



## Stem Cell Transplantation for BCR- ABL Negative Myeloproliferative Disorders

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## Introduction:

The BCR-ABL negative myeloproliferative disorders (MPDs) in adults encompass several distinct clinical entities including agnogenic myeloid metaplasia (AMM), polycythemia rubra vera (PRV) and essential thrombocytosis (ET). The rates for these MPDs range from 0.38-2.8/100 000 adjusted for age and gender within the US population. (1)

The following document summarizes the literature and provides recommendations regarding the role of hematopoietic stem cell transplantation for the MPDs identified above.

## PRV, ET, MMM

PRV has a median age of onset of 60. If left untreated median survival is 2 years. Median survival otherwise is 15 years. 2 ET has a median age at diagnosis of 70, with median survival of 10 years. (3) Myelofibrosis with myeloid metaplasia (MMM) is characterized by a clonal myeloproliferation with bone marrow fibrosis and extramedullary hematopoiesis. (4) It encompasses agnogenic myeloid metaplasia (AMM) as well as the progressive fibrotic phases of PRV and ET. Median age at onset is 65 with a median overall survival of 4 years. (5, 6)

## Risk Stratification in MMM

Several risk scores have been developed to assess prognosis for patients with MMM. Dupriez et al (5), based on a cohort of 195 patients, defined three risk groups based on presence or absence of hemoglobin (Hb) <100 g/L and white blood count (WBC) <4 or >30 X 10<sup>9</sup>/L. Low, intermediate and high risk was defined by numbers of risk factors (0-2). Median survivals for low, intermediate and high risk groups were 93, 26 and 13 months respectively. Cervantes et al (6) defined two risk group, a low and high risk group based on presence or absence of Hb < 100g/L, constitutional symptoms and circulating blasts ≥ 1%. High risk was defined as having two or more adverse factors. Those with low risk (n = 88) had a median survival of 176 months whereas those with high risk (n = 28) had a median survival of 33 months. More recently the International Working Group for Myeofibrosis Research and Treatment defined a risk score based on a cohort of 1054 patients.(7) The authors identified five variables associated with poor prognosis; age>65, constitutional symptoms, Hb<100 g/L, WBC >25X10<sup>9</sup>/L and circulating blasts ≥ 1%. Patients without risk factors (low risk) had a median survival of 135 months, those with 1 risk factor had a median survival of 95

months, those with two risk factors had a median survival of 48 months and those with 3 or more risk factors had median survival of 27 months.

### Myeloablative allogeneic Stem Cell Transplantation

Several series have explored the role of conventional conditioning regimens in the management of MMM, PRV and ET.

Study	Number of patients	Median Age	TRM(%)	OS(%)
Guardiola P et al (8)	MMM = 55	42	27% 1y	47% 5 y
Deeg HJ et al (9)	MMM=38 ET = 10 PRV = 5	43 (10-66)	14% Day 100	58% 3 y
Daly A et al (10)	MMM = 19 ET = 6	48.7 (45.9-50.4)	48% 1 year	41% 2 y

Guardiola et al (8) reported on a cohort consisting primarily of HLA matched related transplants (49/55 (89%) ). The incidence of primary graft failure was 1/55 (2%). The authors identified older age at transplant and abnormal karyotype as predictors of disease recurrence or persistence. On multivariate analysis Hb >100 g/L and lack of osteomyelosclerosis were associated with improved 5 year overall survival. Splenectomized patients experienced a shorter time to neutrophil recovery, however they did not benefit in terms of increased disease free or overall survival.

Deeg et al (9) reported on a cohort consisting of 36/53 (68%) related donor transplants with the remainder being unrelated transplants. Failure of sustained engraftment was noted in 6/53 (11%) patients, all of whom received transplants from unrelated donors. On univariate analysis survival was superior in those conditioned with targeted busulphan and cyclophosphamide, in those that lacked osteomyelosclerosis, in those with normal karyotypes and in those with lower Dupriez scores. There was a suggestion of increasing hazard of death with increasing age, when age was modeled as a continuous variable (p = 0.07). Pretransplant splenectomy, stem cell source and donor type (HLA identical sibling versus alternative donor) did not predict for survival. Splenectomized patients experienced a shorter time to neutrophil engraftment.

Daly et al (10) reported on a cohort consisting of 13/25 (52%) matched related donor transplants with the remainder representing mismatched related donor(8%) and unrelated donor transplants (40%). Primary graft failure occurred in 2/25 (8%) of the cohort. Survival was not influenced by

pretransplant splenectomy, donor type (related versus unrelated), Cervantes score, presence of cytogenetic abnormalities or recipient age. Pretransplant splenectomy influenced time to neutrophil recovery but no other major outcomes.

All three studies provide evidence that engraftment is possible in MMM and that durable remissions are obtained in 50% of patients. Splenectomy while allowing for earlier neutrophil engraftment, does not appear to influence other major outcomes. Patients without significant marrow fibrosis and with lower risk disease have superior outcomes with allotransplantation. Increasing age is associated with worse long term disease control.

### Reduced Intensity Conditioning (RIC) allogeneic Stem Cell Transplantation

Because of the high TRM associated with myeloablative conditioning in MMM, several groups have explored whether outcomes could be improved with RIC allotransplantation.

Study	Number of patients	Median Age	TRM(%)	OS(%)
Rondelli et al (11)	21 MMM	54 (27-68)	10%	86% 2.7y
Kroeger et a (12)	21 MMM	53 (32-67)	16% 1y	84% 3y
Snyder et al (13)	9 MMM	54 (46-68)		56% 32 mo

The myeloproliferative diseases research consortium(11) examined the role of a variety of RIC regimens in a cohort of primarily HLA matched related donor transplants (18/21). 1/21 experienced primary graft failure and 3/21 underwent splenectomy prior to transplant. Both the overall and event free survival curves plateaued.

A single institution study from Hamburg (12) utilized uniform conditioning consisting of fludarabine, busulphan and rabbit ATG. 13/21 patients had a MUD transplant, with the remainder being related. 14/21 patients had high Cervantes scores (6). All patients received PBSCs. 4/21 underwent splenectomy prior to transplant and 3/21 required a stem cell boost. A plateau in the survival curve was again noted.

A further single institution study primarily utilized the combination of fludarabine and melphalan. (13) 7/9 had a MUD transplant. 5/9 patients underwent a pretransplant splenectomy. 1/9 patients experienced primary graft failure. Despite small numbers, the survival curve plateaued.

Two recent abstracts have compared outcomes for those undergoing myeloablative versus nonmyeloablative conditioning in preparation for allotransplantation in the setting of MMM. Gupta et al (14) reported on a cohort of 46 patients, half of whom received myeloablative conditioning. The 2 year progression free and overall survival for those receiving myeloablation versus nonmyeloablation was 48% versus 64% and 57% versus 68% respectively. The

authors further showed that long term survival was better for those above 50 who were conditioned with RIC regimens as opposed to myeloablative regimens. Lissandre et al (15) reported on 39 patients, 15 of whom underwent myeloablative conditioning. The authors were unable to demonstrate a difference in outcome based on age, conditioning regimen or splenectomy status.

RIC transplants for MMM appear well tolerated and are associated with excellent outcomes. For patients with MMM who are above the age of 50, RIC transplants offer a better probability of progression free and overall survival compared with myeloablative conditioning.

### Autologous Stem Cell Transplantation (ASCT)

Anderson et al (16) reported on a cohort of 27 patients with MMM, of whom 21 underwent ASCT. The median age was 59 (45-75). All patients underwent PBSC collection and were conditioned with busulphan. Five patients experienced graft failure. 3/21 patients underwent splenectomy prior to transplant. 2 year actuarial survival for those transplanted was 61%.

### Conclusions

1. Patients with MMM should be risk stratified by the International Working Group for Myeofibrosis Research and Treatment risk score. (7)
2. Patients with MMM who have intermediate to high risk scores and otherwise would meet transplant eligibility should be considered for possible allotransplantation
3. The choice of conditioning regimen in MMM is controversial. There is some suggestion that reduced intensity or nonmyeloablative conditioning is preferable in those aged 50 and above.
4. Pretransplantation splenectomy should not be routinely performed, but may be undertaken if clinically indicated.
5. There is not enough information concerning ASCT in MMM. ASCT in MMM should only be considered in the context of a clinical trial.
6. For patients with PRV or ET who do not have progressive marrow fibrosis, it would be reasonable to consider transplantation in the setting of
  - (i) transformation to acute leukemia
  - (ii) failure of conventional therapy in presence of severe hemorrhagic or thrombotic complications.

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