Multiple Myeloma Research Review™

Making Education Easy

Issue 9 – 2014

In this issue:

Abbreviations used in this issue
CR = complete response
FISH = fluorescent *in situ* hybridisation
HR = hazard ratio
MGUS = monoclonal gammopathy of undetermined significance
MM = multiple myeloma
MRI = magnetic resonance imaging
OS = overall survival
PFS = progression-free survival
SCT = stem-cell transplant
(VG)PR = (very good) partial response

Welcome to the ninth issue of Multiple Myeloma Research Review.

This issue includes Australian research reporting a low uptake rate of upfront autologous SCT for eligible patients with MM, a deficiency that we have also seen in Wellington. Research from the Mayo Clinic reports improved long-term post-SCT outcomes in patients with MM who achieve a stringent CR compared with lesser degrees of response. We also have some data out of Sweden on the natural history of MGUS, as well as research suggesting that focal infiltration patterns on whole-body MRI can help identify patients with MGUS who are at risk of progression into symptomatic disease, although routine use of this investigation is difficult to justify at this stage.

We hope you enjoy the selection for the first issue of 2014, and please feel free to send us your comments, feedback and suggestions.

Kind regards,

Dr David Simpson
davidsimpson@researchreview.co.nz

Dr Ken Romeril
kennethromeril@researchreview.co.nz

DCEP for relapsed or refractory multiple myeloma after therapy with novel agents

Authors: Park S et al.

Summary: This was a retrospective population-based review of 48 patients, median age 58 years, who had received DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin) initiated a median of 34.9 months after a diagnosis of MM; the patients had received a median of three prior lines of therapy and 55 had undergone autohaematopoietic SCT. Among 51 patients evaluable for response, the overall response rate was 45.1%, including one CR, one very good PR and 21 PRs, eight had a minor response and 10 had stable disease. Grade ≥3 neutropenia was common (91.5%), and the treatment-related mortality rate was 14.8%, with febrile neutropenia contributing to 7/8 deaths. The estimated OS and PFS durations were 8.0 months and 3.7 months, respectively.

Comment (KR): Patients who are considered 'double refractory' to proteasome inhibitors and immunomodulatory drugs are in a parlous state and have limited options – especially in NZ. Pomalidomide would be a good option but is difficult to obtain, so the DCEP combination is a definite option although the treatment-related mortality of around 15% is substantial. The median OS of 8 months is worthwhile if the toxicity and high treatment-related mortality could be improved upon.

Reference: Ann Hematol 2014;93(1):99–105
Abstract

Multiple Myeloma Research Review

Independent commentary by Dr David Simpson, MBChB, FRACP, FRCPA, Consultant Haematologist North Shore Hospital. He is also a member of the Pharmacy and Therapeutics Committee at North Shore Hospital and the Tender Subcommittee of PHARMAC.

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Independent commentary by Dr Ken Romeril, FRACP, FRCPA Haematologist specialising in malignant haematology, Wellington Hospital. He is involved in clinical trials, and he is a member of the ALLG Special Advisory Committee and Chair of the ALLG Myeloma Sub-Committee.

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Low uptake of upfront autologous transplantation for myeloma in a jurisdiction with universal health care coverage

Authors: Doo NW et al.

Summary: This analysis of Australian population-based data identified the following patients and disease factors associated with not receiving upfront autologous SCT in 123/225 eligible patients aged <70 years with newly diagnosed MM: i) presence of severe medical comorbidities; ii) MM-associated renal impairment; and iii) initial medical oncology versus haematology referral. Furthermore, only 62% of those aged <65 years at diagnosis (n=121) who had minor or no comorbidities proceeded to upfront autologous SCT.

Comment (KR): This is real-world experience in Melbourne, and shows that a surprisingly low number of patients actually undergo an autologous SCT from an intent-to-treat analysis. The data are skewed by the fact that in Victoria the oncologists treat some myelomas in private and may not refer on for autologous SCT. When the Wellington group analysed a similar group of 150 patients for an ASH abstract, we found that only 62% of the auto-eligible patients at our centre actually received a transplant, reflecting similar issues of medical comorbidity and patient disinclination. There is approximately 1 year's advantage in the transplant option, but with the advent of novel agents, this may not be such an issue. We need further studies utilising a nontransplant option to better advise our patients.

Reference: Clin Lymphoma Myeloma Leuk 2014;14(1):61–7
Abstract

Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma

Authors: Scheid C et al.

Summary: This was a subgroup analysis of 827 HOVON-65/GMMG-HD4 trial participants with newly diagnosed MM who had been randomised to receive three cycles of VAD (vincristine, doxorubicin, dexamethasone) or PAD (bortezomib, doxorubicin, dexamethasone) followed by autologous SCT and maintenance with either thalidomide 50mg daily (VAD recipients) or bortezomib 1.3 mg/m^2 every 2 weeks (PAD recipients). No significant difference was seen between the VAD and PAD arms for renal response rates in participants with a baseline serum creatinine level ≥2 mg/dL (n=81; p=0.31), while the overall myeloma response, CR, 3-year OS and 3-year PFS rates were greater in the PAD arm (89% vs. 64%, 36% vs. 13% [p=0.01], 74% vs. 34% [p<0.001] and 48% vs. 16% [p=0.004], respectively). Similar OS and PFS rates were seen in PAD recipients with a baseline serum creatinine level of ≥2 mg/dL versus <2 mg/dL.

Comment (KR): Approximately 20% of patients with MM present with a creatinine level >2 mg/dL, a factor associated with poorer survival, as shown in the old Durie-Salmon classification (stage B) and in the ISS where an elevated β-2 microglobulin level is associated with abnormal renal function. These classifications were derived prior to the use of bortezomib, and it has been suggested that renal impairment may no longer be a negative prognostic factor. This study by Scheid et al. focused on a subset of patients who were candidates for an autologous SCT with a median creatinine clearance of 26 mL/min. The presence of baseline renal impairment had a detrimental effect in the VAD arm, but the PAD arm appeared to abrogate the negative prognostic influence. This prospective study shows that in transplantation candidates with moderate/severe renal impairment, a bortezomib-based regimen is the standard of care.

Reference: Haematologica 2014;99(1):148–54
Abstract

Addition of thalidomide to melphalan and prednisone treatment prolongs survival in multiple myeloma

Authors: Lund J et al.

Summary: This research of patients treated with MP (melphalan, prednisone) with (MPT; n=274) or without (n=888) thalidomide reported respective median OS durations from initiation of treatment of 2.2 and 4.2 years for first-line therapy (p<0.0001), 1.8 and 2.9 years for second-line therapy (p=0.003), 1.4 and 1.6 years for third-line therapy (p=0.74) and 1.1 and 1.9 years for fourth-line therapy (p=0.235). First- and second-line MPT was associated with significantly lower mortality rates than MP (respective relative risks 0.61 [95% CI 0.45, 0.84] and 0.55 [0.38–0.83]; p<0.01).

Comment (DS): This study would once have been significant in showing a survival improvement over melphalan and prednisone. However, this is no longer the bar. While MPT does have good activity, the responses are poorer and treatment is not better tolerated than proteasome-containing regimens, even in the elderly. The ≥VGPR rate in first-line therapy was 24%, which is low by current standards. The time to next treatment was about 2 years, better than about 14 months with MP, but that is not the standard. MPT does not appear to be a good option for initial treatment of myeloma. It is difficult to know where this regimen fits in the current armamentarium.

Comment (KR): MPT has been considered the treatment of choice in the elderly myeloma patient particularly in the over 75-year age group where bortezomib has increased toxicity. Not all of the MPT studies have shown a benefit from the addition of thalidomide. This large Swedish study looked at all-comers, and confirms an improved survival benefit of MPT and was especially effective in the first-line situation where the OS reached 4.2 years. The decision around whether to use VMP or MPT has to take into account patient preference and associated comorbidities.

Reference: Eur J Haematol 2014;92(1):19–25
Abstract

Monoclonal gammopathy of undetermined significance and risk of lymphoid and myeloid malignancies

Authors: Turesson I et al.

Summary: This ≤30-year follow-up of 728 cases of MGUS in Sweden found that the estimated cumulative risk of developing a lymphoid disorder was 15.4%, the 30-year cumulative risk of MM was 10.6% (annual risk 0.5%) and the 30-year cumulative risk of a myeloid malignancy was <2%. Factors significantly associated with progression were serum free light-chain ratio <0.26 or >1.65, M-protein level ≥1.5 g/dL and reduction of 1 or 2 noninvolved immunoglobulin isotype levels (immunoparesis). Compared with other models, a prediction model with separate effects for these three factors and the M-protein isotype provided nonsignificantly higher discriminatory power.

Comment (DS): Most data on the natural history of MGUS are from population studies in Minnesota. This study showed similar prognostic factors (free light-chain ratio, paraprotein >15 g/L) but adds immune paresis. The overall risk of progression to myeloma was lower at 0.5%, which is good news for those with MGUS. These data help consolidate the selection of cases who do not need intensive follow-up, but they do identify a group with all risk factors who do need careful monitoring.

Reference: Blood 2014;123(3):338–45
Abstract

For more information, please go to http://www.medsafe.govt.nz

Importance of achieving stringent complete response after autologous stem-cell transplantation in multiple myeloma

Authors: Kapoor P et al.

Summary: These researchers investigated degrees of CR in 445 consecutive patients with MM who underwent autologous SCT within 12 months of diagnosis. Compared with patients achieving post-transplant conventional (n=37) and near (n=91) CRs, those who achieved a stringent CR (n=109) had: i) a significantly longer median OS duration ('not reached' vs. 81 and 60 months, respectively; p<0.001), and this remained longer at the 2-year landmark (p=0.007); ii) a higher 5-year OS rate (80% vs. 53% and 47%); and iii) a significantly longer median time to progression (50 vs. 20 and 19 months). A multivariate analysis showed that survival was predicted by post-SCT stringent CR (HR 0.44 [95% CI 0.25, 0.80; p=0.008]), proliferation rate, pretransplant cytogenetics and performance status.

Comment (DS): Depth of response matters! With newer treatments achieving greater depths of response, new categories of response have been invented. This paper showed superior outcomes in those with a stringent CR, even compared with those in CR. Minimal residual disease assessment, usually by flow cytometry, has further defined a group who achieve a deeper response than stringent CR. Minimal residual disease assessment is now considered almost essential in research protocols. Operational cure is now the goal of initial treatment of myeloma; depth of response is the best predictor of this late outcome.

Reference: J Clin Oncol 2013;31(36):4529–35
Abstract

Progression in smoldering myeloma is independently determined by the chromosomal abnormalities del(17p), t(4;14), gain 1q, hyperdiploidy, and tumor load

Authors: Neben K et al.

Summary: This analysis of the 1q21, 5p15/5q35, 9q34, 13q14.3, 15q22, 17p13, t(11;14)(q13;q32) and t(4;14)(p16.3;q32) chromosomal aberrations in 248 patients with smouldering MM found that high-risk aberrations in active disease (del(17p13), t(4;14) and +1q21), which were present in 6.1%, 8.9% and 29.8% of the patients, respectively, were associated with significantly adverse prognoses in smouldering MM (respective HRs 2.90 [95% CI 1.56, 5.40], 2.28 [1.33, 3.91] and 1.66 [1.08, 2.54]), as was hyperdiploidy (1.67 [1.10, 2.54]), which was present in 43% of the patients. An adverse prognosis was also predicted by proportion of malignant bone marrow plasma cells on interphase FISH and the combination of M-protein and plasma cell infiltration as surrogates of tumour load (respective HRs 4.37 [95% CI 2.79, 6.85] and 4.27 [2.77, 6.56]).

Comment (DS): This paper shows that the three critical FISH abnormalities in symptomatic myeloma (del17p13, t(4;14) and +1q21) are useful in predicting early progression of smouldering myeloma; importantly the number of patients who develop bone disease is also higher with these abnormalities. Presumably, combinations of these prognostic groups fare even worse, but we are not told this in the paper. As we are moving more to pre-emptive therapy of high-risk myeloma, assessment of these FISH abnormalities becomes more significant. While a study of treatment of asymptomatic smouldering MM versus delaying treatment until CRAB symptoms (hypercalcaemia, renal failure, anaemia, bone lesions) appear would be required for proof, we are likely to need to advise individuals before full data become available.

Reference: J Clin Oncol 2013;31(34):4325–32
Abstract

Prognostic significance of whole-body MRI in patients with monoclonal gammopathy of undetermined significance

Authors: Hillengass J et al.

Summary: Whole-body MRI detected a focal infiltration pattern in nearly a quarter (23.4%) of 137 consecutive patients with MGUS in this research. Significant independent prognostic factors of progression to symptomatic disease requiring systemic treatment included presence and number of focal lesions and M-protein (p≤0.02). A significant relationship was also seen between lower homogeneous signal intensities in T1-weighted images and physiologically greater bone marrow cellularity in younger patients (p=0.002).

Comment (DS): Whole-body STIR MRI is a useful procedure for identifying bone lesions in myeloma patients. Previous studies have shown that the presence of bone lesions is of prognostic significance in smouldering myeloma, and this paper shows that the same is true of MGUS. Those who had >1 focal lesion (22/137) had a 60% chance of progression at 4 years (although numbers at risk were small). Unfortunately, no clinical factors predicted the presence of bone lesions, so it is difficult to know which patients to select for this investigation. At present it is difficult to justify this investigation in all patients.

Reference: Leukemia 2014;28(1):174–8
Abstract

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