Multiple Myeloma Research Review™

Making Education Easy

Issue 27 – 2018

In this issue:

Abbreviations used in this issue

BCMA = B-cell maturation antigen
CAR = chimeric antigen receptor
CR = complete response
HR = hazard ratio
HSCT/SCT = (haematopoietic) stem-cell transplantation
MM = multiple myeloma
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes
PR/VGPR = (very good) partial response

Welcome to issue 27 of Multiple Myeloma Research Review.

To begin this issue, we have a paper reporting that the prognosis of del(17p) MM remains poor despite improvements seen with autologous HSCT and novel agents. Another included research paper looks at intensifying treatment in MM in CR using autologous SCT and lenalidomide maintenance. Researchers from China found that a regimen of low-dose lenalidomide and dexamethasone was active and well tolerated for patients with newly diagnosed POEMS syndrome. This issue concludes with research reporting that homologous recombination deficiency-related loss of heterozygosity increases as myeloma disease progresses, thereby supporting the investigation of PARP inhibitor use in MM.

Your input is always valued, so please don't hesitate to email us your feedback and suggestions.

Kind regards,

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Treatment patterns and clinical outcomes in high-risk newly diagnosed multiple myeloma patients carrying the 17p deletion

Authors: Cohen YC et al.

Summary: Real-world data and outcomes were retrospectively analysed for an observational cohort of 60 consecutive patients with newly diagnosed del(17p) MM from eight centres. Most of these patients had received bortezomib-based induction, most had undergone autologous HSCT, and 30% had received novel agents via clinical trials, access programmes or private insurance. The respective postinduction ORRs for transplant-eligible and -ineligible patients were 94% and 75%; ORR declined over subsequent treatment lines. The VGPR or better rate was 64%, median OS duration was 43 months, and the respective median PFS durations for transplant-eligible and -ineligible patients were 19 months and 7 months. Predictors of worse PFS were higher M-spike levels, presence of extramedullary disease and >50% of cells with del(17p), and predictors of longer PFS were autologous HSCT and higher haemoglobin level. The OS duration for patients who had access to novel agents was 59 months. Predictors of worse OS were older age and higher M-spike levels, and autologous HSCT predicted favourable OS (59.7 vs. 28.7 months for transplant-ineligible patients).

Comment (KR): Patients with del(17p) have always been a challenge because they carry this poor prognostic factor. It is clear that patients who have high (>50%) copies of the del(17p) do worse, and in the past these patients were not even considered for HSCT. This paper indicates that HSCT and use of novel agents confers better OS, but more novel approaches are clearly indicated.

Reference: Am J Hematol 2018;93:810–5
Abstract

Twice-weekly ixazomib in combination with lenalidomide-dexamethasone in patients with newly diagnosed multiple myeloma

Authors: Richardson PG et al.

Summary: The pharmacokinetics, safety and efficacy profiles of sixteen 21-day cycles of twice-weekly ixazomib 3.0 or 3.7mg, lenalidomide 25mg and dexamethasone 20mg, reduced to 10mg for cycles 9–16, followed by maintenance twice-weekly ixazomib alone were reported in patients with newly diagnosed MM in this phase 1/2 study. There were no dose-limiting toxicities recorded during the first cycle, and the recommended ixazomib dose for phase 2 was set at 3.0mg. Among 62 evaluable patients who received the recommended phase 2 dosing schedule, the confirmed ORR was 94%, with respective VGPR or better and CR rates of 68% and 24%, the median PFS duration was 24.9 months and the median response duration was 36.9 months, which deepened during treatment. The grade 3 drug-related adverse event rate was 64%, including rash in 13%, peripheral neuropathy in 8% and hyperglycaemia in 8%, and 13 participants discontinued due to adverse events; no grade 4 drug-related adverse events were recorded.

Comment (KR): This paper by Paul Richardson and others in Br J Haematol enlarges upon work from the Tourmaline studies. Ixazomib was given to patients in a twice-weekly schedule, and the median age in both arms was around 63 years, so many patients were actually eligible for transplantation. The responses obtained were quite rapid and tended to get deeper with treatment duration, but around a third of patients discontinued early to undergo autologous SCT. This issue was increased toxicity, so this more aggressive approach may not replace the older weekly regimen.

Reference: Br J Haematol 2018;182:231–44
Abstract

Treatment intensification with autologous stem cell transplantation and lenalidomide maintenance improves survival outcomes of patients with newly diagnosed multiple myeloma in complete response

Authors: Mina R et al.

Summary: Outcomes were reported for participants with MM who achieved CR in two phase 3 trials (GIMEMA-RV-MM-PI-209 and RV-MM-EMN-441) that compared high-dose therapy plus autologous SCT (n=95) with a consolidation regimen of lenalidomide with an alkylator (n=71), and lenalidomide maintenance with no maintenance. Compared with lenalidomide-based consolidation, participants who underwent transplantation had superior PFS (HR 0.55 [p=0.01]), second PFS (0.46 [p=0.02]) and OS (0.42 [p=0.03]), with the survival benefit confirmed in subgroups based on age, ISS stage, cytogenetic profile and receipt of maintenance therapy. Compared with participants who received no maintenance, those who received lenalidomide maintenance had a greater 4-year PFS rate (54% vs. 19%; HR 0.43 [p=0.02]), but not second PFS or OS at 4 years (72% vs. 58%; 0.83 [p=0.67] and 79% vs. 72%; 0.82 [p=0.73], respectively).

Comment (KR): This paper analysed a relatively small number of patients in two phase 2 trials. It adds to the body of data indicating that patients treated intensively with high-dose therapy with autologous SCT followed by consolidation and lenalidomide-based maintenance have better outcomes.

Reference: Clin Lymphoma Myeloma Leuk 2018;18:533–40
Abstract

Risk factors for blood stream infections in multiple myeloma

Authors: Sørrig R et al.

Summary: The epidemiology of and risk factors for blood-stream infections in MM were assessed in this research that included 1154 unselected patients from the Danish population. Most blood cultures available for analysis were obtained between 30 days before to 180 days after MM diagnosis. Risk factors for requiring blood culture sampling within the peak period were immunoparesis (HR 1.5 [CI 1.1, 2.1]), ISS III (1.3 [1.0, 1.7]), a high creatinine level (1.4 [1.0, 2.0]) and a high lactate dehydrogenase level (2.8 [1.6, 4.7]), and risk factors for having a blood culture positive for pathogenic microorganisms during the peak period were ISS III (2.0 [1.1, 3.7]) and a high lactate dehydrogenase level (3.4 [1.1, 10.3]).

Comment (KR): This large Danish study reminds us about a not uncommon mode of presentation in MM. In fact a reasonable number of patients are diagnosed following a blood stream infection, such as in pneumococcal sepsis, and it is seen more commonly in advanced stage disease.

Reference: Eur J Haematol 2018;101:21–7
Abstract

Independent commentary by Dr Ken Romeril, FRACP, FRCPA Haematologist specialising in malignant haematology, Wellington Hospital. He trained in Christchurch, Sydney and Southampton, and is currently at the Wellington Blood and Cancer Centre and Aotea Laboratory. Ken has a particular interest in translational myeloma research and genetics. He is involved in clinical trials, is the current Chair of Myeloma New Zealand and a former chair of the ALLG Myeloma Sub-Committee.

Independent commentary by Dr David Simpson, MBChB, FRACP, FRCPA, Consultant Haematologist North Shore Hospital. His interests are in malignant haematology. He qualified and specialised in Auckland and had postgraduate training in Vancouver and Toronto. He was Assistant Professor of Bone Marrow Transplant at Rush Cancer Institute in Chicago. He has first authored a number of journal articles, reviews, abstracts, and a textbook chapter. He is active in clinical research. David is also a member of the Pharmacy and Therapeutics Committee at North Shore Hospital and the Tender Subcommittee of PHARMAC.

Bortezomib maintenance therapy in transplant-ineligible myeloma patients who plateaued after bortezomib-based induction therapy

Authors: Isoda A et al., for the Kanshinetsu Multiple Myeloma Study Group

Summary: These researchers assessed 1 year of biweekly bortezomib maintenance therapy in 36 evaluable transplant-ineligible patients with MM who had plateaued after bortezomib-based induction therapy in a phase 2 trial. During induction, the ORR was 61%, with a stringent CR rate of 6%, a CR rate of 6%, a VGPR rate of 17% and a PR rate of 33%. Bortezomib maintenance was started in 20 patients who had achieved the plateau phase. For the induction and maintenance phases, the respective median PFS durations were 13.8 months and 10.7 months. No grade ≥2 peripheral neuropathy was seen during maintenance therapy, but nor did the quality of response improve.

Comment (KR): This paper is quite relevant to our local practice, as often our transplant-ineligible patients may go on to get five cycles of bortezomib-based therapy, as in CyBorD, which is 20 doses. In this paper, the patients got an additional 26 doses after autologous SCT. However, the researchers found that this approach was not adequate in this group. It is hard to know what to make of these results, but it is becoming clear that melphalan-based autologous SCT confers better results, if it can be delivered.

Reference: Int J Hematol 2018;108:39–46
Abstract

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A prospective phase II study of low dose lenalidomide plus dexamethasone in patients with newly diagnosed polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome

Authors: Li J et al.

Summary: Forty-one patients with newly diagnosed POEMS syndrome were treated with 12 cycles of low-dose (10mg) lenalidomide plus dexamethasone in this phase 2 trial. The complete haematological response rate was 46%, the neurological response rate was 95%, the median serum VEGF (vascular endothelial growth factor) level fell from 5155 to 832 pg/mL, with an overall VEGF response rate of 83%, and the median time to response was 2 months, with a mean VEGF level reduction of 43% after the first month. The treatment was also associated with substantial relief of extravascular volume overload, organomegaly and pulmonary hypertension. There were no treatment-related deaths and no participants experienced lenalidomide-related grade ≥3 adverse events. After a median of 34 months of follow-up, the median OS and PFS durations had not been reached, and the respective estimated 3-year OS and PFS rates were 90% and 75%.

Comment (DS): POEMS is a monoclonal lambda plasma cell disorder. By mechanisms that are as yet unclear, the monoclonal plasma cells induce high levels of VEGF and are associated with a clinical spectrum of side effects including neuropathy. Treating the plasma cell disorder ameliorates symptoms, and the plasma cells seem to respond to the same treatments that are effective for myeloma. Thalidomide can cause issues due to the neuropathy, as can bortezomib, although to a lesser degree. Experience with the non-neurotoxic proteasome inhibitors carfilzomib and ixazomib is limited, although anecdotally carfilzomib seems effective. Lenalidomide is an attractive choice of treatment. This phase 2 trial of 41 patients shows the treatment works in most, but the depth of response seems suboptimal. The dose of lenalidomide used was only 10mg; adding a proteasome inhibitor may prove more effective as it does in myeloma. I am sure daratumumab probably works as well.

Reference: Am J Hematol 2018;93:803–9
Abstract

The presence of large focal lesions is a strong independent prognostic factor in multiple myeloma

Authors: Rasche L et al.

Summary: The prognostic value of focal lesion size in MM was explored in 404 transplant-eligible, newly diagnosed patients. The presence of multiple large focal lesions, on diffusion-weighted MRI with background suppression, was found to be a strong prognostic factor. PFS and OS durations were poor (respective medians 2.3 and 3.6 years) in patients with ≥3 large focal lesions with a product of the perpendicular diameters of >5cm^2. This pattern, which was evident in 13.8% of the patients, was independent of the Revised International Staging System, gene expression profiling-based risk score, gain(1q) and extramedullary disease (respective adjusted HRs for PFS and OS of 2.7 and 2.2). Adjustment for focal lesion size resulted in loss of the negative impact of number of focal lesions on outcome.

Comment (DS): This trial shows that size does matter. Patients with at least three lesions with a product of perpendicular diameters of >5cm conferred poor prognosis independently of other risk scores. The theory is that the discrete lesions are a marker of clonal heterogeneity representing an unstable genome. The technique used to assess the lesions was DWIBS (diffusion-weighted whole-body imaging with background body signal suppression) MRI, a technique used in NZ. This study does not shed light on how to deal with these patients, but it seems a simple factor to factor in when discussing prognosis.

Reference: Blood 2018;132:59–66
Abstract

A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma

Authors: O'Donnell EK et al.

Summary: Fifty-three transplant-ineligible patients with MM received nine 35-day cycles of oral lenalidomide 15mg on days 1–21, subcutaneous bortezomib 1.3 mg/m^2 on days 1, 8, 15 and 22 and oral dexamethasone 20mg on the day of and day after bortezomib, followed by six consolidation cycles of lenalidomide and bortezomib. The ORR (primary objective) was 86%, the VGPR or better rate was 66%, median PFS duration was 35.1 months and median OS duration was not reached at median follow-up of 30 months. The peripheral neuropathy rate was 62%, but only one participant experienced grade 3 symptoms.

Comment (DS): The best initial chemotherapy for myeloma is a proteasome inhibitor, an immunomodulatory drug and a steroid, unless you add daratumumab. This trial used 'RVD lite' in transplant-ineligible patients. Despite the lower lenalidomide dose, the response rate (86%), VGPR rate (66%) after the first four cycles, and PFS (35 months) were better than the FIRST trial of lenalidomide and dexamethasone alone (PFS 25.5 months). It also beats VMP and KMP as used in the CLARION trial. I am not sure if a 35-day cycle, 1.3 mg/m^2 bortezomib dose and steroid dose regimen in the <75-year cohort are optimal, but this regimen is deliverable in older patients and should be considered the standard against which other options are compared.

Reference: Br J Haematol 2018;182:222–30
Abstract

T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma

Authors: Brudno JN et al.

Summary: This report details the first in-human clinical trial of genetically modified CAR (chimeric antigen receptor) T-cells expressing BCMA (B-cell maturation antigen) to target plasma cells in patients with MM. Sixteen patients who had received a median 9.5 prior lines of therapy received a conditioning chemotherapy regimen of cyclophosphamide and fludarabine followed by 9×10^6 CAR-BCMA T-cells/kg (T-cells transduced with a γ-retroviral vector encoding CAR-BCMA). The ORR was 81% and the median event-free survival duration was 31 weeks. Responses included eradication of extensive bone marrow myeloma.

Comment (DS): BCMA is getting a lot of attention as it is an antigen expressed on plasma cells, a few B-cells and little else. Toxin carrying anti-BCMA antibodies show good activity in myeloma. This trial used this antigen to target CAR T-cells to the myeloma cells of patients with few other options. The patients had a median of 9.5 (range 3 to a heroic 19) lines of therapy before protocol enrolment. Cytokine-release syndrome was severe in initial patients with a high marrow burden of disease, prompting a protocol amendment. However, the treatment was of benefit to most patients, although PFS was short at 31 weeks. This is a promising area of pursuit, but it needs more refinement to improve durability and safety to allow its use in patients with better prospects.

Reference: J Clin Oncol 2018;36:2267–80
Abstract

Loss of heterozygosity as a marker of homologous repair deficiency in multiple myeloma: a role for PARP inhibition?

Authors: Pawlyn C et al.

Summary: To explore the hypothesis that homologous recombination deficiency-related loss of heterozygosity can be detected in patients with MM, thereby supporting a role for PARP inhibition in managing MM, these researchers used data from targeted next-generation sequencing studies to analyse such loss of heterozygosity in patients with monoclonal gammopathy of undetermined significance (n=7), smouldering MM (n=30), newly diagnosed MM (n=71), treated MM (n=64) and relapsed MM (n=234). They found that homologous recombination deficiency-related loss of heterozygosity increased as disease progressed, and its extent correlated with high-risk disease markers. In the relapsed MM group, patients with homologous recombination deficiency-related loss of heterozygosity above the third quartile had significantly worse PFS and OS than those with lower levels (p<0.001). Mutations in key homologous recombination genes were seen in some, but not all, cases with an excess of homologous recombination deficiency-related loss of heterozygosity.

Comment (DS): Myeloma cells can have unstable genomes, and this is associated with poor prognosis. In part this can be due to defects in the repair machinery (homologous recombination deficiency) for double-strand DNA breaks. Double stranded breaks often start as a single-strand break, and these are repaired by PARP. Cells with disabled repair are prone to loss of heterozygosity, but vulnerable to lethal defects if PARP is inhibited, leading to overwhelming tumour DNA damage. PARP inhibitors have shown activity in a number of cancers associated with loss of heterozygosity. This paper explored the prevalence of this in myeloma patients and confirmed high rates in poor-risk relapsed myeloma, opening the door to trials using PARP inhibitors in these patients.

Reference: Leukemia 2018;32:1561–6
Abstract