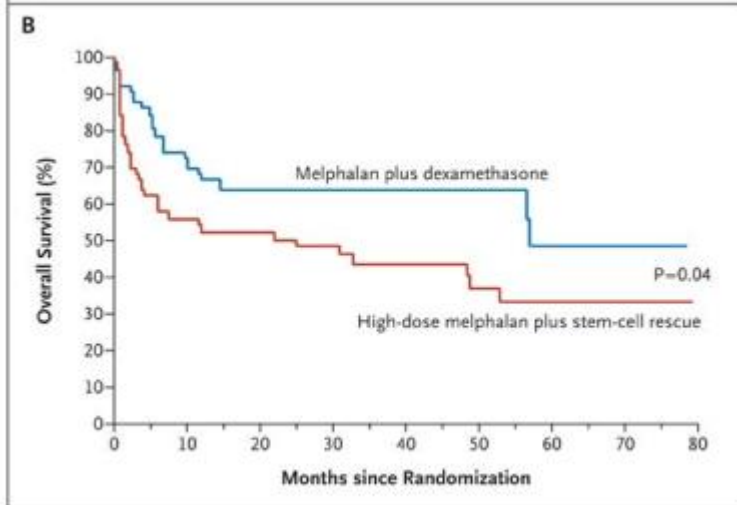
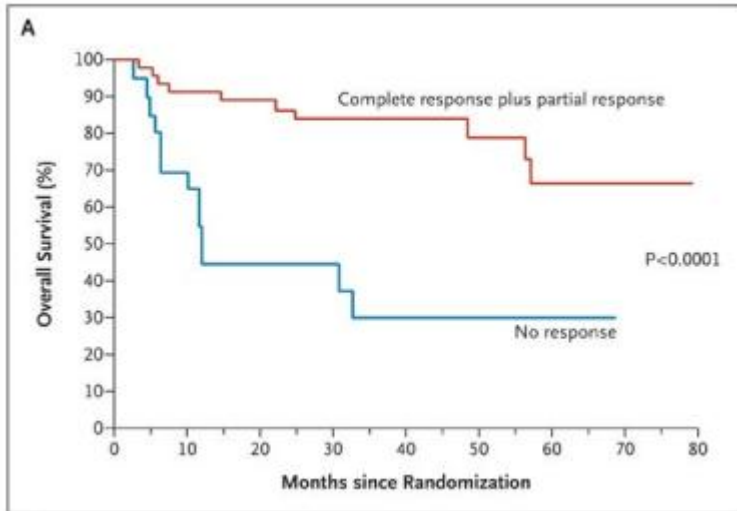
Progression after complete response: Any detectable monoclonal protein or abnormal free light-chain ratio (light chain must double)

Progression after partial response or stable response: 50% increase in serum M protein to >0.5 g/dl or 50% increase in urinary M protein to >200 mg/day with a visible peak; free light-chain increase of 50% to >10 mg/dl

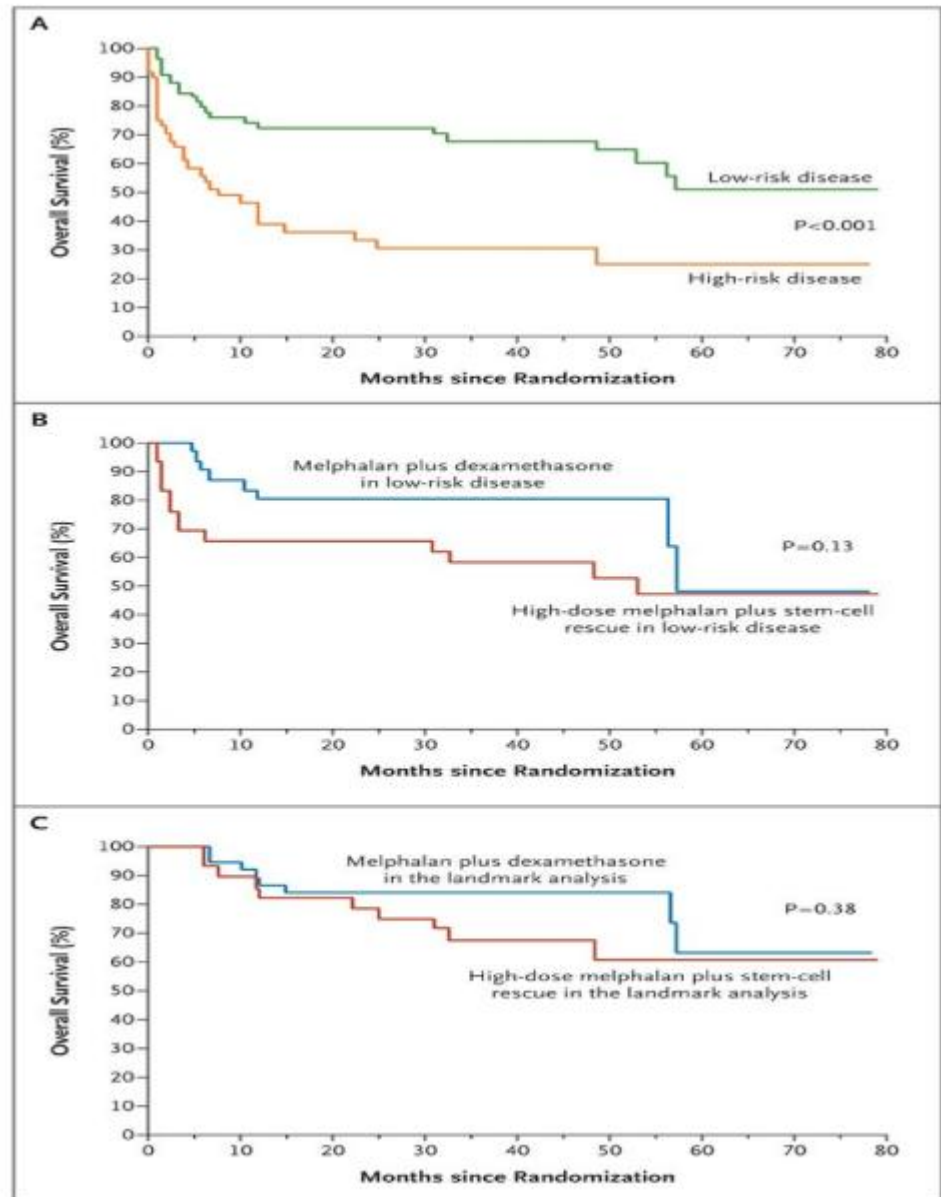
Stable: No complete response, partial response, or progression

* Data are adapted from Gertz et al.⁸

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Survival According to Risk Group, According to the Treatment Group among Patients with Low-Risk Disease, and According to the Treatment Group



Conclusion

- Power to detect 25% survival advantage
- Median Survival longer in non transplant group
- 2/3 patients with standard therapy had durable haematological responses
- Mortality is as for other multi centre studies but higher than for single centre experiences
- Late transplant : 48 days from enrolment to transplant
- Inclusion criteria not as stringent as North American trials



Criticism

- TRM twice as high as other centres doing transplant for AL
- 36% patients transplanted had 3+ organ involvement
- 10/37 patients transplanted received inadequate Melphalan dose
- French Multi centre trial sites should not be doing transplants for AL

Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation

Vaishali Sanchorawala, Martha Skinner, Karen Quillen, Kathleen T. Finn, Gheorghe Doros and David C. Seldin

Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation

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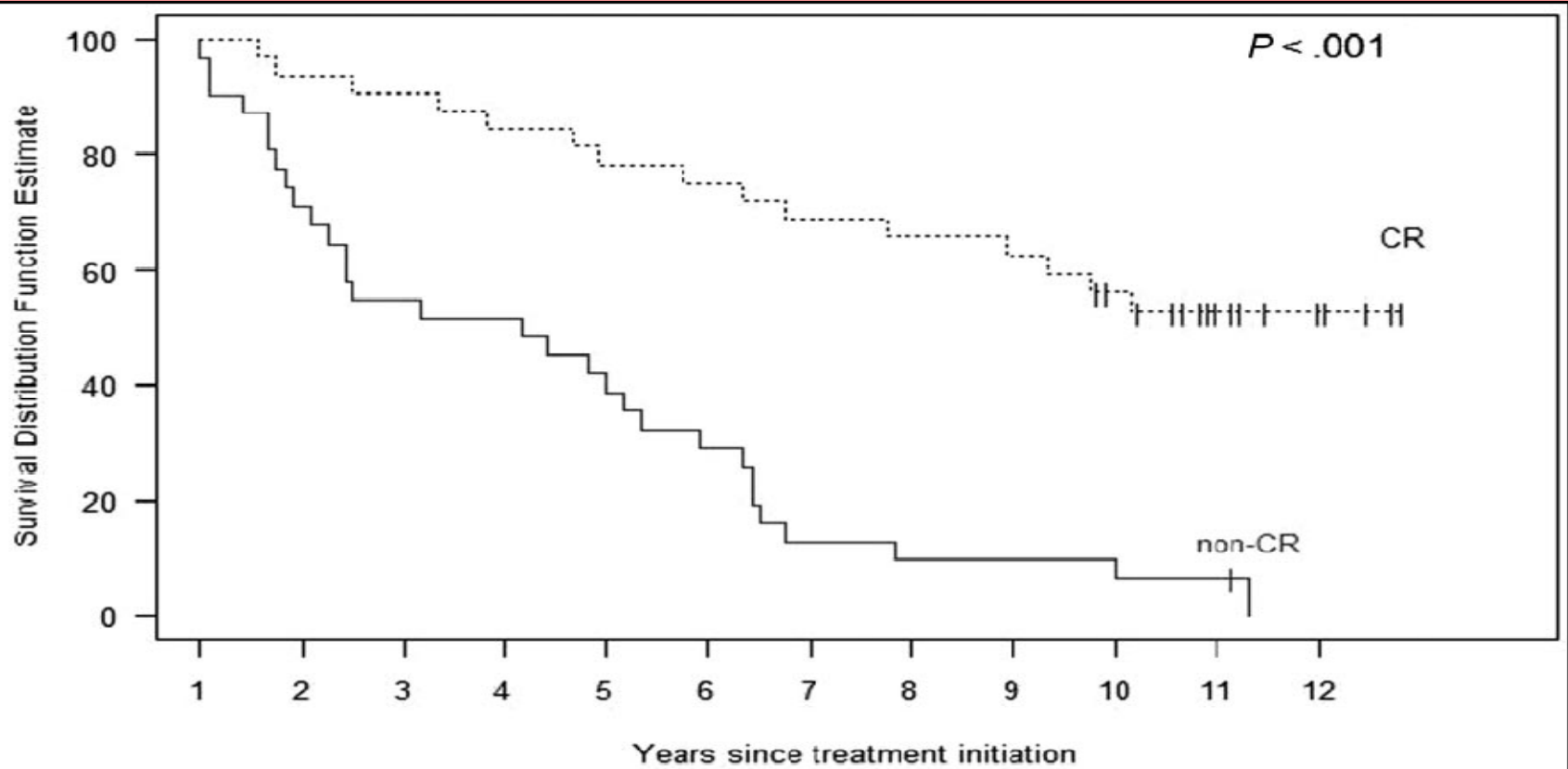
Long-term survival and outcome were determined for 80 patients with immunoglobulin light chain (AL) amyloidosis treated with high-dose melphalan and stem cell transplantation (HDM/SCT) more than 10 years ago. Seventeen (21%) patients died within the first year of treatment, of treatment-related complications (14%) or progressive disease

(8%). Of the 63 surviving evaluable patients at one year, 32 (51%) achieved a complete hematologic response (CR). For all 80 patients, the median survival was 57 months (4.75 yrs). The median survival exceeds 10 years for patients achieving a CR after HDM/SCT, compared with 50 months for those not achieving a CR ($P < .001$). In conclu-

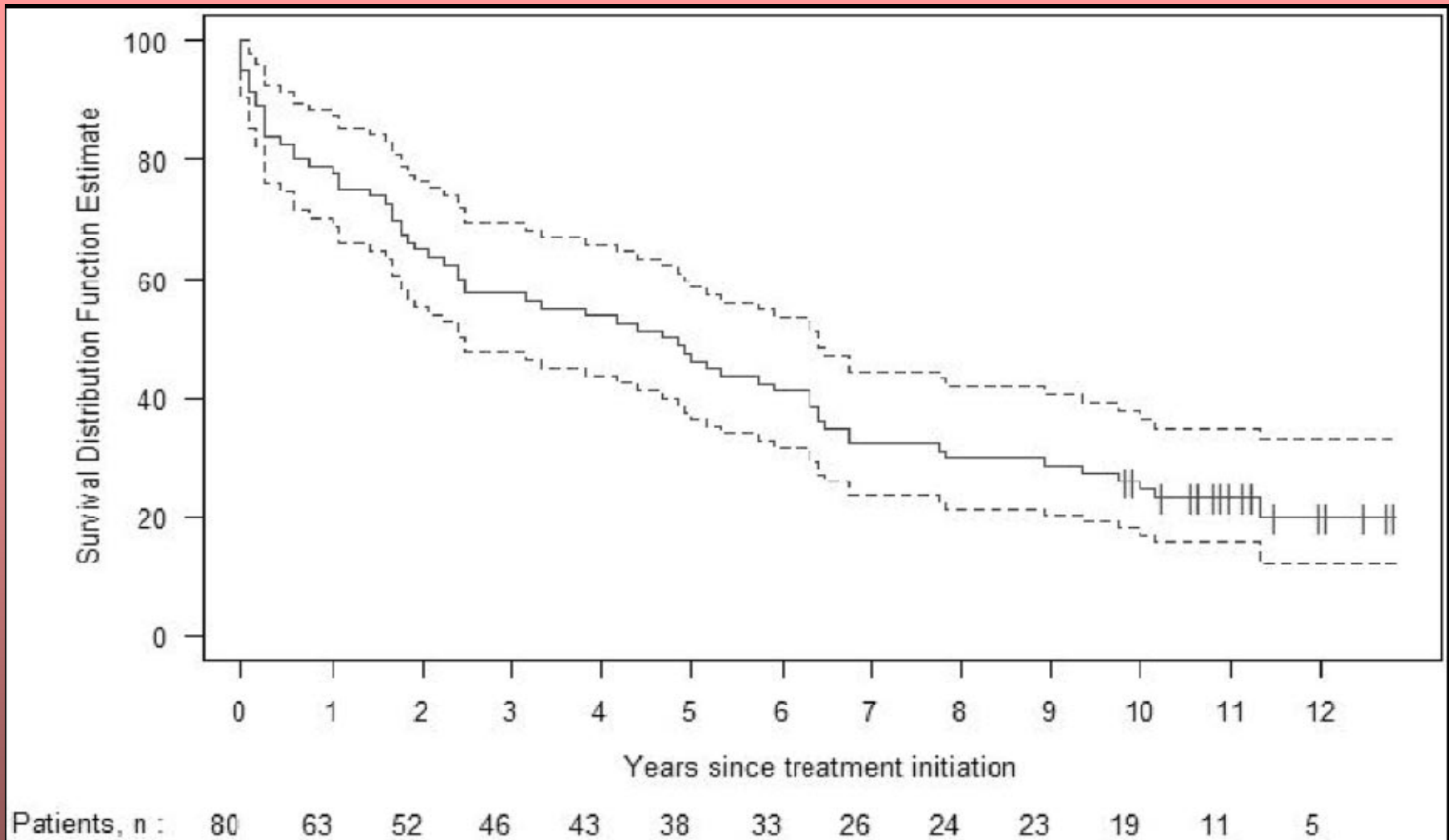
sion, HDM/SCT leads to durable remissions and prolonged survival, particularly for those patients who achieve a hematologic CR. (Blood. 2007;110: 3561-3563)

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Kaplan-Meier estimates of survival according to haematologic response



Patients, n	1	2	3	4	5	6	7	8	9	10	11	12
CR:	32	30	29	27	25	24	22	21	20	16	9	5
non-CR:	31	22	17	16	13	9	4	3	3	3	2	0



Kaplan-Meier estimate of overall survival, with 95% confidence intervals, for all 80 patients treated with #DM/SCT more than 10 years ago (1994-1997). SWOG

SWOG Blood 15 Nov 2007

- 23.5% 10 year survival with transplant
- 2% 10 year survival with oral M & P
- Transplant outcome heavily biased by response
- No long term studies show any better survival with non transplant strategies

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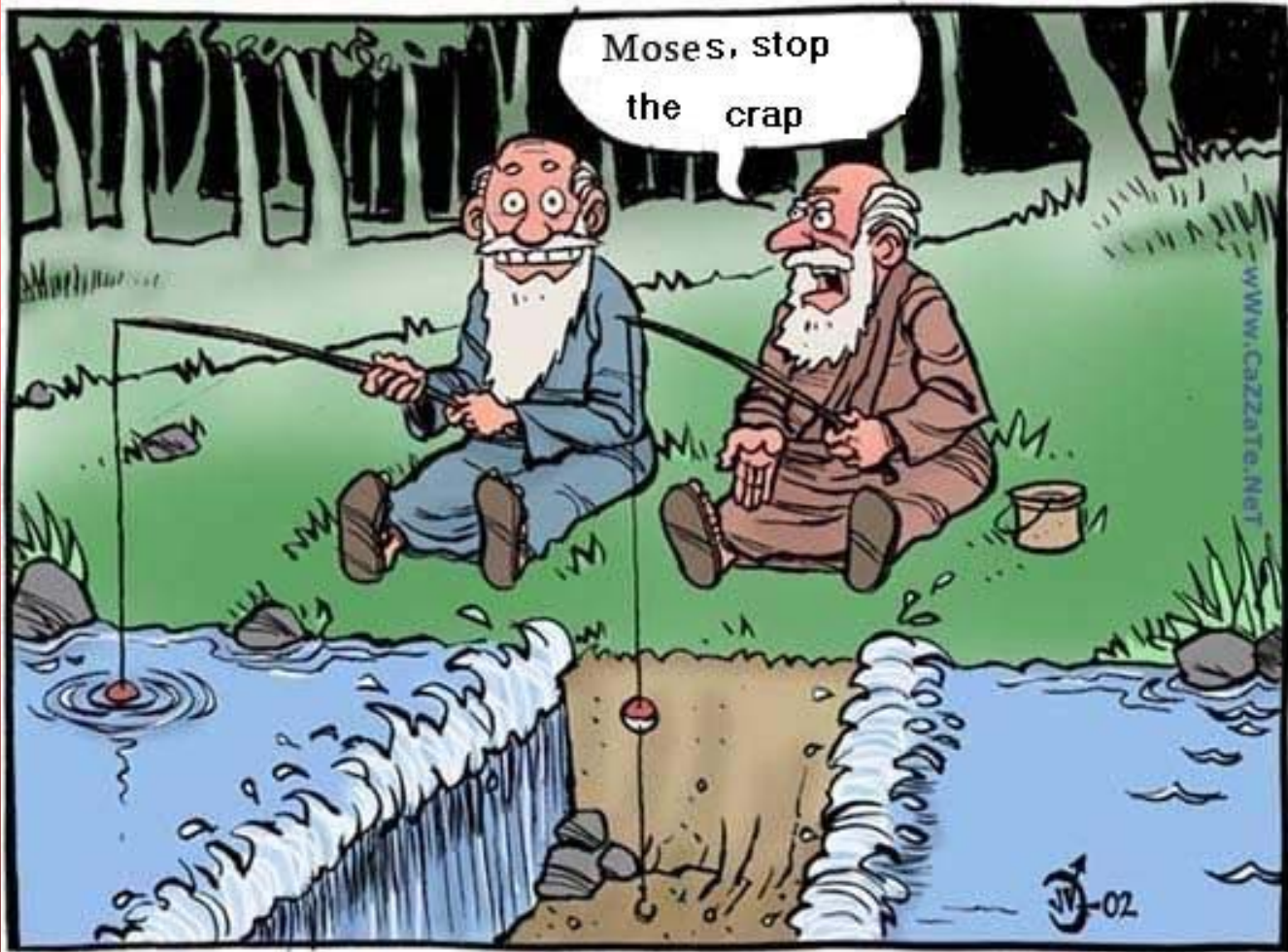
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Summary

It is concluded that the previously reported poor quantity and quality of lifespan largely reflect failure to make a correct diagnosis and this is often coupled with persistence of inappropriate palliative treatments justified on the basis that high-dose chemotherapy, with or without haematopoietic stem cell rescue, has a poor record. As long as such a nihilistic approach deters early referral these cases will be denied options, albeit expensive and of high-risk, that have the potential for disease eradication. It emphasised that such protocols require additional approval by Ethics and Research Committees as well as Institutional Review Boards. They should specifically incorporate not only currently acceptable options but also risk-stratification for innovative approaches that range from the use of monoclonal antibodies to transplantation. Such a broadly based choice, to accommodate all stages of an evolving disease, is an obligation for centres wishing to accept responsibility for these cases.

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the crap

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