Salvage Autologous Stem Cell Transplantation (ASCT) in Multiple Myeloma

Arnon Nagler, M.D., M.Sc
Director Hematology Division
BMT and Cord Blood Bank
Chair Israeli BMT Association
Chaim Sheba Medical Center, Tel-Hashomer, Israel

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Natural History of MM

MGUS or smoldering myeloma

MGUS, monoclonal gammopathy of undetermined significance
Role of Salvage Autologous Transplant in Multiple Myeloma

- Salvage ACST defined as second autologous transplant, due to disease progression in a patient who underwent prior ASCT
- The main role of salvage ASCT in patient that relapsed post previous ASCT is to control the disease for a long time and maintain the patient’s quality of life

Second ASCT in Patients with Relapsed Multiple Myeloma

- For patients who relapsed after initial ASCT no broadly accepted salvage strategy has been established and various therapeutic options have been applied extending from conventional chemotherapy and novel agents to second ASCT and alloSCT
- As per CIBMTR data: 9% of relapsing MM receive second ASCT with constant increase from 2001, improvement results from 2004 and currently with >300 pts./year
- Similar data are coming from EBMT (15.8% of relapsing patients receive 2nd ASCT)
- However, no randomized control trial has compared 2nd ASCT to novel agents as salvage therapy for relapsing MM patients
Second salvage ASCT is used in only in minority of MM patients relapsing after 1st ASCT.
Data of retrospective studies with >40 patients with relapsed MM after an initial ASCT and their outcomes after a second auto-graft.
Role of Salvage ASCT in Multiple Myeloma

Outcome

- Data from 15 studies revealed ORR of 55.3-97.5%
- PFS after second ASCT ranged between 8.5-40 months
- TRM and transplant related toxicity are similar to those observed at first ASCT with TRM of 0-7.3%
- Data on long term toxicity is limited; incident of SPM is about 5% (2.1-8.2%)*

Patient presentation

- 62 old year male – IgA kappa Multiple Myeloma
- Anemia, lytic lesions
- Bone marrow – 70% monoclonal plasma cells

Treatment:
- 4 cycles of VCD => VGPR
- ASCT (MEL200) => nCR
- Maintenance – Vd – 14 cycles (2 years from diagnosis)
Patient Medical History

- Stable nCR – 2.5 years
- Relapse after 3 year of F/U, 4 years from 1\textsuperscript{st} ASCT
  - Anemia
  - New lytic lesions
  - Rapidly elevation of Kappa light chain

Recurrent Treatment

Salvage → Re induction

- Novel agents +/- chemotherapy
- Second ASCT
- Allo transplant
Factors affecting treatment decisions in relapsed Multiple Myeloma

Patient related factors:
- age, co-morbidities, blood count, PN

Disease related factors:
- HR/ SR disease (cytogenetic, extramedullary disease)

Salvage therapy

First line therapy with ASCT

Response to first therapy

Second line therapy +/- ASCT
mSMART Guidelines for RR MM (2016)

First relapse: off-study

On maintenance

- **Fit patients**
  - KPd or CyBorD if Rev maintenance*
  - KRd or KPd if Vel maintenance*

- **Indolent relapse or Frail patients**
  - ICd if Rev maintenance*
  - RID or Rd-Elo if Vel maintenance*

Off-therapy / unmaintained

- **Fit patients**
  - KRd*

- **Indolent relapse or Frail patients**
  - RID or Rd-Elo*

Second or later relapse† (not PCL or EMD): off-study

- **Dual-refractory (Bortezomib and Lenalidomide)§**
  - Pom-Dex plus daratumumab

- **Triple-refractory (Bortezomib, Len and Carfilzomib)§**

- **Triple-refractory (Bortezomib, Len, and Pomalidomide)§**
  - Dara-based regimen; or alkylator-based regimen if alkylator naïve; or proteasome inhibitor plus panobinostat

- **Quadruple-refractory (Len, Pomalidomide, Bortezomib, and Carfilzomib)**
  - VDT-PACE x 2 cycles if possible;
  - Auto transplant if candidate;
  - if not, treat with regimens patient is not known to be refractory to

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*Consider salvage auto SCT in patients eligible for ASCT who have not had transplant before; Consider 2nd auto SCT if eligible and >18 months unmaintained or >36 months maintained response to first auto; †If single refractory, refer to First Relapse algorithm; §Auto transplant is an option, if transplant candidate and feasible; ‡CVAD or similar regimen can be used in place of VDT-PACE in older patients or patients with poor functional status

https://nebula.wsimg.com/6c6ce81602349729f49f567b4d6e761a?AccessKeyId=A0994494BBBCBE4A0363&disposition=0&alloworigin=1; Accessed June 2016
Treatment Decision in Relapse MM post ASCT: Factors to be Considered

- Relapse characteristic: number, aggressiveness
- Prior therapy regimen (no. of treatment lines > or < 5)\(^1\)
- Response to prior therapy: depth- PR, VGPR, CR
  duration- <12mos., 18mos., >36mos.
- Side effects & toxicities in prior therapy
- Patient age and co-morbidities (>55, 60, 65y?)\(^2,3,4\)
- Second ASCT have to be considered in fitting patients
- Patient preference
- Re-induction with at least three drugs

\(^1\)Olin RL. et al BMT 2009; 43:417-422
\(^3\)Cook G et al. BBMT 2011;17:1638-1645
\(^4\)Lemieux E et al. BBMT 2013;19:445-449
The patient was treated with 4 cycles of KRD => VGPR

- Salvage
- KRD – 4 cycles
- VGPR
- KRD maintenance
- Second ASCT
- Allogenic transplant
Role of Salvage Autologous Transplant in Multiple Myeloma

The main questions/ uncertainties

- Who are the patients that are likely to benefit the most from second ASCT
- What is the optimal timing for the second ASCT
- Whether salvage ASCT as a third line treatment or later would confer the same degree of advantage as seen with salvage ASCT at first relapse
- How safe is second ASCT regarding late toxicity and especially SPM
- Are there known predictors for second ASCT outcome
Role of Salvage Autologous Transplant in Multiple Myeloma

The main questions/ uncertainties

- Is second ASCT still beneficial in the era of the new novel agents, monoclonal Ab and cellular therapies
- What will be the effect of cytogenetic and molecular risk stratification at relapse on the role of second salvage ASCT
- What is the role of consolidation and maintenance post second ASCT
- What is the optimal maintenance therapy after second ASCT
- No randomized controlled trial explored the role of second salvage ASCT in the era of novel therapies
Role of Salvage ASCT in relapse Multiple Myeloma

Scandinavian study compared between various treatment strategies in MM patients that relapsed post ASCT

- Second ASCT: n = 111
- Re-treated with conventional chemotherapy: n = 91
- Treatment with novel agents (PI’s and/or IMiD’s): 362
- Overall Survival: second ASCT – 4y
  - Novel agents – 3.3y
  - Chemotherapy retreatment – 2.5y
- Second ASCT also resulted in a significantly longer second TTP and a significantly longer time to next treatment

Grovdal M. et al BMT 2015;50:808-812
Second salvage ASCT is associated with significantly longer TTNT2 and OS2 compare to novel drug therapy.

Figure 2. Time to next treatment and OS according to the type of second-line treatment. (a) TTNT2, (b) OS1 and (c) OS2.

Grovdal M. et al BMT 2015; 50: 808-812
Phase 3 prospective study: ASCT at relapse

BSBMT/UKMF Myeloma X – Final results

- The first prospective randomized Phase III trial
- Pts (n=174), median age 61, in relapse following 1 prior ASCT at least 12 months previously
- The primary endpoint was time to progression (TTP)

**Induction**

PAD x 4 cycles
(bortezomib, doxorubicin, dexamethasone)
n=174

**Randomization**

MEL200-ASCT
n=89

Cyclophosphamide
400 mg/m2 /W x 12W
n=85

Cook G et al. Lancet Oncol 2014
Phase 3 prospective study: ASCT at relapse
BSBMT/UKMF Myeloma X – Final results

• Results (median follow-up 12 months)
  – Response to PAD induction
  • 79.2% ORR: 16.5% sCR/CR, 20.9% VGPR

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<td>Median TTP</td>
<td>19 months</td>
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<td>&lt; 0.0001</td>
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<td>3-year OS</td>
<td>80.3%</td>
<td>62.9%</td>
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• OS was also superior in the salvage ASCT arm - 67 vs. 52 months; (p=0.0169)

• **Conclusion:**
  First prospective study to demonstrate superior duration of response for salvage ASCT

*Cook G et al. Lancet Oncol 2014*
Durability of response (ITT)
Myeloma X – Final results

- PD detected in 64% of ASCT patients & 80% in C-weekly.
- Median TTP (ITT) for ASCT is 19 mos (95% ci 16, 25) vs 11mos (95% ci 9, 12) for C-weekly (HR 0.36 (95% ci 0.25, 0.53); p<0.0001)

Cook G et al, Lancet Oncology, 2014
TTP & Durability of ASCT1

Myeloma X – Final results

ASCT1 TTP >24mns

ASCT1 TTP ≤24mns

Cook G et al, Lancet Oncology, 2014
Independent Prognostic Factors

Myeloma X – Final results

- **Response at e**
  - sCR or CR (n=54)
  - VGPR or PR (n=84)
  - SD (n=6)

- **β₂ microglobulin at registration**
  - <3.5 mg/L (n=112)
  - <3.5 mg/L (n=47)

- **iFISH cytogenetic risk**
  - Unfavourable vs favourable (n=75)
  - Adverse (n=13)

- **Overall (n=174)**

**P-value**

- **0.071**
- **0.002**

Cook et al, Lancet Oncology, 2014
Role of Salvage ASCT in Multiple Myeloma

BSBMT/UKMF Myeloma X study

Concluded (con...)

- TRM, frequency and grading of toxicities (mainly hematologic) are similar between the first and the second ASCT
- Limited data on second primary malignancies (SPM) incidence, especially treatment-related myelodysplasia
- During extended follow-up, 15 patients developed SPM (7 in the ASCT group and 5 in the cyclophosphamide group)
- 5 years after trial entry, the cumulative incidence of SPM was 5.2%

Cook G et al. Lancet Oncol 2014
Final Results of BSBMT/UKMF Myeloma X study

- n – 297 (174 randomized – second ASCT-89; p.o. Cy – 85)
- 51 UK centers
- 174 relapse >24mos from first ASCT
- 43% (n-75) died during F/U
  - Second ASCT 35% (n-31)
  - p.o. Cy 52% (n-44)
- Time to disease progression: 19mos vs. 11mos.; HR – 0.45 (p<0.0001)
- Median OS: 67mos. vs. 62mos.; HR-0.56; (p=0.022)
- Time to second objective disease progression: 67mos. vs. 35mos.; HR – 0.37; (p<0.0001)
- 15 SPMs in 12 pts. (second ASCT-7; p.o. Cy – 5)
  at 60mos 5.2%
Salvage ASCT as third or fourth line therapy is not effective as for PFS

The effect of first relapse management on PFS2
(A) By randomized treatment. (B) By randomized treatment with the weekly Cy group separated by pts who later received salvage ASCT after subsequent disease progression as part of third-line or fourth-line treatment (weekly Cy and salvage ASCT) and not (weekly Cy).
(C) Forest plot of subgroup analysis done for PFS2 using Cox proportional hazards regression. p(het) refers to likelihood ratio test assessing heterogeneity of treatment effect between subgroups. PFS2=time to second progression or death from any cause.
The effect of first relapse management on overall survival

A) By randomized treatment.
(B) By randomized treatment with the weekly Cy group separated by patients who later received salvage ASCT after subsequent disease progression as part of third-line or fourth-line treatment (weekly Cy and salvage ASCT) and not (weekly Cy).
(C) Forest plot of subgroup analysis done for overall survival using Cox proportional hazards regression.

Conclusion:
The delay of salvage ASCT to third line treatment or later might not confer the same degree of advantage as seen in salvage ASCT in 1st relapse.
Survival Benefit for Salvage ASCT for Relapse MM: The Japanese Experience
Muta T. Acta Hematol. 139:35-44, 2018

- n = 446; 70 – second salvage ASCT
- Second ASCT reduced the risk of mortality after relapse p=0.041
- The patients that benefit the most were patients with stage I or II MM (p=0.040), good PS (p=0.043) and no/mild renal co-morbidity (p=0.029)
- The benefit is for those that relapse >24mos post 1st ASCT
- Patients with early relapse, poor PS, moderate/severe renal co-morbidity and progressive disease did not benefit (p<0.001)
OS according to time from 1st ASCT (<7mos; 7-36mos; >36mos) and year of transplant (<or>2009)

Fig. 1. OS from the time of relapse following up-front ASCT. a The entire patient cohort was included with 95% CIs (30.3–41.5; dotted lines (n = 446, median OS 36.9 months, 95% CI 30.3–41.5). b Comparison among patients who relapsed within 7 months after initial ASCT (red; n = 94, median OS 14.9 months), those who relapsed between 7 and 36 months (black; n = 296, median OS 42.4 months), and those who relapsed after 36 months (green; n = 56, median OS 61.2 months). c Comparison between those who relapsed before 2009 (red; n = 149, median OS 25.3 months) and those who relapsed during or after 2009 (black; n = 297, median OS 44.2 months).
OS from the time of salvage ASCT. a Comparison among patients who relapsed within 12 months after initial ASCT (red; n = 23, median OS 28.1 months), those who relapsed between 12 and 24 months (black; n = 25, median OS 36.2 months), and those who relapsed after 24 months (green; n = 22, median OS 83.7 months). b The unfavorable prognostic factors for OS after salvage ASCT consisted of an ECOG-PS of 2, 3, or 4 before salvage ASCT, a moderate or severe renal comorbidity before salvage ASCT, time to relapse within 7 months after the initial ASCT, and PD before salvage ASCT. No unfavorable factors: black (n = 48, median OS 83.7 months); ≥1 unfavorable factors: red (n = 22, median OS 15.5 months).
Outcome of a Salvage Third ASCT in MM

- 2\textsuperscript{nd} and 3\textsuperscript{rd} ASCT for relapse; n = 88; median PFS 8mos; median OS 15mos
- Prognostic factors: chemo-sensitivity and Karnofsky >70
- SPMs – 7%
- A salvage 3\textsuperscript{rd} ASCT is of value for relapse MM in pts. with long duration of response to second ASCT and chemo-sensitive disease

Garderet L. et al. BBMT 2018
OS post 3rd salvage ASCT correlates with relapse free interval post 2nd ASCT

- Median OS after 3rd ASCT – 7mos if RFI <6mos; 13 mos if RFI 6-18mos and 27 mos if RFI >18mos (p<0.001)
Role of Salvage ASCT in Multiple Myeloma

**Prediction factors for success of salvage ASCT**

- According to the available data, a second ASCT should be considered in patients in whom remission duration after first ASCT has been at least 1.5 years.
- The greatest benefit is obtained in patients relapsing beyond 3 years from the first ASCT.
- Pts. with relapse <12mos. post 1st ASCT should MP not referred to second ASCT.
- Depth of response.
- Patient age.
- Number of prior treatment lines.
- $\beta_2 m < 2.5 mg/l$

Olin RL. et al BMT 2009; 43:417-422
Cook G et al. BBMT 2011;17:1638-1645
Lemieux E et al. BBMT 2013;19:445-449
Role of Salvage ASCT in Multiple Myeloma

Maintenance therapy after second ASCT: Considerations

- Most patients will relapse after salvage ASCT due to residual disease
- Consolidation and/or maintenance after salvage ASCT seems as a potential approach for long term control of the disease
- No clear evidence exist as for consolidation and maintenance in the salvage setting post second ASCT
- No data regarding cytogenetic and molecular risk stratification at second ASCT
- Some data for a positive role for IFNα and IMiDs as maintenance therapy post second ASCTa
- Most of the retrospective studies addressing the question of maintenance after salvage ASCT suggest that some form of continuous therapy, preferably with novel agents, is necessary to sustain responses in these patients
- The role of this approach have to be examined in retrospective controlled trails

IFNα and IMiDs maintenance post 2nd salvage ASCT for MM

- 30/81 pts. (37%) underwent some form of maintenance therapy after salvage ASCT
- The duration of response after salvage ASCT was significantly affected by the use of maintenance therapy
- In MVA prognostic factor for PFS were: a short duration of response after 1st ASCT; a response less than VGPR after salvage therapy and no maintenance treatment after salvage ASCT
Lenalidomide Maintenance post salvage second ASCT for relapsed Multiple Myeloma

- N – 86 (second ASCT – 61; chemotherapy – 25)
- PFS 30.2mos vs. 13mos (p=0.0262)
- OS 129.6mos vs. 33.5mos (p=0.0003)
- Pts. with relapse >12mos benefit the most from second ASCT (PFS2 – p=0.0179 and OS2 p=0.0009)
- Lenalidomide after ASCT2 was associated with longer PFS and better OS as compared to pts. with no maintenance
American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group Consensus Conference on Salvage Hematopoietic Cell Transplantation in Patients with Relapsed Multiple Myeloma  

Giralt S. BBMT 2015 21:2039-2051

Abstract
In contrast to the upfront setting in which the role of high-dose therapy with autologous hematopoietic cell transplantation (HCT) as consolidation of a first remission in patients with multiple myeloma (MM) is well established, the role of high-dose therapy with autologous or allogeneic HCT has not been extensively studied in MM patients relapsing after primary therapy. The International Myeloma Working Group together with the Blood and Marrow Transplant Clinical Trials Network, the American Society of Blood and Marrow Transplantation, and the European Society of Blood and Marrow Transplantation convened a meeting of MM experts to: (1) summarize current knowledge regarding the role of autologous or allogeneic HCT in MM patients progressing after primary therapy, (2) propose guidelines for the use of salvage HCT in MM, (3) identify knowledge gaps, (4) propose a research agenda, and (5) develop a collaborative initiative to move the research agenda forward. After reviewing the available data, the expert committee came to the following consensus statement for salvage autologous HCT: (1) In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with HCT as part of salvage therapy should be considered standard; (2) High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of more than 18 months; (3) High-dose therapy and autologous HCT can be used as a bridging strategy to allogeneic HCT; (4) The role of postsalvage HCT maintenance needs to be explored in the context of well-designed prospective trials that should include new agents, such as monoclonal antibodies, immune-modulating agents, and oral proteasome inhibitors; (5) Autologous HCT consolidation should be explored as a strategy to develop novel conditioning regimens or post-HCT strategies in patients with short (less than 18 months remissions) after primary therapy; and (6) Prospective randomized trials need to be performed to define the role of salvage autologous HCT in patients with MM relapsing after primary therapy comparing it to “best non-HCT” therapy. The expert committee also underscored the importance of collecting enough hematopoietic stem cells to perform 2 transplantations early in the course of the disease. Regarding autologous HCT, the expert committee agreed on the following consensus statements: (1) Autologous HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT and/or high-risk features (i.e. cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase); (2) Autologous HCT should be performed in the context of a clinical trial if possible; (3) The role of postautologous HCT maintenance therapy needs to be explored in the context of well-designed prospective trials; and (4) Prospective randomized trials need to be performed to define the role salvage autologous HCT in patients with MM relapsing after primary therapy.
CONSENSUS GUIDELINES FOR SALVAGE AUTOLOGOUS HCT

The consensus committee agreed on the following guideline statements:

1. In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with autologous HCT as part of salvage therapy should be considered standard.

2. High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of more than 18 months.

3. High-dose therapy and autologous HCT can be used as a bridging strategy to allogeneic HCT.

4. The role of postsalvage HCT maintenance needs to be explored in the context of well-designed prospective trials that should include new agents, such as monoclonal antibodies, IMiDs, and oral proteasome inhibitors.

5. Autologous HCT consolidation should be explored as a strategy to develop novel conditioning regimens or post-HCT strategies in patients with short remission (less than 18 months).

6. Prospective randomized trials need to be performed to define the role of salvage autologous HCT in patients with MM relapsing after primary therapy comparing to “best non-HCT” therapy.

Giralt S. BBMT 2015 21:2039-2051
Is there still a role for alloSCT in relapse Multiple Myeloma

Retrospective Comparisons of Autologous versus Allogeneic HCT for Patients Relapsing after an Initial Autograft

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Giralt S. BBMT 2015 21:2039-2051
CONSENSUS GUIDELINES REGARDING ROLE OF ALLOGENEIC HCT IN RELAPSED MYELOMA

The expert committee agreed on the following guideline statements:

1. Allogeneic HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT or with high-risk features (i.e., cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) provided that they responded favorably to salvage therapy before allogeneic HCT.
2. Whenever possible, allogeneic HCT should be performed in the context of a clinical trial.
3. The role of postallogeneic HCT maintenance therapy needs to be further explored.
4. Prospective randomized trials need to be performed to define the role of salvage allogeneic HCT in patients with MM relapsing after primary therapy.
Patient presentation

- 62 year old male – IgA kappa Multiple Myeloma
- stable nCR – 2.5 years
- Relapse after 3 year of F/U, 4 years from 1\textsuperscript{st} ASCT
- Salvaged - 4 KRD cycles + second ASCT => VGPR
Conclusions & practical points

- Second ASCT should be considered for patients relapsing after first ASCT with initial remission duration of at least 18 months.
- Need for adequate stem cell collection and storage for at least two transplants should be advised at time of first collection (in the NCRI myeloma X relapse trial 30% of the pts. allocated for salvage ASCT could not receive the transplant due to poor SC collection. Plerixafor may be indicated).
- Most MM patients are currently receiving continuous lenalidomide maintenance after first ASCT, which may further impair stem cell collection.
# IFM Plerixafor-based mobilization for second salvage ASCT

P.I. Pr. M. Mohty

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Conclusions & Practical Points

- Prospective randomized controlled trials, including with cytogenetic and molecular profiling are in need for:
  - Assessing the clinical benefit of second ASCT in the era of novel therapies
  - Defining individual characteristics and prognostic factors that may help in selecting the patients that will benefit the most from a second ASCT
  - Assessing the role of consolidation (?) and maintenance post salvage second ASCT
  - Defining a very selected group of patients that can still benefit from allogeneic transplant for relapse MM
• Dr. Hila Magen
  Director MM Center, Hematology Division, Chaim Sheba Medical Center, Israel

• Pr. Mohamad Mohty
  Chef Hematology Division, Hopital St. Antoine, Paris, France