LEOPARD: A Phase II Study of Maintenance Lenalidomide and Prednisolone Post Autologous Stem Cell Transplantation for Myeloma, Incorporating Minimal Residual Disease Assessments

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Background
Multiple myeloma (MM), a clonal malignancy of plasma cells, is still an incurable disease. Despite improvements in ORR, PFS and OS following the introduction of high dose melphalan ASCT and novel agents, relapse is inevitable. Maintenance therapy following ASCT improves depth of response and prolongs both PFS and OS.

MRD detection is considered standard in many haematologic malignancies, but is still investigational in MM. Data from studies using highly sensitive techniques such as MFC and ASO-PCR suggest that the more stringent the definition used for CR, the greater prognostic significance of achieving that degree of response. Sequential MRD measurements are crucial to determine what level of MRD requires treatment, and newer techniques such as NGS and MRD measurements in addition to Frelikr measurement in total are currently being assessed.

Aims
Primary
To document change in disease response in post-ASCT MM patients who receive RAP maintenance therapy (according to MRD criteria).

Secondary
To sequentially quantify MRD by Frelikr chain (FLC) and multi-parameter flow cytometry (MFC) in patients who achieve immunisation (IF) negative CR.

To assess PFS/OS.

To assess safety/tolerability of lenalidomide maintenance.

Methods/Study design
Phase II single-arm, multi centre (5 Hospitals in Victoria, Australia) open-label study of maintenance therapy with RAP (lenalidomide 10mg/continuous daily increasing to 10mg after 852 and alternate day prednisone 50mg) in newly diagnosed MM patients commencing 8-8 weeks following induction and single MELDEO ASCT and continuing until toxicity/relapse.

LEOPARD study schema

Key inclusion/exclusion criteria:
- < 12 months prior standard dose chemotherapy
- no previous high dose chemotherapy
- at day 42 post ASCT:
  - evidence of haemopoietic reconstitution (ANC > 1.5 x 10^9/L, platelets unsupported > 50 x 10^9/L)
- no progressive MM.

Lab Methods/materials
- BAFFx performed 4 months after the first day following achievement immunisation (IF) negative CR, then 6 monthly thereafter.
- Plasma cell quantification was performed on fresh whole BM collected in EDTA by multi-parameter flow cytometry by the NAVIDO 2 analyzer using a 5 color 3 tube validated assay with a sensitivity of 0.01%.
- Serum samples for FLC were collected every 2 months on all patients were frozen and processed as a batch according to manufacturers instructions using the Binding Site SPA Plus analyzer (immunoassay/automated assay). Ratios were compared to normal ranges.

Results
After a median 23 months (range 12-36) following commencement of RAP maintenance,
- 33 patients remain on therapy.
- 15 ceased/progressed.
- 13 ceased due to AEs.
- 1 withdrew due to poor compliance.
- 11 patients have died, 7 due to progressive disease, 2 due to therapy related AML, 2 other.

 Patients (n) 30
 Sex: Male 22 Female 8 Age at registration (y), median (range) 61 (47 - 81)
 ISS at diagnosis unknown 20 low risk 3 intermediate risk 3
CR status at registration unknown 17 partial remission 12 complete remission 5
Paraprotein type
- Light chain only 13
- Light chain type
  - Kappa 27 Lambda 23
- Plasma cell ratio K/L > 100 5
- Plasma cell ratio K/L > 30 15
- Plasma cell ratio K/L > 10 20
- Plasma cell ratio K/L > 5 40
- Plasma cell ratio K/L > 2 50

Overall response achieved were:
- CR: 36 (90%) - 25 (75%) CR, VGPR: 21(50%) and
- PR: 2 (5%).

Response
- 33 patients improved their post ASCT response on RAP.
- Best response was achieved in a median of 112 days following commencement of RAP (range 28-469) days.
- Overall responses achieved were:
  - AML: 36 (90%), 25 (75%) CR, VGPR: 21(50%) and
  - PR: 2 (5%).

MRD studies – Multiparameter flow cytometry and Free Lite Chain

30 of 36 patients in CR went on to have MRD studies
21/30 were multiply MRD-1 (by MFC) and 9/30 were multiply MRD-pos. There was no difference in PFS between MRD-pos and MRD-neg patients (p=0.3).

Of the MRD-neg patients:
- >1-21 had predominantly normal FLC ratio (cCR),
- >3-152 MRD-neg patients released, 3 had normal FLC ratios.
- Of the MRD-pos patients:
- >9 had normal FLC ratios (cCR),
- >9 MRD-pos released.
- Correlation between MRD neg and cCR was poor (p<0.05).
- There was no difference in relapse rate between patients achieving MRD-neg versus those who achieved cCR.

Safety
Infections (UTI, LRTI, VZV reactivation) were the most frequent AEs, followed by diarhoea and insomnia.

AEs leading to discontinuation from study
- myelosuppression, (9)
- Second primary malignancy (2)
- AML and adenocarcinoma of bowel (1)
- Retinal vein thrombosis (1)
- Knee (1)

Haematologic/AEs All grade Grade 3-4
Anemia 5 (15%) 1 (3%)
Neutropenia 3 (10%) 2 (6%)
Thrombocytopenia 4 (13%) 3 (9%)

Toxicity

Fludarabine
- Peripheral neuropathy 12 (20%)
- Muscle cramps 11 (18%)
- Hypoglycaemia 7 (12%)

Conclusions
- RAP maintenance improved depth of response post ASCT (including conversion to deeper response categories >4 months), with high rates of CR/VR (80%).
- Neither MFC or FLC demonstrated superiority over the other for prediction of outcome and correlation between the two was poor.
- Less pronounced earlier findings of an interim analysis, patients with >1gpl had inferior PFS/OS,
- suggesting that this group may benefit less from RAP maintenance.
- Only 21% of patients discontinued RAP due to toxicity, comparable to IFM 2005-2 and CALGB 100104 studies.

Proportion of patients (MRD neg by MFC or cCR by FLC) who remained relapse free over time