Timing of Autologous Stem Cell Transplant in MM: Early vs. Late

Pankaj Malhotra
PGIMER, Chandigarh, India

Early Transplant

- Definition
- Patient population
- Concept of CR
- Different levels of CR
- Problems with late transplant
- International guidelines

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What is early and late transplant?

Early: After 3-4 cycles of chemotherapy, harvest and do transplant

Late: After 3-4 cycles of chemotherapy, harvest. Transplant as rescue patients developing primary resistance or at relapse in responders

High-Dose Therapy and Autologous Peripheral Blood Stem Cell Transplantation in Multiple Myeloma: Up-front or Rescue Treatment? Results of a Multicenter Sequential Randomized Clinical Trial

By Jean-Paul Fermand, Philippe Ravaud, Sylvie Chevret, Marine Divine, Véronique Leblond, Coralie Belanger, Margaret Macro, Edouard Pertuiset, François Dreyfus, Xavier Mariette, Catherine Boccacio, and Jean-Claude Brouet for the Group "Myélome Autogreffe"*

Blood, Vol 92, No 9 (November 1), 1998: pp 3131-3136

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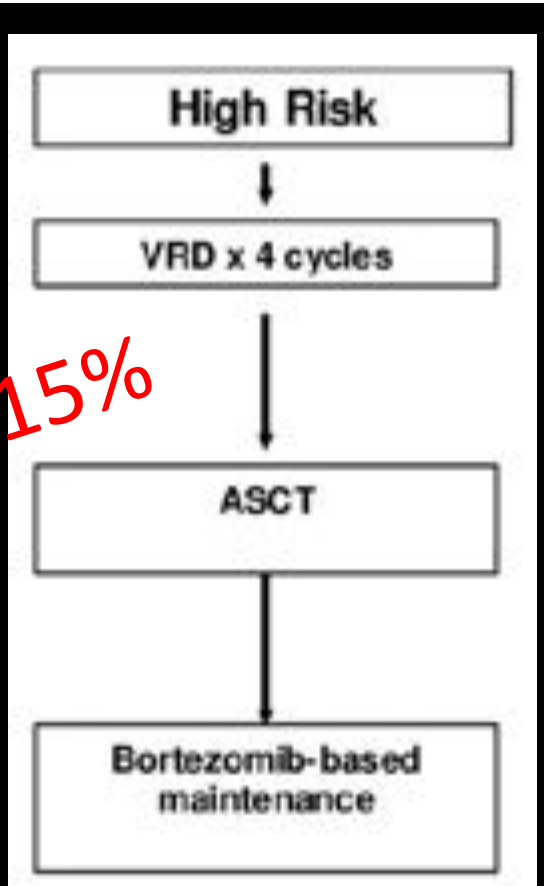
Am. J. Hematol. 87:79–88, 2012.

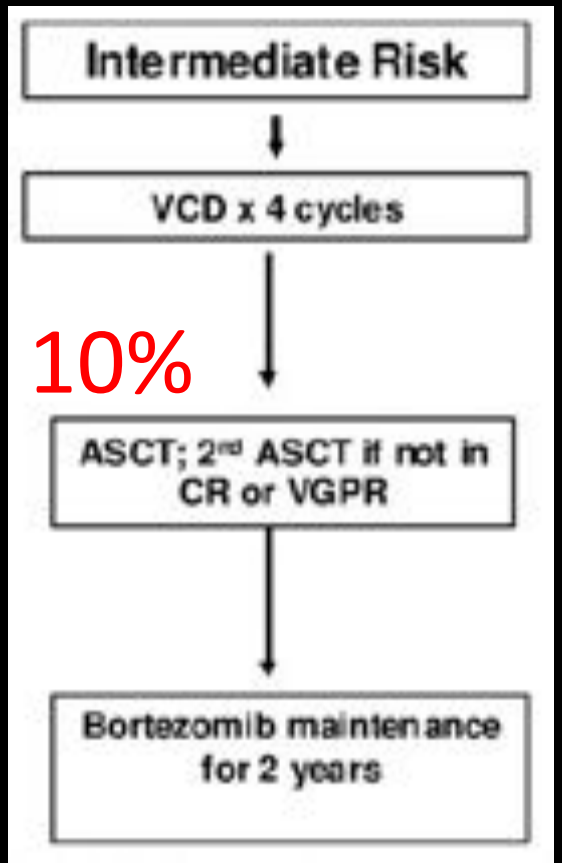
Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management

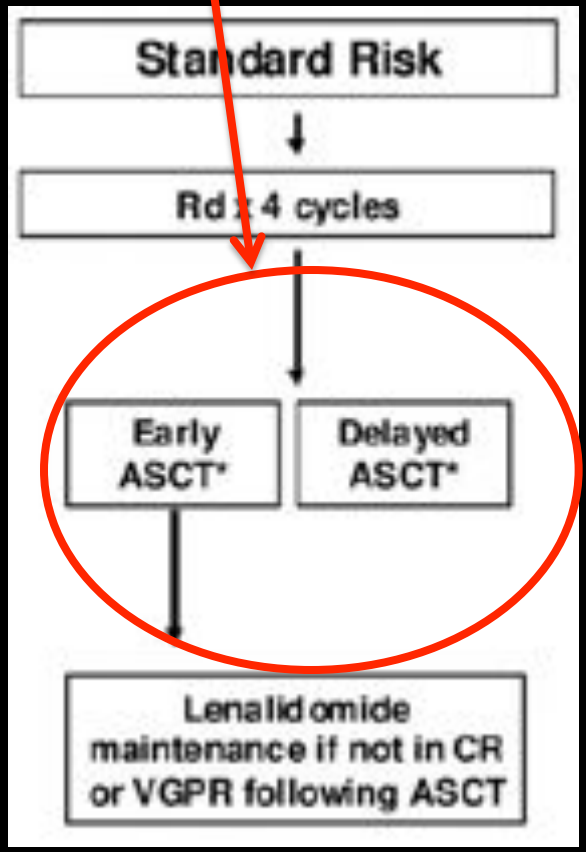
S. Vincent Rajkumar

Debate

A Newly Diagnosed Myeloma Eligible for Transplantation







Age wise prevalence of MM

Age group	MM prevalence	Transplant
>75	37%	No
65-74	26%	±
<65	37%	Yes, Early vs Late

75% standard risk

27%

30% renal failure, hence high-risk

18%

20% Chemo resistance/Co-morbidities

15%

Early vs late

This debate is to discuss SCT
early vs late strategy
only for 15% patients of MM

85% MM patients would require either early transplant because of high-risk disease or are not eligible because of age and co-morbidities

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Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma

Helgi J.K. van de Velde, Xiangyang Liu, Gang Chen, Andrew Cakana, William Deraedt, Martine Bayssas

(overall survival and event-free/progression-free survival). Both meta-analyses also provided evidence of highly significant associations between maximal response following induction therapy and long-term outcomes (overall survival and event-free/progression-free survival).

Key words: long-term survival, progression-free survival, high-dose therapy, multiple myeloma.

Haematologica 2007; 92:1399-1406. DOI: 10.3324/haematol.11534

International uniform response criteria for multiple myeloma

Leukemia (2006) 20, 1467–1473

Response Subcategory	Response criteria
CR	Negative immunofixation on the serum and urine, Disappearance of any soft tissue plasmacytomas, <5% plasma cells in BM
sCR	Normal FLC ratio, absence of clonal plasma cells in BM by immunohistochemistry
VGPR	M component detected by IF but –ve on SPE or 90% or greater reduction in serum M protein + urine M protein <100mg/24 hours
PR	≥50% reduction of serum M protein and reduction in urine M protein >90% or <200mg/24 hours

CR rates with different anti-myeloma treatment

Treatment Regimen	CR rates
Melphalan/Pred	3%
VAD	11-16%
Thal/Dexa	8%
Autologous Stem Cell Transplant	22-44%

The obvious choice is ASCT

A PROSPECTIVE, RANDOMIZED TRIAL OF AUTOLOGOUS BONE MARROW TRANSPLANTATION AND CHEMOTHERAPY IN MULTIPLE MYELOMA

Abstract

Background The median survival of patients with myeloma after conventional chemotherapy is three years or less. Promising results have been reported with high-dose therapy supported by autologous bone marrow transplantation. We conducted a randomized study comparing conventional chemotherapy and high-dose therapy.

Methods Two hundred previously untreated patients under the age of 65 years who had myeloma were randomly assigned at the time of diagnosis to receive either conventional chemotherapy or high-dose therapy and autologous bone marrow transplantation.

Results The response rate among the patients who received high-dose therapy was 81 percent (including complete responses in 22 percent and very good partial responses in 16 percent), whereas it was 57 percent (complete responses in 5 percent and very good partial responses in 9 percent) in the group treated with conventional chemotherapy ($P<0.001$). The probability of event-free survival for five years was 28 percent in the high-dose group and 10 percent in the conventional-dose group ($P=0.01$); the overall estimated rate of survival for five years was 52 percent in the high-dose group and 12 percent in the conventional-dose group ($P=0.03$). Treat-

Conclusions High-dose therapy combined with transplantation improves the response rate, event-free survival, and overall survival in patients with myeloma. (N Engl J Med 1996;335:91-7.)

Table 2. Response Rates According to Treatment Group.*

Type of Response	Conventional Dose (N = 100)	High Dose (N = 100)
	no. of patients	
Complete	5	22
Very good partial	9	16
Partial	43	43
Minimal	18	7
Progressive disease	25	12

*$P<0.001$ for the comparison of the various response categories between the two groups by the chi-square test. Seventy-four patients in the high-dose group underwent autologous bone marrow transplantation.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Chemotherapy with Hematopoietic Stem-Cell Rescue for Multiple Myeloma

J. Anthony Child, M.D., Gareth J. Morgan, Ph.D., Faith E. Davies, M.D., Roger G. Owen, M.D., Susan E. Bell, D.Phil., Kim Hawkins, M.Sc., Julia Brown, M.Sc., Mark T. Drayson, Ph.D., and Peter J. Selby, M.D., for the Medical Research Council Adult Leukaemia Working Party*

Table 2. Maximal Response to Treatment.*

Variable	Standard Therapy (N=200)	Intensive Therapy (N=201)	P Value†
	no. of patients (%)		
Complete response	17 (8)	89 (44)	<0.001

group than in the standard-therapy group. As compared with standard therapy, intensive treatment increased median survival by almost 1 year (54.1 months [95 percent confidence interval, 44.9 to 65.2] vs. 42.3 months [95 percent confidence interval, 33.1

ASCT in MM-Proof of concept

- High chances of getting CR
- Achievement of CR leads to progression free survival

What is the impact of novel agents for achievement of CR in newly diagnosed MM patients?

CR rates with newer drugs

Treatment Regimen	CR rates
Melphalan/Pred	3%
VAD	11-16%
Thal/Dexa	8%
Melphalan/Pred/Thal	16%
Melphalan/Pred/Len	24%
Len/Dexa	18%
Bortezomib based regimens	13-36%
Autologous stem cell Transplant	22-44%

JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Individualizing Treatment of Patients With Myeloma in the Era of Novel Agents

Jesús San-Miguel, Jean-Luc Harousseau, Douglas Joshua, and Kenneth C. Anderson

VOLUME 26 · NUMBER 16 · JUNE 1 2008

Table 2. Changes in Response Rate Before and After ASCT in Patients Treated With Novel Agents as Induction Therapy

Regimen	CR and nCR (%)	
	Pre-ASCT	Post-ASCT
Bortezomib and Dex[7]	21	41
Bortezomib and Dex[10]	21	33
Bortezomib and Dex (alt)[9]	13	40
Bortezomib, doxorubicin, and Dex[13]	32	54
PAD[12]	16	54
Bortezomib, Thal, and Dex[14]	19	31
Bortezomib, Thal, and Dex[8]	36	57
TAD[5*]	4	16

Abbreviations: ASCT, autologous stem-cell transplant; CR, complete response; nCR, near CR; Dex, dexamethasone; alt, alternate; Thal, thalidomide; PAD, bortezomib, doxorubicin, dexamethasone; TAD, thalidomide, doxorubicin, and dexamethasone.

*CR + very good partial response for pre-ASCT = 32%; for post-ASCT = 49%.

ASBMT
American Society for Blood and Marrow Transplantation

Complete Remission Status before Autologous Stem Cell Transplantation Is an Important Prognostic Factor in Patients with Multiple Myeloma Undergoing Upfront Single Autologous Transplantation

Jin Seok Kim,[1] Kihyun Kim,[2] June-Won Cheong,[1] Yoo Hong Min,[1] Cheolwon Suh,[3] Hawk Kim,[4] Deog Yeon Jo,[5] Hun Mo Ryoo,[6] Sung Soo Yoon,[7] Jae Hoon Lee[8]* and the Korean Multiple Myeloma Working Party*

95% confidence interval = 1.25 to 6.37). We conclude that patients with MM who are in CR before ASCT have a better OS than those in PR before ASCT. Continued CR after ASCT may be an important prognostic factor as well. Our findings suggest that the development of more effective induction regimens, including novel antimyeloma agents to improve initial response, should be pursued to enhance clinical benefits post-ASCT.

Biol Blood Marrow Transplant 15: 463-470 (2009)

www.thelancet.com Vol 376 December 18/25, 2010

Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study

Michele Cavo, Paola Tacchetti, Francesca Patriarca, Maria Teresa Petrucci, Lucia Pantani, Monica Galli, Francesco Di Raimondo, Claudia Crippa,

Background Thalidomide plus dexamethasone (TD) is a standard induction therapy for myeloma. We aimed to assess the efficacy and safety of addition of bortezomib to TD (VTD) versus TD alone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma.

Interpretation VTD induction therapy before double autologous stem-cell transplantation significantly improves rate of complete or near complete response, and represents a new standard of care for patients with multiple myeloma who are eligible for transplant.

	VTD (n=236)	TD (n=238)	p value
After induction therapy			
Complete response	44 (19%, 13·7–23·6)	11 (5%, 2·0–7·3)	<0·0001
Complete or near complete response*†	73 (31%, 25·0–36·8)	27 (11%, 7·3–15·4)	<0·0001
After first autologous stem-cell transplantation			
Complete response	89 (38%, 31·5–43·9)	54 (23%, 17·4–28·0)	0·0004
Complete or near complete response*	123 (52%, 45·7–58·5)	74 (31%, 25·2–37·0)	<0·0001
After second autologous stem-cell transplantation			
Complete response	98 (42%, 35·2–47·8)	72 (30%, 24·4–36·1)	0·0105
Complete or near complete response*	130 (55%, 48·7–61·4)	98 (41%, 34·9–47·4)	0·0024
After consolidation therapy			
Complete response	116 (49%, 42·8–55·5)	82 (34%, 28·4–40·5)	0·0012
Complete or near complete response*	147 (62%, 56·1–68·5)	108 (45%, 39·1–51·7)	0·0002
Best response to overall treatment protocol			
Complete response	136 (58%, 51·3–63·9)	97 (41%, 34·5–47·0)	0·0001
Complete or near complete response	168 (71%, 65·4–77·0)	128 (54%, 47·4–60·1)	<0·0001

Oral Session

Clinical Results - Autologous Transplantation: Multiple Myeloma

Outcome with Lenalidomide Plus Dexamethasone Followed by Early Autologous Stem Cell Transplantation In the ECOG E4A03 Randomized Clinical Trial

David Samuel diCapua Siegel, MD, PhD[1], Susanna Jacobus, MS[*,2], S. Vincent Rajkumar, MD[*,3], Rafat Abonour, MD[*,4], Natalie Scott Callander, MD[5], Michael S Katz, BS., MBA[*,6], Rafael Fonseca[7], David H. Vesole, MD, PhD[8] and On behalf of the Eastern Cooperative Oncology Group[*,9]

[1] John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA,
[2] Biostatsitcs, Eastern Cooperative Oncology Group, Boston,
[3] Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA,
[4] Indiana University School of Medicine, Indianapolis, IN, USA,
[5] Dept. of Hematology, University of Wisconsin, Madison, WI, USA,
[6] International Myeloma Foundation, North Hollywood, CA, USA,
[7] Hematological Malignancies, Mayo Clinic, Scottsdale, AZ, USA

vs lenalidomide with low-dose dexamethasone (Ld) (Rajkumar et al Lancet Oncol 2010; 11: 29–37). Upon completing four cycles of therapy, pts had the option of ASCT or continuing on the assigned therapy. The purpose of this abstract is to determine the outcome of patients on this trial pursuing early ASCT according to

RESULTS: In all three age-groups studied, 1, 2, and 3-year survival probability estimates with ASCT were excellent (Tables 1, 2, and 3). For patients under the age of 65 who survived the first 4 cycles of therapy, overall survival at 3-years was 94% with early ASCT, 78% in pts continuing protocol therapy. Although

CONCLUSIONS: This analysis shows that the strategy of lenalidomide plus dexamethasone induction followed by early ASCT has a remarkably good outcome in terms of overall survival in all age groups studied and supports the continued role of early consolidative ASCT in newly diagnosed patients. The risk of early mortality was notably low in the first year in all age groups. The risk of early mortality seems to increase at 2 years for the LD pts not choosing early ASCT and at 3 years for the Ld pts not choosing early

blood

2012 120: 1589-1596
Prepublished online July 12, 2012;
doi:10.1182/blood-2012-02-408922

Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study

Laura Rosiñol, Albert Oriol, Ana Isabel Teruel, Dolores Hernández, Javier López-Jiménez, Javier de la Rubia, Miquel Granell, Joan Besalduch, Luis Palomera, Yolanda González, Mª Asunción Etxebeste, Joaquín Díaz-Mediavilla, Miguel T. Hernández, Felipe de Arriba, Norma C. Gutiérrez, Mª Luisa Martín-Ramos, Mª Teresa Cibeira, Mª Victoria Mateos, Joaquín Martínez, Adrián Alegre, Juan José Lahuerta, Jesús San Miguel and Joan Bladé

cated to VTD (130), TD (127), or VBMCP/VBAD/B (129). The CR rate was significantly higher with VTD than with TD (35% vs 14%, $P = .001$) or with VBMCP/VBAD/B (35% vs 21%, $P = .01$). The median progression-free survival (PFS) was significantly longer with VTD (56.2 vs 28.2 vs 35.5 months, $P = .01$). In an intention-to-treat analysis, the post-ASCT CR rate was higher with VTD than with TD (46% vs 24%, $P = .004$) or with VBMCP/VBAD/B (46% vs 38%, $P = .1$). Patients with high-risk cytogenetics had a shorter

Induction with novel agents are complementary rather than alternative treatment approaches

Early Transplant

- Definition
- Patient population
- Concept of CR
- Different levels of CR
- Problems with late transplant
- International guidelines

blood

2009 114: 3139-3146
Prepublished online Jul 28, 2009;
doi:10.1182/blood-2009-03-201053

The role of complete response in multiple myeloma

Jean-Luc Harousseau, Michel Attal and Herve Avet-Loiseau

In multiple myeloma (MM), the impact of complete response (CR) could be shown only after introduction of high-dose therapy plus autologous stem cell transplantation (ASCT). In the context of ASCT, achieving CR (negative immunofixation and normal bone marrow) or at least very good partial response is associated with longer progression-free survival and in most studies longer survival. With novel agents, high CR rates are achieved and

this prognos
shown as w
newly diagn
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type of treat
all patients.
ments induc
toxic. Althou
sary in patie
might not be
more indolen

ing treatment after CR achievement. Finally, there are several levels of CR and in the future it will be necessary to confirm the prognostic impact of immunophenotypic or molecular CR or of CR defined by imaging procedures. (Blood. 2009;114: 3139-3146)

Sustained CR

Complete Remission Sustained 3 Years From Treatment Initiation Is a Powerful Surrogate for Extended Survival in Multiple Myeloma

Bart Barlogie, MD[1]
Elias Anaissie, MD[1]
Jeffrey Haessler, MS[2]
Fritz van Rhee, MD[1]
Mauricio Pineda-Roman, MD[1]
Klaus Hollmig, MD[1]
Yazan Alsayed, MD[1]
Joshua Epstein, DSc[1]
John D. Shaughnessy Jr, PhD[1]
John Crowley, PhD[1]

CONCLUSIONS. In all 3 trial settings the survival benefit of SUS-CR was independent of metaphase abnormalities as a dominant adverse parameter. Given its bleak prognosis despite high CR rates, SUS-CR should be evaluated as a primary trial endpoint in high-risk myeloma. ***Cancer* 2008;113:355–9.**

ORIGINAL ARTICLE

CR represents an early index of potential long survival in multiple myeloma

M Wang, K Delasalle, L Feng, S Thomas, S Giralt, M Qazilbash, B Handy, JJ Lee and R Alexanian

University of Texas, M.D. Anderson Cancer Center, Houston, TX, USA

To assess the impact of CR on survival in multiple myeloma. Retrospective evaluation of response and survival among 758 myeloma treated at a received intensive the cells within the first y after 1 and 2 years f the basis of the respo the subsequent media with CR, 4.4 years f patients with NR (attributed in part to i myeloma of 67% of p induced CR in 26% of did not prolong sur primary therapy. Fo Cox regression ana dominant prognostic f stage I disease, PR and intensive treatment as independent factors. A cure fraction of 2% was identified for nine patients who have remained in CR >10 years.

Bone Marrow Transplantation advance online publication, 27 July 2009; doi:10.1038/bmt.2009.176

cells within the first year. Survival times were calculated after 1 and 2 years from the start of chemotherapy. On the basis of the response status after a 2-year landmark, the subsequent median survival was 9.7 years for patients with CR, 4.4 years for those with PR and 2.7 years for patients with NR ($P<0.001$). Longer survival was attributed in part to intensive therapy that converted the myeloma of 67% of patients with NR to PR or CR, and induced CR in 26% of patients with PR. Intensive therapy

blood

2011 118: 529-534
Prepublished online April 11, 2011;
doi:10.1182/blood-2011-01-332320

Long-term prognostic significance of response in multiple myeloma after stem cell transplantation

Joaquin Martinez-Lopez, Joan Blade, María-Victoria Mateos, Carlos Grande, Adrián Alegre, José García-Laraña, Anna Sureda, Javier de la Rubia, Eulogio Conde, Rafael Martinez, Felipe de Arriba, Maria C. Viguria, Joan Besalduch, Rafael Cabrera, José D. Gonzalez-San Miguel, José Luis Guzman-Zamudio, Maria Carmen Gomez del Castillo, José Maria Moraleda, Juan C. García-Ruiz, Jesús San Miguel, Juan José Lahuerta and for the GEM (Grupo Español de MM) and PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatía Maligna) Cooperative Study Groups

For establishing the true effect of different response categories in patients with multiple myeloma (MM) treated with autologous stem cell transplantation, we evaluated, after a median follow-up of 153 months, 344 patients with MM who received a transplant between 1989 and 1998. Overall survival (OS) at 12 years was 35% in complete response (CR) patients, 22% in near complete response (nCR), 16% in very good partial response (VGPR), and 16% in partial response (PR)

35% patients in the CR group and 11% in the nCR+VGPR+PR group are alive at 17 years; 2 cases had relapsed in the nCR+VGPR+PR group. In conclusion, MM achieving CR after autologous stem cell transplantation is a central prognostic factor. The relapse rate is low in patients with > 11 years of follow-up, possibly signifying a cure for patients in CR. (*Blood*. 2011;118(3):529-534)

International uniform response criteria for multiple myeloma

Leukemia (2006) 20, 1467–1473

Response Subcategory	Response criteria
CR	Negative immunofixation on the serum and urine, Disappearance of any soft tissue plasmacytomas, <5% plasma cells in BM
sCR	Normal FLC ratio, absence of clonal plasma cells in BM by immunohistochemistry
VGPR	M component detected by IF but –ve on SPE or 90% or greater reduction in serum M protein + urine M protein <100mg/24 hours
PR	≥50% reduction of serum M protein and reduction in urine M protein >90% or <200mg/24 hours
MRD -ve	**Multiparameter flow cytometer remission**

blood

2008 112: 4017-4023
Prepublished online Jul 31, 2008;
doi:10.1182/blood-2008-05-159624

Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation

Minimal residual disease (MRD) assessment is standard in many hematologic malignancies but is considered investigational in multiple myeloma (MM). We report a prospective analysis of the prognostic importance of MRD detection by multiparameter flow cytometry (MFC) in 295 newly diagnosed MM patients uniformly treated in the GEM2000 protocol (VBMCP/VBAD induction plus autologous stem cell transplantation [ASCT]). MRD status by MFC was determined at day 100 after ASCT. Progression-free survival (PFS; median 71 vs 37 months, $P < .001$) and overall survival (OS; median not reached vs 89 months, $P = .002$) were longer in patients who were MRD negative versus MRD positive at day 100 after ASCT. Similar prognostic differentiation was seen in 147 patients who achieved immunofixation-negative complete response after ASCT. Moreover, MRD$^-$ immunofixation-negative (IFx$^-$) patients and MRD$^-$ IFx$^+$ patients had significantly longer PFS than MRD$^+$ IFx$^-$ patients. Multivariate analysis identified MRD status by MFC at day 100 after ASCT as the most important independent prognostic factor for PFS (HR = 3.64, $P = .002$) and OS (HR = 2.02, $P = .02$). Our findings demonstrate the clinical importance of MRD evaluation by MFC, and illustrate the need for further refinement of MM response criteria. This trial is registered at http://clinicaltrials.gov under identifier NCT00560053. (Blood. 2008;112:4017-4023)

VOLUME 29 · NUMBER 12 · APRIL 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Comparison of Immunofixation, Serum Free Light Chain, and Immunophenotyping for Response Evaluation and Prognostication in Multiple Myeloma

Bruno Paiva, Joaquin Martinez-Lopez, Maria-Belen Vidriales, Maria-Victoria Mateos, Maria-Angeles Montalban, Elena Fernandez-Redondo, Lourdes Alonso, Albert Oriol, Ana-Isabel Teruel, Raquel de Paz, José-Garcia Laraña, Enrique Bengoechea, Alejandro Martin, Joaquin Diaz Mediavilla, Luis Palomera, Felipe de Arriba, Joan Bladé, Alberto Orfao, Juan-Jose Lahuerta, and Jesus F. San Miguel

Purpose

To investigate the impact of immunophenotypic response (IR) versus complete response (CR) and CR plus normal serum free light chain (sFLC) ratio (stringent CR) in elderly patients with multiple myeloma (MM) treated with novel agents.

Conclusion

Achieving an IR translates into superior PFS and TTP compared with conventional CR or stringent CR. These techniques provide complementary information and thus, an effort should be made to refine response criteria in MM.

J Clin Oncol 29:1627-1633.

Early Transplant

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- International guidelines

Leukemia (2012) 26, 149–157

ORIGINAL ARTICLE

Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study

SK Kumar[1], JH Lee[2], JJ Lahuerta[3], G Morgan[4], PG Richardson[5], J Crowley[6], J Haessler[6], J Feather[5], A Hoering[6], P Moreau[7],

Promising new drugs are being evaluated for treatment of multiple myeloma (MM), but their impact should be measured against the expected outcome in patients failing current therapies. However, the natural history of relapsed disease in the current era remains unclear. We studied 286 patients with relapsed MM, who were refractory to bortezomib and were relapsed following, refractory to or ineligible to receive, an IMiD (immunomodulatory drug), had measurable disease, and ECOG PS of 0, 1 or 2. The date patients satisfied the entry criteria was defined as time zero (T_0). The median age at diagnosis was 58 years, and time from diagnosis to T_0 was 3.3 years. Following T_0, 213 (74%) patients had a treatment recorded with one or more regimens (median = 1; range 0–8). The first regimen contained bortezomib in 55 (26%) patients and an IMiD in 70 (33%). A minor response or better was seen to at least one therapy after T_0 in 94 patients (44%) including ⩾partial response in 69 (32%). The median overall survival and event-free survival from T_0 were 9 and 5 months, respectively. This study confirms the poor outcome, once patients become refractory to current treatments. The results provide context for interpreting ongoing trials of new drugs.

Leukemia (2012) **26**, 149–157; doi:10.1038/leu.2011.196; published online 29 July 2011

Minor clone provides a reservoir for relapse in multiple myeloma

F Magrangeas, H Avet-Loiseau, W Gouraud, L Lodé, O Decaux, P Godmer, L Garderet, L Voillat, T Facon, AM Stoppa, G Marit, C Hulin, P Casassus, M Tiab, E Voog, E Randriamalala, KC Anderson, P Moreau, NC Munshi and S Minvielle

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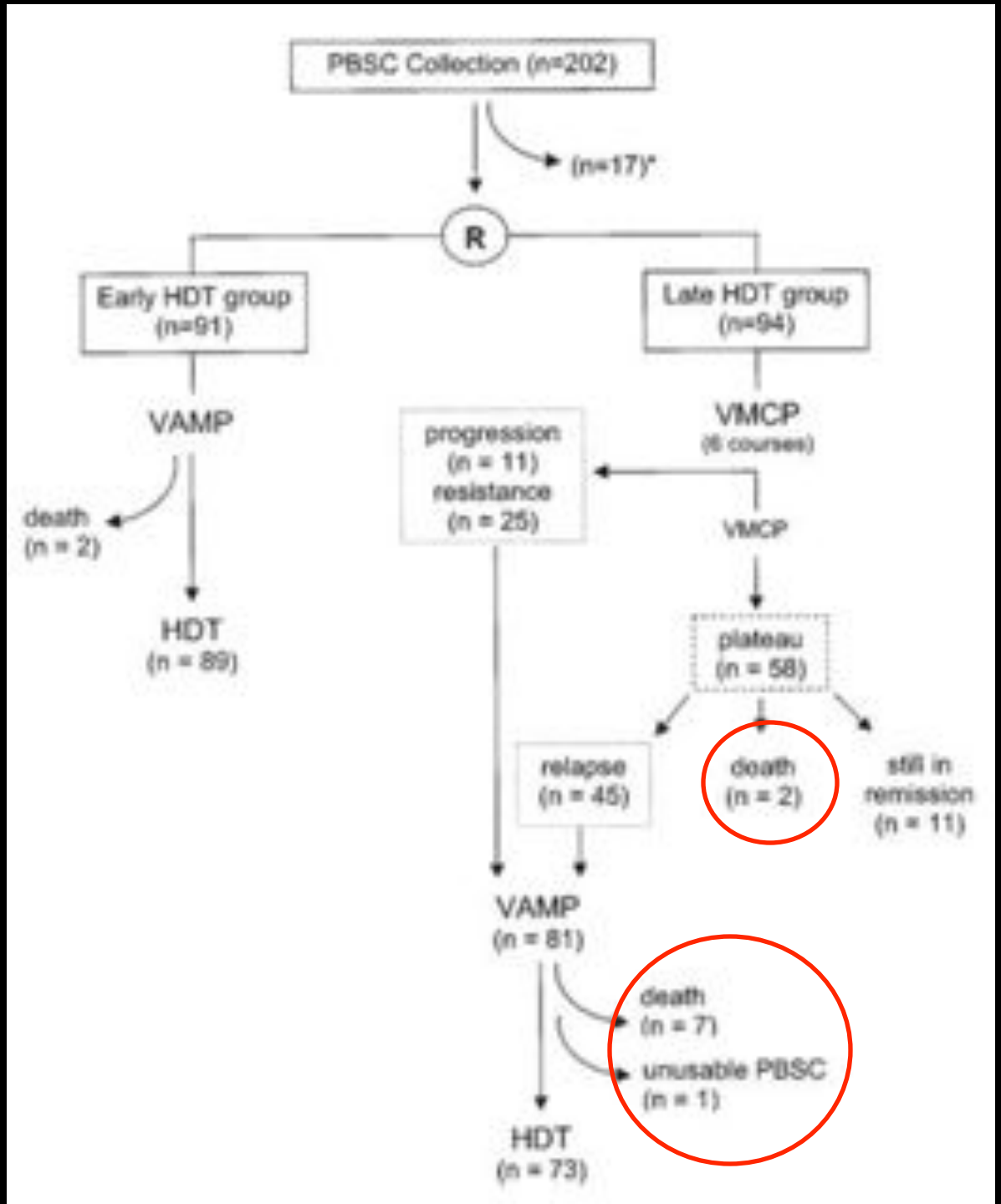
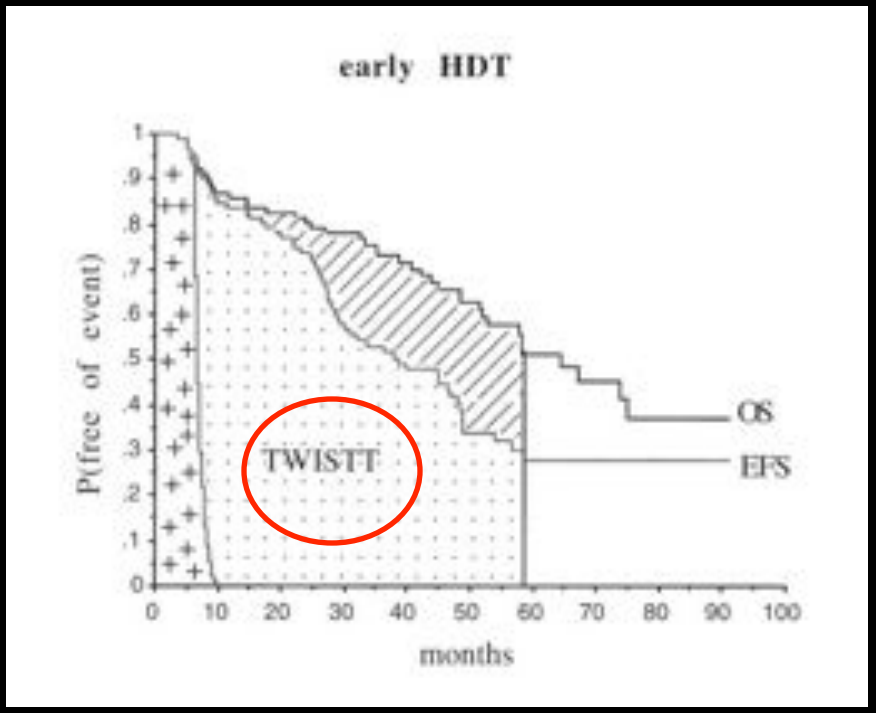
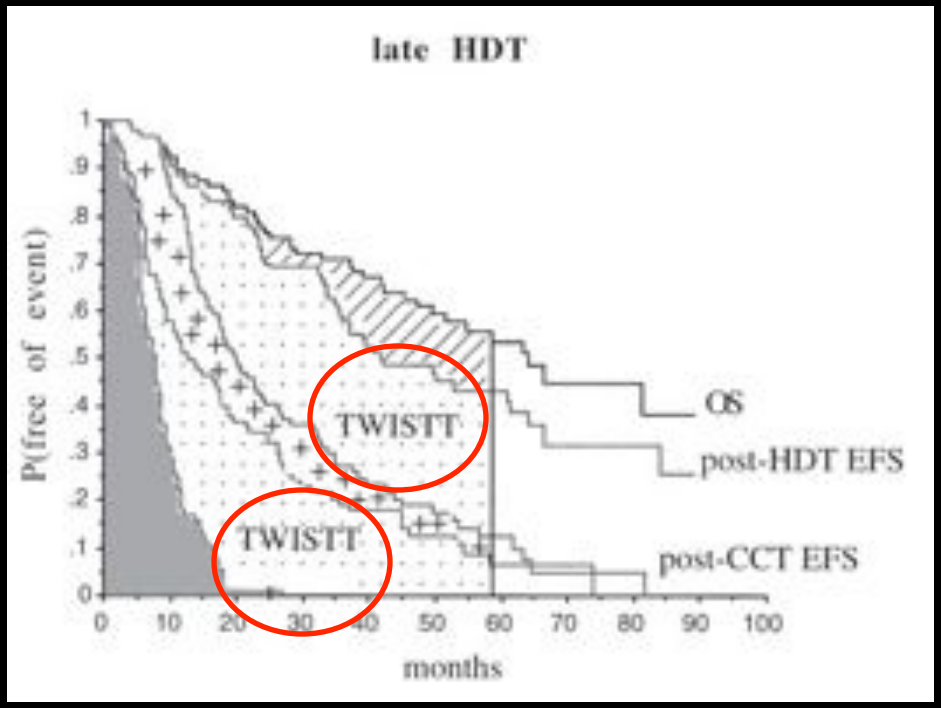
Blood, Vol 92, No 9 (November 1), 1998: pp 3131-3136

High-Dose Therapy and Autologous Peripheral Blood Stem Cell Transplantation in Multiple Myeloma: Up-front or Rescue Treatment? Results of a Multicenter Sequential Randomized Clinical Trial

By Jean-Paul Fermand, Philippe Ravaud, Sylvie Chevret, Marine Divine, Véronique Leblond, Coralie Belanger, Margaret Macro, Edouard Pertuiset, François Dreyfus, Xavier Mariette, Catherine Boccacio, and Jean-Claude Brouet for the Group "Myélome Autogreffe"*


PBSC Collection (n=202)
(n=17)*
R
Early HDT group
(n=91)
Late HDT group
(n=94)
VAMP
VMCP
(6 courses)
death
(n = 2)
HDT
(n = 89)
progression
(n = 11)
resistance
(n = 25)
VMCP
plateau
(n = 58)
relapse
(n = 45)
death
(n = 2)
still in
remission
(n = 11)
VAMP
(n = 81)
death
(n = 7)
unusable PBSC
(n = 1)
HDT
(n = 73)


early HDT
P(free of event)
months
TWISTT
OS
EFS


late HDT
P(free of event)
months
TWISTT
TWISTT
OS
post-HDT EFS
post-CCT EFS

Time without symptoms, treatment and treatment toxicity (TWiST)

two in the other. Thus, we also evaluated time without symptoms, treatment (ie, chemotherapy), and treatment toxicity, adapted from the TWiST recently used in breast cancer and in human immunodeficiency virus infection.[20,21] As shown in Fig 3, the distribution of the periods spent with or without chemotherapy was different between the two groups and the latter was longer in the early HDT group. This suggests a clinical benefit for early treatment but the repercussion on

In this multicenter study, PBSC transplantation alone (without any hematopoietic growth factor) supported a highly intensive treatment, and TRM during the first posttransplant year were 9% and 14% in the early and late groups, respec-

Bone Marrow Transplantation, (1999) 23, 221–226

Early harvest and late transplantation as an effective therapeutic strategy in multiple myeloma

MA Gertz[1], MQ Lacy[1], DJ Inwards[1], MG Chen[2], AA Pineda[3], DA Gastineau[1], PR Greipp[1], JA Lust[1], A Tefferi[1], TE Witzig[1], RA Kyle[1] and MR Litzow[1]

[1]*Division of Hematology and Internal Medicine,* [3]*Division of Transfusion Medicine, and* [2]*Division of Radiation Oncology, Mayo Clinic and Mayo Foundation, Rochester, MN, USA*

ease. Of the 118 patients, 67 had transplants, nine died of progressive disease before transplantation, and 42 remain alive in plateau phase. The median survival of

Chinese Medical Journal 2012;125(4):593-598

The more, the less: age and chemotherapy load are predictive of poor stem cell mobilization in patients with hematologic malignancies

YANG Shen-miao, CHEN Huan, CHEN Yu-hong, ZHU Hong-hu, ZHAO Ting and LIU Kai-yan

Conclusion Older age and a heavy load of previous chemotherapy are the negative risk factors for PBSC mobilization.

Guidelines for the diagnosis and management of multiple myeloma 2011

Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH) and UK Myeloma Forum

Jennifer M. Bird,[1] Roger G. Owen,[2] Shirley D'Sa,[3] John A. Snowden,[4] Guy Pratt,[5] John Ashcroft,[2] Kwee Yong,[3] Gordon Cook,[2]

Table VII. Comparison of side effects related to myeloma treatment with novel agents.

	Thalidomide	Bortezomib	Lenalidomide
Neutropenia	No	No	Yes
Thrombocytopenia	No	Yes	Yes
Neuropathy	Yes	Yes	No
Constipation	Yes	Low risk	Low risk
Diarrhoea	No	Yes	No
Somnolence	Yes	No	No
Fatigue	Yes	Yes	Yes
Thrombotic risk	Yes	No	Yes
Route of administration	Oral	Intravenous	Oral

Impairment of Filgrastim-Induced Stem Cell Mobilization after Prior Lenalidomide in Patients with Multiple Myeloma

Uday Popat,[1] Rima Saliba,[1] Rupinderjit Thandi,[1] Chitra Hosing,[1] Muzaffar Qazilbash,[1]

Biol Blood Marrow Transplant 15: 718-723 (2009) © 2009

received lenalidomide ($P < .001$). In a multivariate analysis, prior lenalidomide use (odds ratio: 5.9; 95% confidence interval [CI]: 2.4-14.3) and mobilization more than 1 year after diagnosis (odds ratio: 4.6; 95% CI: 1.9-11.1) were significantly associated with failed mobilization. Twenty-one of 26 patients in whom mobilization

Myocarditis During Lenalidomide Therapy

Joseph R Carver, Sunita Nasta, Elise A Chong, Mark Stonecypher, James E Wheeler,

1840 ■ *The Annals of Pharmacotherapy* ■ *2010 November, Volume 44*

Non-thromboembolic pulmonary hypertension in multiple myeloma, after thalidomide treatment: A pilot study

C. Lafaras[1*], E. Mandala[2], E. Verrou[3], D. Platogiannis[1], N. Barbetakis[1], T. Bischiniotis[1] & K. Zervas[3]

Annals of Oncology 19: 1765–1769, 2008
doi:10.1093/annonc/mdn287
Published online 13 May 2008

Cardiovasc Toxicol (2012) 12:184–187

Bortezomib-Induced Congestive Cardiac Failure in a Patient with Multiple Myeloma

Ajay Gupta · Anvita Pandey · Sumit Sethi

Int J Hematol (2008) 88:219–222

Acute severe cardiac failure in a myeloma patient due to proteasome inhibitor bortezomib

Abdullah Hacihanefioglu · Pinar Tarkun · Emel Gonullu

Int J Hematol (2010) 91:903–906

Ischemic heart disease associated with bortezomib treatment combined with dexamethasone in a patient with multiple myeloma

Hiroyuki Takamatsu · Takeshi Yamashita · Takeharu Kotani · Aiko Sawazaki · Hirokazu Okumura · Shinji Nakao

toris on day 5 after the therapy. Bortezomib's antitumor effect is due to the inhibition of proteasome activity. This inhibition may increase endothelial progenitor cell apoptosis and decrease endothelial nitric oxide synthase/nitric oxide (eNOS/NO), thus leading to coronary spasm. It is,

EDITORIAL

Too much of a good thing is bad: proteasome inhibition induces stressed hearts to fail

Lucie Carrier[1,2,3]*

EUROPEAN SOCIETY OF CARDIOLOGY®

Cardiovascular Research (2010) **88**, 389–390
doi:10.1093/cvr/cvq315

This editorial refers to 'Proteasome functional insufficiency activates the calcineurin–NFAT pathway in cardiomyocytes and promotes maladaptive remodelling of stressed mouse hearts' by M. Tang et *al.*, pp. 424–433, this issue.

Early Transplant

- Definition
- Patient population
- Concept of CR
- Different levels of CR
- Problems with late transplant
- International guidelines

bjh guideline British Journal of Haematology, 154, 32–75

Guidelines for the diagnosis and management of multiple myeloma 2011

Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH) and UK Myeloma Forum

Jennifer M. Bird,[1] Roger G. Owen,[2] Shirley D'Sa,[3] John A. Snowden,[4] Guy Pratt,[5] John Ashcroft,[2] Kwee Yong,[3] Gordon Cook,[2]

9.3 Timing of ASCT

The encouraging results reported with novel agents have challenged the role of ASCT as part of upfront therapy. Several groups have reported early results of prospective studies evaluating the use of ASCT at the time of disease progression after initial induction and consolidation using novel agent combinations. It is, however, likely that ASCT will further increase the rate and depth of responses achieved with induction therapy with a consequent improvement in PFS. There is therefore currently no evidence to support deferral of the first ASCT until the time of first relapse, though prospective studies are underway to explore this possibility further.

blood

2011 117: 6063-6073
Prepublished online March 29, 2011;
doi:10.1182/blood-2011-02-297325

International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation

Michele Cavo, S. Vincent Rajkumar, Antonio Palumbo, Philippe Moreau, Robert Orlowski, Joan

Up-front use of these induction treatments, in particular 3-drug combinations, has affected unprecedented rates of complete response that rival those previously seen with conventional chemotherapy and subsequent ASCT. Autotransplantation applied after novel-agent-based induction regimens provides further improvement in the depth of response, a gain that translates into extended progression-free survival and, potentially, overall survival.

blood

2011 117: 6063-6073
Prepublished online March 29, 2011;
doi:10.1182/blood-2011-02-297325

International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation

Michele Cavo, S. Vincent Rajkumar, Antonio Palumbo, Philippe Moreau, Robert Orlowski, Joan

The usual choice of giving 3 to 6 cycles of induction therapy to maximize the depth of response before early ASCT represents a reasonable balance between maximum benefit and minimum

patients treated with lenalidomide-based regimens, peripheral blood stem cells should be collected early, after 4 to 6 cycles of induction therapy. The best timing of ASCT in the novel agent era represents an area of active debate and major interest. Unless final results of ongoing clinical trials comparing early versus late ASCT plus novel agents will be available, ASCT up-front should continue to be considered the preferred approach for a patient who is eligible to tolerate HDT. More recently, the treatment paradigm for

Conclusions

Motto

- Citius
- Altius
- Fortius

- Faster
- Higher
- Stronger

Early Transplant just follows the Olympic motto