Multiple Myeloma Research Review™

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In this issue:

Abbreviations used in this issue

CMV = cytomegalovirus
FISH = fluorescence *in situ* hybridisation
(H)SCT = (haematopoietic) stem-cell transplantation
IV = intravenous
MM = multiple myeloma
MTD = maximum tolerated dose
OS = overall survival
PFS = progression-free survival
PI = proteosome inhibitor
SNP = single-nucleotide polymorphism
(VG)PR = (very good) partial response

Welcome to the seventeenth issue of Multiple Myeloma Research Review.

An excellent review on the feasibility of autologous HSCT as an effective treatment for elderly patients with MM begins our first issue for 2016. Other research included suggests that the poor prognosis seen in patients with MM with gain 1q21 is not overcome with the use of high-dose treatment, immunomodulatory drugs or PIs (proteasome inhibitors). Researchers from Italy have claimed that while MM consolidation therapy with chemotherapy plus lenalidomide has a better toxicity profile, high-dose melphalan and autologous SCT is still the preferred option in transplant-eligible patients. This issue concludes with a study suggesting that carfilzomib with dexamethasone can also be considered for relapsed/refractory MM when bortezomib with dexamethasone is a potential treatment option. We hope you find these and the other selected studies informative.

Research Review is ten!! The first ever issues of Research Review were delivered to inboxes in February 2006. Fast forward ten years and we now publish 48 regular reviews to which there are over 160,000 subscriptions. We're grateful to each and every one of you for your support and are looking forward to even bigger and better things over the coming years.

We enjoy your feedback, comments and suggestions, so please keep them coming.

Kind regards,

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Autologous haematopoietic cell transplantation in elderly patients with multiple myeloma

Authors: Auner HW et al.

Summary: These authors reviewed autologous HSCT outcomes in elderly patients with MM, noting the increased frequency of this therapeutic modality in these patients, despite lack of evidence from randomised controlled trials. Their review of retrospective and prospective studies suggests that key outcomes in appropriately selected older patients are the same as for their younger counterparts. It was concluded that more study is needed in areas such as: i) autologous HSCT in the context of conventional therapies, particularly the role of consolidation with autologous HSCT versus continuous/maintenance therapy; ii) the development of evidence-based patient selection, iii) optimal conditioning regimens with respect to melphalan dosing and the use of novel agents; iv) second transplants for relapse; v) maintenance therapy following autologous HSCT; and vi) the health economics of autologous HSCT versus novel agents.

Comment (KR): This review is an excellent summary of the many studies trying to sort out the controversial issue regarding the utility of autologous HSCT in the >65-year-old group, particularly in the era of novel agents. Clinicians also tend to reduce the melphalan dose down to M140 in this age group. In the recent Heidelberg study, the use of M200 was shown to have comparable toxicity rates in selected patients. In summary, the authors feel that elderly patients up to the age of 75 years who are able to tolerate standard induction therapy and who are ECOG score 0–1 should be considered for autologous HSCT.

Reference: Br J Haematol 2015;171(4):453–62
Abstract

Independent commentary by Dr Ken Romeril, FRACP, FRCPA Haematologist specialising in malignant haematology, Wellington Hospital. He has a particular interest in translational myeloma research and genetics. **For full bio CLICK HERE**

Independent commentary by Dr David Simpson, MBChB, FRACP, FRCPA, Consultant Haematologist North Shore Hospital. His interests are in malignant haematology. **For full bio CLICK HERE**

Outcomes among high-risk and standard-risk multiple myeloma patients treated with high-dose chemotherapy and autologous hematopoietic stem-cell transplantation

Authors: Kazmi SM et al.

Summary: This research reported outcomes for 670 patients with high-risk versus standard-risk MM who underwent autologous HSCT at a single institution; high-risk myeloma was defined as –13/del(13q) or hypodiploidy in ≥2 metaphases of conventional cytogenetics, or –17/del(17p), t(4;14), t(14;16), t(14;20), hypodiploidy (<45 chromosomes excluding –Y), or chromosome 1 abnormalities (+1q, –1p, t[1;x]) on FISH or conventional cytogenetics. Compared with standard-risk patients, high-risk patients (n=74) had a lower overall response rate (74% vs. 85% [p<0.01]), shorter median PFS duration (10.3 vs. 32.4 months [p<0.001]) and shorter OS duration (28 months vs. not reached [p<0.001]). Independent predictors of better PFS and OS in high-risk patients were presence of only 1 high-risk cytogenetic abnormality and VGPR or better post-transplant.

Comment (KR): This is a very large cohort of autologous HSCT patients from the MD Anderson Cancer Center and is not randomised as per usual. The figure of only 11% being considered high risk seems low compared with other studies, including our own local cohort where up to 25% are in this category. The conclusion reached that despite novel therapies, high-risk patients do significantly worse is in keeping with recent studies. The question remains about what to do about this subgroup and no answers were provided.

Reference: Clin Lymphoma Myeloma Leuk 2015;15(11):687–93
Abstract

Cytomegalovirus reactivation in patients with multiple myeloma

Authors: Hasegawa T et al.

Summary: This was a retrospective evaluation of CMV (cytomegalovirus) reactivation in 120 consecutive patients with newly diagnosed MM; 58 patients underwent CMV antigenaemia testing. CMV reactivation was seen in 20% of the patients in a median of 5.0 months from MM diagnosis, and 11% had proven/suspected CMV disease requiring antiviral therapy, including those who had not undergone SCT. A comparison of these patients and 34 CMV antigenaemia-negative patients was conducted. CMV reactivation was more likely in patients with extramedullary disease and in those with a low absolute lymphocyte count.

Comment (KR): CMV reactivation is well known to be an issue in the transplantation setting, but this Japanese study has also found a high incidence in conventionally treated MM patients. MM-related innate immunodeficiency can involve various immune systems including numerical abnormalities of T- and NK-cells. We need to look for CMV reactivation early on in the disease course and especially in extramedullary disease.

Reference: Eur J Haematol 2016;96(1):78–82
Abstract

Proteasome inhibitors and IMiDs can overcome some high-risk cytogenetics in multiple myeloma but not gain 1q21

Authors: Nahi H et al.

Summary: This study of consecutive hospitalised patients with MM looked at the impact of treatment modality on the prognostic importance of specific chromosomal aberrations, particularly gain of 1q21; 119 patients had 1q21 gain, 105 patients had other aberrations (i.e. del[13q], del[17p], t[4,14] and/or [14;16]) and 123 had no aberrations. Median follow-up of survivors at the time of analysis was 29 months overall and 40 months for high-dose-treated patients. Compared with patients with other aberrations and those with no aberration, those with gain of 1q21 had a lower 3-year OS rate, as did the subgroups treated with PIs or immunomodulatory drugs and those who received high-dose treatment. Outcomes in patients with other aberrations who received high-dose treatment, PIs or immunomodulatory drugs approached those of patients with no aberrations.

Comment (KR): The gain of chromosome 1q involves the 1q21 region, which encodes for the cell-cycle-associated gene *CKSIB*, which is associated with an adverse prognosis. This large study echoes the findings of a study by Biran (2014) where the current triplet regimens could not overcome the abnormality. The gain of 1q21 is an important chromosomal aberration that should be included in the diagnostic FISH panel.

Reference: Eur J Haematol 2016;96(1):46–54
Abstract

Understanding the role of hyperdiploidy in myeloma prognosis: which trisomies really matter?

Authors: Chretien M-L et al.

Summary: These researchers conducted a high-throughput SNP array analysis after plasma cell sorting in 965 patients with MM, including 168 patients with t(4;14) and 126 with del(17p), to explore the possibility that better outcomes might be related to concomitant 'good-risk' chromosomal changes. It was determined using the LASSO model that only chromosome 3, when trisomic, was associated with improved PFS and that three trisomies modulated OS, with trisomies 3 and 5 associated with significant OS improvements and trisomy 21 associated with worse OS. Trisomies 3 and/or 5 appeared to overcome poor prognosis in patients with t(4;14).

Comment (DS): This study looked at trisomies using SNP array, which looks at gains and losses but not translocations, and combined this with FISH data, only looking for del(17p) and t(4;14) in historically treated patients, many of whom had received VD (bortezomib, dexamethasone) followed by transplant, but also including 18% who received VAD (vincristine, doxorubicin, dexamethasone) induction. They found trisomies of 3 and 5 were associated with improved outcomes in those with adverse FISH. The data are interesting, but it is not clear that it is worth doing SNP arrays, especially as differential responses to different treatments were not explored in this study.

Reference: Blood 2015;126(25):2713–9
Abstract

Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma

Authors: Shah JJ et al.

Summary: Thirty-two patients with relapsed or lenalidomide-refractory MM received 28-day cycles of the MTDs of IV carfilzomib 20/27 mg/m^2 on days 1, 2, 8, 9, 15 and 16, pomalidomide 4mg once daily on days 1–21 and oral or IV dexamethasone 40mg on days 1, 8, 15 and 22 (CPD) in phase 2 of this open-label, dose-escalation study. The haematological adverse event rate was ≥60%, including 11 participants who developed grade ≥3 anaemia. Ten participants experienced dyspnoea and peripheral neuropathy was uncommon; both were limited to grades 1–2. Eight participants needed dose reductions, there were seven adverse event-related discontinuations and there was one death from pneumonia and another from pulmonary embolism.

Comment (DS): The CPD regimen combines the best-in-class PI with the best-in-class immunomodulatory drug. The regimen was well tolerated, despite the heavily pretreated population with a median of six prior regimens. The total response rate, including minor responses, was 66%, including 16% achieving VGPR, although most responses were not durable, which is not unexpected in this patient population. While this regimen could be used in these highly refractory patients, early data are more compelling for PD-1 blockade. This combination is likely to be better used in the upfront setting to drive deep responses, and in this setting, with patients having better bone marrow reserve, the MTD of carfilzomib is likely to be higher than 27 mg/m^2.

Reference: Blood 2015;126(20):2284–90
Abstract

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Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma

Authors: Richardson PG et al., on behalf of the 1703 study investigators

Summary: Adults with MM were entered into phase 2 of this open-label, dose-escalation study. They were stratified according to number of previous therapies and prior immunomodulatory drug treatment, and randomised to receive 28-days cycles of IV elotuzumab 10 mg/kg (n=36) or 20 mg/kg (n=37) on days 1, 8, 15 and 22 for the first two cycles and then on days 1 and 15 along with oral lenalidomide 25mg on days 1–21 and dexamethasone 40mg once per week until disease progression or unacceptable toxicity. At data cutoff, six participants from the elotuzumab 10 mg/kg arm and seven from the 20 mg/kg arm were still on treatment. The respective objective response rates in the elotuzumab 10 mg/kg and 20 mg/kg arms were 92% and 76%, the respective VGPR rates were 47% and 38% and the respective PR rates were 28% and 27%. Diarrhoea (66%), muscle spasms (62%) and fatigue (56%) were common adverse events of any grade. The grades 3–4 adverse event rate was 78%, the most common being lymphopenia (21%) and neutropenia (19%). None of the three deaths were related to the investigational agents.

Comment (DS): This study compared two doses of elotuzumab, 10 mg/kg and 20 mg/kg, combined with the same doses of lenalidomide and dexamethasone in relapsed myeloma patients. Preclinical studies demonstrated that both doses should achieve therapeutic concentrations, and reassuringly they found that both doses had the same efficacy. They also found the side effect profiles, with fatigue and diarrhoea presumed to be due to stimulation of the innate immune system, similar, in keeping with an on-target effect. Responses were better than historically reported for lenalidomide/dexamethasone alone, and PFS duration was 18 months compared with about 12 months for lenalidomide/dexamethasone, but were not as good as in the ASPIRE trial using KRd (carfilzomib/lenalidomide/dexamethasone), which was 27 months. Elotuzumab 10 mg/kg is the dose being used in phase 3 studies going forward.

Reference: Lancet Haematol 2015;2(12):e516–27
Abstract

Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma

Authors: Gay F et al.

Summary: In this phase 3 study, 389 transplant-eligible patients aged ≤65 years with newly diagnosed MM received lenalidomide and dexamethasone induction, then cyclophosphamide followed by G-CSF (granulocyte colony-stimulating factor) for stem-cell mobilisation and collection. Eligible participants were then randomised with a 2 × 2 partial factorial design to consolidation with cyclophosphamide 300 mg/m^2 on days 1, 8 and 15, dexamethasone 40mg on days 1, 8, 15 and 22 and lenalidomide 25mg on days 1–21 (n=159) or two courses of melphalan 200 mg/m^2 and autologous SCT (n=127), and maintenance with lenalidomide 10mg on days 1–21 with (n=117) or without (n=106) prednisone 50mg every second day. Median follow-up was 52.0 months. Consolidation chemotherapy plus lenalidomide was associated with significantly shorter median PFS than high-dose melphalan and autologous SCT (28.6 vs. 43.3 months [p<0.0001]), with no significant difference between maintenance lenalidomide plus prednisone versus lenalidomide alone (37.5 vs. 28.5 months). There were fewer grades 3–4 adverse events with chemotherapy plus lenalidomide than with high-dose melphalan and autologous SCT, with haematological events (26% vs. 84%), gastrointestinal events (5% vs. 20%) and infection (5% vs. 19%) the most common. Two chemotherapy plus lenalidomide recipients and no high-dose melphalan and autologous SCT recipients experienced serious haematological events, and the respective nonhaematological serious adverse event rates were 10% and 7%. There were no significant differences between the lenalidomide plus prednisone and lenalidomide alone maintenance arms for adverse events; the most frequent grades 3–4 events were neutropenia (8% vs. 13%), infection (8% vs. 5%) and systemic toxicities (6% vs. 2%), and the serious nonhaematological adverse event rates were 11% and 9%. There were two deaths from infections during induction and one during consolidation, and one death due to cardiac toxic effects.

Comment (DS): This study confirms the role of autologous bone marrow transplantation in the initial treatment of myeloma. It showed the addition of high-dose melphalan adds to the duration of response and survival of those induced with lenalidomide and dexamethasone. Using lenalidomide and dexamethasone induction, only two-thirds of the study population made it to the transplant/consolidation randomisation, and this is likely to be lower in nonstudy populations. So the induction therapy needs to be better, probably by the addition of a PI, to achieve optimal outcomes. In addition, only 43% of those eligible for a delayed transplant actually received it despite having had stem cells collected, so delaying transplant is not an effective strategy. The second randomisation of adding prednisone to lenalidomide did not significantly improve outcomes, but there was some late divergence of the curves and further follow-up is needed.

Reference: Lancet Oncol 2015;16(16):1617–29
Abstract

Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR)

Authors: Dimopoulos MA et al. for the ENDEAVOR investigators

Summary: Patients with relapsed/refractory MM were randomised 1:1 to receive IV carfilzomib 20 mg/m^2 on days 1–2 of the first cycle and 56 mg/m^2 thereafter (n=464) or IV or subcutaneous bortezomib 1.3 mg/m^2 (n=465) with IV or oral dexamethasone 20mg until disease progression in this open-label, multicentre, phase 3 study; randomisation was stratified by prior PI therapy, previous treatment line, disease stage and planned route of bortezomib administration if randomly assigned to the bortezomib arm. The median follow-up durations in the carfilzomib and bortezomib arms were 11.9 months and 11.1 months, respectively. In an interim intent-to-treat analysis, the carfilzomib arm had a significantly longer median PFS duration than the bortezomib arm (primary endpoint; 18.7 vs. 9.4 months; hazard ratio 0.53 [95% CI 0.44, 0.65]) and a similar on-study mortality rate (4% vs. 3%). The respective serious adverse event rates in the carfilzomib and bortezomib arms were 48% and 36%, with the most frequent grade ≥3 adverse events being anaemia (14% and 10%), hypertension (9% and 3%), thrombocytopenia (8% and 9%) and pneumonia (7% and 8%).

Comment (DS): A direct head-to-head comparison of two drugs of the same class is a bold move for a company challenging an incumbent, as failure could be disastrous for drug development. In this case it paid off, as carfilzomib resulted in deeper responses and improved PFS from about 9 to 19 months in relapsed myeloma. The dose of carfilzomib was high at 56 mg/m^2 and bortezomib was given at the standard MTD, but despite this the side-effect profiles were similar with more neuropathy with bortezomib and more cardiopulmonary events including hypertension with carfilzomib. Deaths on treatment were the same in both arms. A similar level of benefit was seen in participants who were bortezomib-naïve or not, indicating carfilzomib is a more effective PI against myeloma cells. While carfilzomib moves to the top of the class for PIs, the place of carfilzomib/dexamethasone is less clear cut, as the PFS is less than the 27 months seen with KRd (carfilzomib/lenalidomide/dexamethasone) in the ASPIRE study in a similar population.

Reference: Lancet Oncol 2016;17(1):27–38
Abstract

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