Multiple Myeloma RESEARCH REVIEW™

Making Education Easy

Issue 34 – 2020

In this issue:

Abbreviations used in this issue

BCMA = B-cell maturation antigen
BITE = bispecific T-cell engager
CR = complete response
FISH = fluorescence *in situ* hybridisation
HR = hazard ratio
ISS = International Staging System
MM = multiple myeloma
MRD = minimal residual disease
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
PI = proteasome inhibitor
SCT = stem-cell transplantation

Welcome to issue 34 of Multiple Myeloma Research Review.

The t(14;16) translocation is present in only a small proportion of patients with newly diagnosed MM, but has been associated with adverse outcomes. The first paper in this issue describes the characteristics and outcomes for the largest reported cohort of such patients to date. Local research is included in the form of an evaluation of the impact of age, ethnicity and socioeconomic deprivation among NZ patients in the novel antimyeloma agent era. There is also research reporting that mutations in the genes for immunomodulatory agent and PI targets do not appear to be the main reason for resistance to these agents in MM, instead differential yet converging evolution of subclones is implicated. This issue concludes with a phase 2 trial of ibrutinib combined with bortezomib and dexamethasone for relapsed/refractory MM reporting that although clinical responses were seen, toxicity was an issue.

We hope you enjoy this update in MM research. We welcome any feedback or suggestions you wish to send us.

Kind regards,

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A multicenter retrospective study of 223 patients with t(14;16) in multiple myeloma

Authors: Goldman-Mazur S et al.

Summary: Characteristics and outcomes were described for a real-world retrospective cohort of 223 patients from 25 centres with t(14;16) MM. Renal impairment at presentation was recorded for 24% of the patients, and 56% had haemoglobin levels <10 g/dL at presentation. First-line therapy was an immunomodulatory drug plus PI combination for 35% of the patients, and 42% underwent autologous SCT. After median follow-up of 4.1 years, the respective median PFS and OS durations from first-line therapy were 2.1 years and 4.1 years. Age >60 years and revised ISS score 3 vs. 2 were significant predictors of worse OS (respective HRs 1.65 [95% CI 1.05, 2.58] and 2.59 [1.59, 4.24]).

Comment (KR): This paper was of interest to me because my personal experience with this uncommon translocation has not been good, and several patients have had very poor outcomes with survivals of only 6–9 months and they tended to be bortezomib-resistant. This study cohort was the largest ever accrued because it was multicentre. The OS of 4.1 years was much better than expected, but still well short of the usual OS that is currently being achieved in myeloma patients with novel agents.

Reference: Am J Hematol 2020;95:503–9
Abstract

Independent commentary by Dr Ken Romeril, FRACP, FRCPA

Ken is a haematologist specialising in malignant haematology. He trained in Christchurch, Sydney and Southampton, and is currently at the Bowen Icon Cancer Centre. 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, a former chair of the ALLG Myeloma Sub-Committee, and is the NZ representative on the International Myeloma Working Group, which has around 200 members.

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

Daratumumab, lenalidomide, bortezomib, & dexamethasone for transplant-eligible newly diagnosed multiple myeloma

Authors: Voorhees PM et al.

Summary: Autologous SCT-eligible patients with newly diagnosed MM were randomised to a standard regimen of four cycles of RVD (lenalidomide, bortezomib dexamethasone) induction, autologous SCT, two cycles of RVD consolidation and 26 cycles of lenalidomide maintenance with (n=103) or without (n=103) the addition of daratumumab (induction, consolidation and maintenance) in the phase 2 GRIFFIN trial. The addition of daratumumab to RVD was associated with a significantly greater stringent CR rate at the end of consolidation treatment (42.4% vs. 32.0%; odds ratio 1.57 [95% CI 0.87, 2.82]) and at median follow-up of 22.1 months (62.6% vs. 45.4% [p=0.0177]), and a greater MRD negativity rate (51.0% vs. 20.4% [p<0.0001]). The respective 24-month PFS rates in the RVD and RVD plus daratumumab arms were 89.8% and 95.8%. There was a greater incidence of grade 3–4 haematological adverse events, but not infections, in the RVD plus daratumumab group.

Comment (KR): This important study looked at the addition of daratumumab to RVD, which is currently considered the standard induction therapy in many countries but not in NZ at present. The daratumumab arm yielded very impressive stringent CR rates that continued to improve over time, as well as the rates of MRD negativity. The 24-month PFS rate of 95.8% in the daratumumab plus RVD arm was very impressive. Daratumumab is clearly an important addition to initial induction therapy and this is where it is most active. When it is being used locally at the moment as a single agent in heavily treated individuals, then the responses tend to be short-lived.

Reference: Blood; Published online April 23, 2020
Abstract

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Impact of age, sex, ethnicity, socio-economic deprivation and novel pharmaceuticals on the overall survival of patients with multiple myeloma in New Zealand

Authors: Chan HSH & Milne RJ

Summary: Incidences, prevalences and survival of NZ patients diagnosed with MM over the 2004–2016 period were reported. Over this time, there were increases in the crude incidence rate (from 5.42 to 8.47 per 100,000) and the age-standardised rate (from 4.01 to 5.28 per 100,000). At Dec 2016, the estimated prevalence was 37.8 per 100,000. Median OS duration increased between the 2004–2007 and 2012–2016 periods, from 34.8 to 50.7 months. Among patients aged >70 years, median OS duration increased from 19.4 to 28.6 months after bortezomib became publicly funded. For patients aged ≤70 years who did not undergo autologous SCT, median OS duration increased from 49.1 to 62.7 months, but there was no significant change for those who did not undergo autologous SCT. No increase in survival was seen for Māori/Pasifika people or those in the most deprived quintile after bortezomib became funded.

Comment (KR): This paper by Richard Milne and Henry Chan came about as a result of a restricted grant provided through Myeloma New Zealand to provide data for the extensive Burden of Disease report launched at Parliament in June 2019. It was a unique document and is the most detailed analysis on any type of cancer ever done in NZ. This paper in the Br J Haematol looks at some aspects of the data analysed and highlights the increased crude incidence rate that we have all noticed from our clinic lists. The fact that the median OS rate for patients aged over 70 years with the introduction of bortezomib use was significant emphasises that it is important to try and offer this drug to the older population. The novel agents have also had an impact on median OS in people aged under 70 years who do not get an autologous SCT. This paper and also the BOD report have also shown the adverse prognostic factors of Māori and Pasifika ethnicity. There is emerging evidence from a paper from Hilary Blacklock with data from the Monash Registry that the Māori population have an increased incidence of adverse FISH high-risk signatures, which could explain some of the poorer outcomes.

Reference: Br J Haematol 2020;188:692–700
Abstract

Venous thromboembolism risk with contemporary lenalidomide-based regimens despite thromboprophylaxis in multiple myeloma

Authors: Chakraborty R et al.

Summary: This was a systematic review with meta-analysis of 51 phase 1–3 clinical trials (n=9069) reporting the incidence of VTE (venous thromboembolism) in patients with newly diagnosed, relapsed or refractory MM treated with lenalidomide-based regimens and receiving thromboprophylaxis (mostly with aspirin, low-molecular-weight heparin or warfarin). In patients with median treatment durations of 2–34 cycles, the estimated pooled incidence of VTE was 6.2% or 1.2 events per 100 patient-cycles. The VTE event rate was lower in patients receiving lenalidomide and low-dose dexamethasone treatment compared with lenalidomide with low-dose dexamethasone and a PI (0.2 vs. 1.3 per 100 patient-cycles).

Comment (KR): The increased risk of VTE in lenalidomide-based regimens has been known for some time, but the approach to thromboprophylaxis has been varied with no standard approach. A risk-based strategy has been advocated taking into account previous thrombotic history, obesity, etc. The thrombotic risk appears to be higher during the induction phase and in the relapsed/refractory group. Thromboprophylaxis is not indicated in the maintenance setting, but if there is concomitant use of combination therapy with steroids and a PI, it would be worth considering.

Reference: Cancer 2020;126:1640–50
Abstract

The relative importance of factors predicting outcome for myeloma patients at different ages

Authors: Pawlyn C et al.

Summary: These authors report the relative contributions of disease and patient factors to MM outcomes relative to patient age. Based on analysis of 3894 patients with newly diagnosed MM enrolled in the phase 3 Myeloma XI clinical trial, they found that age changed the relative impact of different factors on survival. In contrast to younger patients, elderly patients had reduced PFS and OS as well as decreased renal function. The impact of molecular risk factors such as chromosomal abnormalities was more pronounced in younger patients, with survival in elderly patients determined more by physical functioning at diagnosis than degree of myeloma disease. Performance status was uniformly a predictor of outcome across all ages.

Comment (KR): This very large MRC trial looked at the effect mainly of lenalidomide maintenance, but the authors have drilled down in this paper to look at such variables as the revised ISS and also the molecular risk that occurs with age. The median age of the patients in the trial was 68 years, and the authors found that patients over the age of 80 years had particularly bad outcomes. The patients had an OS of only 40% compared with 80% in patients aged <60 years. They observed that high-risk signatures like t(4;14) were only found in 5% of older patients, which is very similar to my own studies in the older group, but 1q amplification was more common. Also renal function deterioration was a significant predictor of poor outcome. These data are of interest because often older patients are excluded from clinical trials.

Reference: Leukemia 2020;34:604–12
Abstract

NZMA New Zealand Medical Association

Independent commentary by Dr Henry Chan

Dr Henry Chan is a consultant haematologist at North Shore Hospital in Auckland. Following completion of specialist training in clinical and laboratory haematology, he completed a clinical fellowship in multiple myeloma and lymphoma at Princess Margaret Cancer Centre in Toronto. He is currently actively involved in clinical research, registrar teaching and patient education.

Biological and clinical significance of dysplastic hematopoiesis in patients with newly-diagnosed multiple myeloma

Authors: Da Silva Maia CA et al.

Summary: Prospective screening of bone marrow samples from 285 PETHEMA/GEM2012MENOS65 trial participants revealed that 33 exhibited MDS-associated phenotypic alterations. In a group of 67 patients, targeted sequencing revealed that clonal haematopoiesis was detected in a greater proportion of patients with versus without MDS-associated phenotypic alterations (50% vs. 22%); the most frequently mutated genes were *TET2* and *NRAS*. In 80% of 86 evaluable patients, MDS-associated phenotypic alterations persisted (if present at baseline) or remained absent (if absent at baseline) after autologous SCT. It was infrequent for MDS-associated mutations to emerge after high-dose therapy. Patients with MDS-associated phenotypic alterations had altered haematopoiesis and regulatory T-cell distribution in the tumour microenvironment. The presence of monocytic MDS-associated phenotypic alterations at diagnosis was associated with increased risk of haematological toxicity and was independently associated with inferior PFS and OS (respective HRs 1.5 and 1.7 [p values 0.02 and 0.01]).

Comment (HC): After analysing samples from various prospective studies, this Spanish group found a significant number of patients with a myelodysplastic phenotype on EuroFlow at the time of diagnosis (11.6%). Clinically, these patients were generally older, had a greater disease burden and experienced more treatment-related neutropenia and anaemia. Biologically, these patients were found to have a higher frequency of clonal haematopoiesis, expanded myeloid/erythroid precursors, reduced lymphoid precursors, maturation arrest in the immature neutrophil stages, reduced γ-δ-naïve T-cells and expansion of CCR7-negative regulatory T-cells. Interesting as these data may be, the causality of many of these findings remains uncertain. Could the myelodysplastic phenotype be just a marker of clonal haematopoiesis that has perpetuated the expansion of the malignant plasma cell clone via immune dysregulation? What was clinically interesting is their observation of an inferior survival associated with myelodysplastic phenotype that was independent of ISS, lactate dehydrogenase level and FISH in those who did not have immunomodulatory drug maintenance. This may be less relevant now for transplant-eligible patients with lenalidomide maintenance becoming the standard of care, but this may potentially be useful in patients who are transplant-ineligible if continuous immunomodulatory drug-based treatment becomes available.

Reference: Blood; Published online April 16, 2020
Abstract

Integrative analysis of the genomic and transcriptomic landscape of double-refractory multiple myeloma

Authors: Zicchedda B et al.

Summary: This research included 42 patients with MM refractory to both PIs and immunomodulatory agents – 40 underwent whole-exome sequencing and 27 underwent RNA sequencing. More mutations including subclonal mutations were detected than had been identified at diagnosis, and the mutational landscape differed from that previously described for samples taken at diagnosis. The most frequently inactivated pathway was TP53 (45% of patients), but point mutations in genes associated with immunomodulatory drug resistance were rare and always subclonal. Refractory patients exhibited a unique mutational signature linked to alkylating agent exposure. RNA sequencing revealed that neither treatment nor mutations influenced clustering, which was influenced by karyotypic events. A cluster with both amp(1q) and del(13) characterised by *CCND2* upregulation and also overexpression of *MCL1* was described, representing a novel target for experimental treatments. High-risk features were detected in 65% of the patients; however, survival was predicted only by 1q amplification.

Comment (HC): Despite focusing on a cohort of patients who were resistant to PIs and immunomodulatory drugs, the authors were unable to detect any specific pattern to fully explain the mechanism of drug resistance. Although abnormalities in the immunomodulatory drug resistance and proteasome subunit genes were found, they were rare and only found in the subclones. Meanwhile, gene expression analysis also failed to show a significant difference in expression levels of genes associated with resistance to PIs or immunomodulatory drugs. They did find enrichment of 1q amplification and biallelic inactivation of the TP53 pathway. However, how these changes have led to drug resistance remain elusive. It is therefore assumed that the development of drug resistance is the result of convergent evolution, where each subclone acquires its ability via different mechanisms. This highlights the difficulties in finding a single druggable target to overcome treatment resistance and the importance of using a multidrug regimen, especially in patients with advanced disease.

Reference: Blood Adv 2020;4:830–44
Abstract

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Anti-B-cell maturation antigen BiTE molecule AMG 420 induces responses in multiple myeloma

Authors: Topp MS et al.

Summary: In this phase 1, first-in-human study, 42 patients with relapsed/refractory MM received up to ten 6-week cycles of dose-escalated intravenous AMG 420 (an anti-BCMA BITE [bispecific T-cell engager]) 0.2–800 µg/day by 4-week continuous infusions; a median of one cycle was given with only three participants receiving the full 10 cycles. Discontinuations were due to disease progression (n=25), adverse events (n=7), death (n=4) and withdrawn consent (n=1). Two participants were still on treatment at the time of reporting. The serious adverse event rate was 48%, and the response rate was 31%. At the maximum tolerated dosage (400 µg/day), the ORR was 70%, including five MRD-negative CRs, one partial response and one very good partial response. All responses at the maximum tolerated dose were observed during cycle one, and responses lasted for a median of 9 months.

Comment (HC): This is a first-in-human phase 1 study on a BITE that binds to CD3 and BCMA. The high rate of serious adverse events (48%) is concerning, with 33% of the patients experiencing infections (mostly grade 3, but there were two deaths) and five patients developing liver impairment (including one death). Polyneuropathy also appears to be increased, while cytokine-release syndrome was mostly mild and manageable. The ORR of 70% amongst the ten patients who received 400 µg/day in the dose-escalation and expansion cohorts is not that dissimilar to other treatments that target BCMA (e.g. belantamab mafodotin and anti-BCMA CAR [chimeric antigen receptor] T-cell therapy). However, due to the size of the molecule, the treatment is given as a continuous infusion over 4 weeks in a 6-weekly cycle. This, in conjunction with the toxicities, may limit the widespread adoption of this drug in clinical practice in the future. A half-life extended anti-BCMA BITE that can be administered once weekly (AMG701) is currently being trialled, and hopefully this will have a better toxicity profile.

Reference: J Clin Oncol 2020;38:775–83
Abstract

First-line therapy with either bortezomib-melphalan-prednisone or lenalidomide-dexamethasone followed by lenalidomide for transplant-ineligible multiple myeloma patients

Authors: Larocca A et al.

Summary: Pooled data from the GIMEMA-MM-03-05 and EMN01 trials, both of which randomised patients with newly diagnosed MM to receive bortezomib, melphalan, prednisone (VMP; n=257) or lenalidomide plus dexamethasone induction followed by lenalidomide maintenance (Rd-R; n=217), were included in subgroup analyses. PFS and OS did not differ between the two treatments among standard-risk participants, but high-risk VMP recipients had lower probabilities of progression and death than Rd-R recipients (respective HRs 0.54 and 0.73). Standard-risk participants aged >75 years derived less benefit from VMP than from Rd-R (respective HRs for PFS and OS, 0.96 and 1.81).

Comment (HC): Recently, the regimen of Rd-R, where patients receive lenalidomide monotherapy following an initial phase of Rd induction, is gaining popularity. However, similar to other lenalidomide-based regimens, this has never been compared head-to-head with an established bortezomib-based regimen in the frontline setting for elderly patients. The results from these two European studies show that VMP and Rd-R are equivalent in most standard-risk patients. However, VMP appears to be better for patients with high-risk cytogenetics, while there is a trend for better OS for Rd-R in those older than 75 years. The results from this study highlight the need for a more tailored approach for transplant-ineligible patients and the importance of cytogenetics even in this patient group. The previous one-size-fits-all approach for transplant-ineligible patients is outdated, and more research is needed for a risk- and frailty-adapted approach.

Reference: Haematologica 2020;105:1074–80
Abstract

A phase 2 study of ibrutinib in combination with bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma

Authors: Hajek R et al.

Summary: Patients with relapsed/refractory MM who had received 1–3 prior therapies received an ibrutinib, bortezomib and dexamethasone combination regimen in this phase 2 open-label trial; 74/76 enrolled participants received ≥1 dose of the study regimen. Median follow-up was 19.6 months, after which the median PFS duration was 8.5 months and the median OS duration had not been reached. The ORR was 57% with a median response duration of 9.5 months. The grade 3–4 adverse event rate was 73% and the fatal adverse event rate was 15%. Major haemorrhages occurred in 5% of participants, resulting in one death. Enrolment into the trial was suspended.

Comment (HC): Despite preclinical data demonstrating the increased expression of Bruton's tyrosine kinase in myeloma cells and possible association with drug resistance via increased expression of efflux pumps, the results from the majority of the early-phase studies on ibrutinib in myeloma have been disappointing. Gastrointestinal toxicity appears to be common across the various ibrutinib combinations (Jamil F *et al.* Blood 2018;132[Suppl 1]:1948 – ASH 2018), and it is no exception with bortezomib in this study. The rate of infection in this study is unacceptably high, including eight fatal infections. In view of the biology and drug action, the increased risk of infection, especially those of the respiratory tract, may be the result of marked hypogammaglobulinaemia induced by the treatment. Unfortunately, the authors have not presented any data on the participants' immunoglobulin levels, leaving one to wonder whether regular immunoglobulin replacement could have potentially improved the safety profile of this combination.

Reference: Eur J Haematol 2020;104:435–42
Abstract