Multiple Myeloma Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ASCT = autologous stem cell transplantation
BTZ = bortezomib
DWS = diffusion weighted sequences
^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/CT
HDM = high-dose melphalan
HR = hazard ratio
HS = heparin sulfate
IMiD = immunomodulatory drugs
MM = multiple myeloma
MMAS = 4-item Morisky Medication Adherence Scale
ORR = Objective response rate
OS = overall survival
PFS = progression-free survival
PI = proteasome inhibitors
PR = partial response
QoL = quality of life
RR = relapsed or refractory
SPM = second primary malignancies
WBCT = whole body computed tomography
WBMRI = whole body magnetic resonance imaging
WM = Waldenstrom macroglobulinemia

Welcome to the April edition of Multiple Myeloma Research Review.

In this month's edition we begin with long term follow up data from the HOVON group on transplant outcomes in the era of routine proteasome inhibitor use and we also focus on ASCT in the difficult subgroup of MM patients with the t(4;14) translocation. In addition, we examine data from the Swedish Myeloma registry as well as the latest ASCO guidelines on the use of bone modifying agents. We complete this month's review with a study highlighting the economic disadvantage experienced by MM patients and we review 2 promising new examples of therapeutic targeting in MM.

As always I hope you find the content of this month's review educationally rewarding and of benefit to your practice and I look forward to your feedback.

Kind Regards,

Professor Philip Campbell

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Comparison of whole body magnetic resonance imaging (WBMRI) to whole body computed tomography (WBCT) or ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) in patients with myeloma

Authors: Gariani J et al.

Summary: These UK researchers performed a systematic review and attempted a meta-analysis of European (German, Italian, French, British and Irish) single-centre studies that compared the diagnostic performance of 3 high-performance cross-sectional imaging modalities for the initial assessment of myeloma. The aim was to compare whole body MRI (WBMRI) including diffusion weighted sequences (DWI) to whole body computed tomography (WBCT) and ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT). A search of databases including PubMED and EMBASE yielded 2,857 articles that were screened to exclude case reports, case series' of less than 10 patients, narrative reviews, letters and conference abstracts. 6 articles (n = 147) with patients 39-88 years of age (including both newly diagnosed and relapsed) were suitable for review. Methodological heterogeneity and a lack of independent reference standards rendered meta-analysis impossible. A comparison between WBMRI and ^{18}F-FDG PET/CT found WBMRI to be more sensitive at detecting lesions (68-100% vs 47-100%) but less specific (37-83% vs 62- 85.7%). The authors concluded that there is currently a lack of high quality research in imaging for MM diagnosis and this may impact clinical management.

Comment: This proved to be an ambitious but ultimately unsuccessful attempt to determine the cross-sectional imaging modality of choice at diagnosis through a comprehensive literature review and meta-analysis. Despite an initial search of almost 3000 papers, only 6 papers were considered suitable for review. All 3 imaging techniques are increasingly available and used by Australian haematologists and the technique used may depend on where the patient is in the natural history of their disease. At diagnosis the axial skeleton will be the main site of disease in more than 90% of patients whereas extra-medullary involvement may be a feature in ultra-high risk or heavily pre-treated patients. Just as standardisation of imaging protocols and independent central review of CT/PET has been so informative in lymphoma, future prospective studies of myeloma imaging will also need to be as methodologically rigorous.

Reference: Critical Reviews in Oncology Hematology 2018;124: 66-72
Abstract

Bortezomib before and after high-dose therapy in myeloma

Authors: Goldschmidt H et al.

Summary: This report presents the long-term follow-up and data on second primary malignancies (SPM) from the phase III HOVON-65/GMMG-HD4 trial that investigated the efficacy of bortezomib (BTZ) during induction and maintenance on progression-free survival (PFS) in MM patients. The trial randomised 613 patients to Arm A (induction treatment with classic cytotoxic agent VAD [vincristine, doxorubicin & dexamethasone] followed by high-dose melphalan (HDM) 200mg/m^2 and autologous stem cell transplantation (ASCT) and maintenance with thalidomide 50mg daily for 2 years) or Arm B (induction treatment with PAD [bortezomib, doxorubicin & dexamethasone] followed by HDM and ASCT and maintenance with BTZ 1.3mg/m^2 2-weekly for 2 years). The trial concluded that BTZ during induction and maintenance achieved superior PFS. At 96- months median follow-up, Arm B (BTZ induction and maintenance) had significantly prolonged PFS (hazard ratio (HR)=0.76, 95% confidence interval (95% CI) of 0.65–0.89, *P*=0.001) compared to Arm A. The 2 arms had similar overall survival (OS) (HR=0.89, 95% CI: 0.74–1.08, *P*=0.24), OS from first relapse/progression (HR=1.02, *P*=0.85) and incidence of SPM (7% each, *P*=0.73). At long-term follow-up, BTZ induction and maintenance treatment continued to abrogate the negative prognostic effects on PFS and OS of cytogenetic aberration deletion 17p13 and renal impairment at baseline (serum creatinine >2 mg dl^{-1}). The authors concluded that BTZ induction and maintenance treatment resulted in increased survival rates at long term follow-up compared to classic cytotoxic agents and thalidomide maintenance without an increased risk of SPM.

Comment: This HOVON study, first published 6 years ago, established bortezomib-based induction and maintenance therapy as the standard of care in transplant-eligible newly diagnosed MM patients. The benefit of this proteasome inhibitors (PI)-based approach was particularly evident in adverse prognosis patients with renal impairment at baseline and 17p deletion. With so many treatment options at relapse, long-term observations from well designed, randomised studies in MM have an important role in demonstrating sustainability of survival benefit without late sequelae, such as second malignancies. Although there was no overall survival benefit in this study at 8 years follow up due to the effectiveness of salvage therapy, PFS improvement was sustained and the incidence of SPMs was similar in both arms. The anthracycline-containing PAD regimen used in this study has largely been replaced by the upfront use of PI and immunomodulatory drugs (IMiD) combinations and so long term observation of these patients will assume equal importance in future.

Reference: Leukemia 2018;32:383-90
Abstract

Single-center experience in treating patients with t(4;14) multiple myeloma with and without planned frontline autologous stem cell transplantation

Authors: Chan H et al.

Summary: This Canadian retrospective study analysed 75 tertiary-centre translocation t(4;14) MM patients to assess real world outcomes. After 41-month median follow-up, the median PFS was 33.5 months and OS 69.6 months. PFS was higher in patients who received up-front ASCT compared to chemotherapy alone (median PFS, 24.2 months vs. 41.5 months; *P* = .01). A significantly lower OS was noted in patients co-harbouring del(19p) with t(4;14) (HR, 4.0; 95% CI, 1.4-11.4).

Comment: Historically MM patients harbouring the t (4;14) translocation have poor outcomes. Characteristically these patients experience a prompt response to therapy followed by early disease progression following ASCT due to alkylator resistance. However contemporary frontline use of bortezomib-based treatment appears to overcome the prognostic impact of t(4;14) to the point where the MAYO Clinic's mSMART classification now stratifies these patients as intermediate rather than high risk in the current treatment era. This retrospective Canadian study of 75 transplant-eligible patients also suggests patients are doing better with bortezomib, although in their experience, hypercalcaemia and presence of the 17p deletion have an adverse effect on prognosis. In contrast to the IFM99 trials, haemoglobin and B2micorglobin had no prognostic significance on multivariable analysis. The authors also observed a trend towards superior PFS at 3 years in the 23 patients receiving tandem ASCT (39% v 67%; p=0.1). There are very few publications focusing on outcomes in cohorts of t(4;14) patients alone and this study provides useful data in the era of routine novel agent use. Although these patients are doing better, t(4;14) patients remain high risk and further studies are required to determine whether survival curves can be shifted further to the right with new monoclonal antibody combinations.

Reference: Clinical Lymphoma, Myeloma & Leukemia 2018;18(3):225-34
Abstract

Melphalan 140 mg/m^2 or 200 mg/m^2 for autologous transplantation in myeloma: results from the Collaboration to Collect Autologous Transplant Outcomes in Lymphoma and Myeloma (CALM) study

Authors: Auner H et al.

Summary: This report by the European Society for Blood and Marrow Transplantation Chronic Malignancies (EBMT) Working Party gives results from the retrospective, observational Collaboration to Collect Autologous Transplant Outcomes in Lymphoma and Myeloma study. The researchers used a series of Cox proportion-hazards models to analyse 1,964 single first single autologous transplantation episodes to determine the optimum pre- autologous hematopoietic stem cell transplantation conditioning dose of melphalan – 200mg/m^2 or 140 mg/m^2 for different groups of MM patients. There was no difference between melphalan dose groups (140 mg/m^2, *n*=245; 200mg/m^2, *n*=1,719) in OS, PFS (calculated using the Kaplan-Meier estimator), incidence of relapse or second primary malignancy rates (calculated by the proper non-parametric estimator for outcomes with competing risk). The only tested variable that influenced key transplant outcomes including OS and PFS on multivariable subgroup analysis was disease status at transplantation. Patients transplanted in less than partial response showed a better response to melphlan 200mg/m^2 whereas patients in very good partial or complete response had a higher OS with melphalan 140mg/m^2 dose.

Comment: Studies confirming the superiority of high dose melphalan and ASCT over conventional chemotherapy in MM have established Mel 200 as the conditioning regimen of choice. However, some studies demonstrate excess morbidity and mortality associated with Mel 200 dosing in older patients, particularly in those patients with renal impairment. This retrospective analysis of nearly 2000 patients from the EBMT set out to evaluate 'real world' outcomes in European MM patients transplanted between 2008 and 2012. Only 12% of the cohort received Mel140 and these patients tended to be older, have lower Karnofsky scores (median age 59 v 64; p=0.001 and 72% v 62%; p=0.002) and more significant renal impairment. Although there was no significant difference in OS or PFS between the 2 conditioning regimens, subgroup analysis suggested Mel140 transplants could be a safer alternative to Mel200 in those patients achieving excellent responses to induction therapy. As more patients currently achieve deeper responses to induction therapy, this paper suggests further investigation of the optimum melphalan dose prior to ASCT is warranted.

Reference: Haematologica 2018;103(3):514-21
Abstract

Outcome and survival of myeloma patients diagnosed 2008–2015. Real-world data on 4904 patients from the Swedish Myeloma Registry

Authors: Blimark C et al.

Summary: This study presents data on MM patients from the prospective, population-based Swedish Myeloma Registry to report real-world treatments and outcomes. Swedish MM patients (*n*= 4904, 97% coverage from the compulsory Swedish Cancer Registry) from 74 centres diagnosed in the 8-year period between 2008 (when the registry was established) and 2015 were included covering a time when newer drugs were implemented into standard practice. In the study period, treatment was guided by the British/Nordic treatment program for multiple myeloma (2005), and the Swedish 2010 National Guidelines (up-dated in 2013). At baseline, median age was 71-years, 24% of patients were ≥ 80 years of age and 28.3% of patients were < 65 years. The total crude incidence of myeloma was 7.0 cases per 100,000 inhabitants per year. 1-year follow up data was available for 92% (*n*=3558) of initial patients. 77% of patients < 66 years old received high-dose therapy with autologous stem cell transplantation. Over the study period the percent of patients receiving bortezomib, thalidomide and/or lenalidomide rose from 31% in 2008 to 81% in 2014. The median relative survival for active myeloma was 7.7 years for patients ≤ 65 years and 3.4 years in patients ≥ 66 years. Patients diagnosed more recently had a significantly higher survival, hazard ratio of 0.84 (95%CI: 0.77–0.92; *P*<0.05).

Comment: The Swedish Myeloma Registry was established in 2008 and this excellent summary of population-based data on disease and patient characteristics, treatment and outcome is the first report from the registry. The authors claim to have captured 97% of all Swedish myeloma diagnoses between 2008 and 2015 and this is reflected by the higher incidence of MM and median age at diagnosis than seen in other studies due to the more rigorous inclusion of older patients (72% were 65 years and older). In addition, all Swedish cancer patients are treated in the public hospital system providing the registry with powerful insight into access to care, uniformity of treatment and evolving patterns of care. As observed in other publications, increased use of novel agents resulted in improved response rates and outcomes, although somewhat surprisingly, depth of response (PR, VGPR or CR) did not result in significant differences in survival in younger MM patients (< 65 years). This is in contrast to many randomised studies and suggests the 'biological robustness' of these younger patients may enable continual and successful exposure to multiple lines of active therapy. Disease-specific registries of this size and coverage provide valuable 'real world' data for treating physicians, health authorities and regulatory agencies.

Reference: Haematologica 2018;103(3):506-13
Abstract

Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma

Authors: Raje N et al.

Summary: This international, double-blind, double-dummy, randomised, active-controlled, phase 3 study assessed the safety and efficacy of the monoclonal antibody denosumab in comparison to zoledronic for the prevention of skeletal-related events in MM patients. 1718 newly diagnosed adult patients (> 18 years of age) who had at least one documented lytic bone lesion were enrolled from 259 centres across 29 countries and randomised 1:1 to either subcutaneous denosumab 120mg or intravenous zoledronic acid 4mg every 4 weeks. Both groups received a placebo via the alternative route of administration and all patients received a first-line anti-myeloma therapy. At the primary end point of time to first skeletal-related event, denosumab was non-inferior to zoledronic acid (hazard ratio 0·98, 95% CI 0·85–1·14; $p_{non\text{-}inferiority}$=0·010). Some grade 3 or worse adverse events were noted including neutropenia, thrombocytopenia, anaemia and pneumonia but rates did not vary significantly between treatment groups. One treatment-related death occurred in the zoledronic acid group (cardiac arrest).

Comment: The RANKL inhibitor denosumab is a fully humanised monoclonal antibody that reduces the frequency and severity of skeletal-related events in patients with advanced solid tumours through inhibition of osteoclast function. This largest study to date directly comparing the 2 antiresorptive agents in MM, demonstrates denosumab to be non-inferior to zolendronic acid and to have a favourable safety profile as well as similar rates of ONJ. The subcutaneous administration route and lower incidence of renal toxicity makes it particularly attractive to MM patients, particularly when combined with oral treatment regimens in the community setting. This study did see increased PFS in denosumab-treated patients suggesting a direct anti-MM effect associated with RANKL targeting and goes some way towards reassuring physicians who may be reluctant to omit a bisphosphonate based on the clear disease-modification seen in the Myeloma IX trial some years ago.

Reference: Lancet Oncology 2018;19(3):370-81
Abstract

Role of bone-modifying agents in multiple myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update

Authors: Anderson K et al.

Summary: This American Society of Clinical Oncology Clinical Practice Guideline Update, published in 2017, focuses on the role of bone-modifying agents in MM. 35 studies (randomised controlled trials, systematic reviews, meta-analyses, clinical practice guidelines and observational studies) were identified from a literature search of the online databases PubMed and the Cochrane Library and contributed to the updated recommendations. The key recommendations for the prevention of skeletal-related events in MM patients (with or without imaging evidence of bone damage) are up to 2 years of treatment with either intravenous pamidronate (90mg over ≥ 2 hours) or either zoledronic acid (4mg over ≥ 15mins) or denosumab. For patients with renal impairment either denosumab or a reduced dose of pamidronate are recommended. Less frequent dosing schedules can be considered for patients with stable disease and treatment should be re-initiated at relapse. More information can be found at www.asco.org/hematologic-malignancies-guidelines and www.asco.org/guidelineswiki.

Comment: ASCO first published clinical practice guidelines on the use of bisphosphonates in MM in 2002, which were subsequently updated in 2007. This update is timely however, particularly as new agents such as denosumab have a much stronger evidence base in MM and deeper and more sustainable responses are now seen with modern therapy, questioning the optimum duration and dosing of these agents, which have a small but not insignificant risk of toxicity. The key points from this position paper relate to agent choice in renal impairment and duration of therapy. Pamidronate is recommended in MM patients with severe renal impairment (creatinine clearance < 30mls/min) and the authors recommend bone-targeting treatment should continue for up to 2 years in all MM patients with less frequent dosing schedules considered an option for patients with inactive, responsive or stable disease. Importantly, the paucity of data on the use of resorption markers in this setting led the panel to recommend against their routine use in MM. A lot has happened in the world of MM since 2007 and these updated guidelines are a welcome resource for physicians managing bony disease in MM.

Reference: Journal of Clinical Oncology 2018;36(8):812-18
Abstract

Multiple Myeloma Research Review™

Independent commentary by Philip Campbell

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Assessing the effect of adherence on patient-reported outcomes and out of pocket costs among patients with multiple myeloma

Authors: Gupta S et al.

Summary: This US cross-sectional study (n=162) utilised self-reported surveys to assess the real-world impact of MM on outcomes such as quality of life (QoL), healthcare resource usage, out of pocket costs and impairment of work productivity. They also investigated how patient-reported adherence impacted these outcomes. Online surveys including the Work Productivity and Activity Impairment questionnaire and Functional Assessment of Cancer Therapy–Multiple Myeloma (FACT-MM) were used and patients stratified according to their 4-item Morisky Medication Adherence Scale (MMAS-4) score. Descriptive statistics were calculated for all study variables. The mean adherence MMAS-4 score for oral medication users was 3.2 ± 1.1. QoL score for FACT-MM was 98.5 ± 29.3. MM patients had high work productivity impairment (57.3% ± 31.7%) and overall activity impairment (49.9% ± 29.5%). Mean out of pocket costs for 3 months was $709 ± $1307.30 with the greatest contributor being prescription medications. All measures of QoL were improved in patients who self-reported greater adherence on the MMAS-4.

Comment: The diagnosis and treatment of MM has been demonstrated in many studies to be associated with impaired quality of life but it also comes with a significant economic impact. As MM patients survive longer and transition through different lines of therapy, many of which are administered orally, treatment adherence becomes a potentially important driver of outcomes. This US study comprehensively addresses the economic burden facing MM patients as well as QoL. The authors found patients with higher adherence scores generally reported a lower burden than those with poor levels of treatment adherence. The data from this study lends support to efforts aimed at increasing treatment compliance through the use of nurse and pharmacist-led clinics as well as smart phone technology and apps.

Reference: Clinical Lymphoma, Myeloma & Leukemia 2018;18(3):210-18
Abstract

Safety and efficacy of selinexor in relapsed or refractory multiple myeloma and Waldenstrom macroglobulinemia

Authors: Chen C et al.

Summary: This report presents results for the first-in-class orally bioavailable selective inhibitor of nuclear export compound selinexor (KPT-330) in heavily pre-treated RR MM (≥ 3 lines of prior therapy including at least one alkylating agent, an IMiD, a PI and a steroid; median of 6 prior systemic therapies) and Waldenstrom macroglobulinemia (WM) patients from a multi-centre, phase 1 study in patients with advanced hematologic malignancies (n = 285). Based on MM xenograft mouse models that showed single-agent anti-myeloma cell activity of selinexor as well as augmentation of glucocorticoid (such as dexamethasone) activity, even in MM cells with resistance to GCs, selinexor was tested alone and in combination with dexamethasone. Between July 2012- September 2015, 84 patients (81 with MM and 3 with WM) were recruited. The study was divided into 2 sections. The dose escalation portion involved 25 patients who received daily oral selinexor at doses ranging from 3-60mg/m^2 at various schedules with or without 20mg dexamethasone. The maximum tolerated dose could not be determined. The most common adverse effects were cytopenia, fatigue and GI (nausea, anorexia, vomiting, weight loss). The dose-expansion phase compromised 59 MM patients who received twice-weekly 45 (n= 12) or 60 (n= 15) mg/m^2 selinexor (28- day cycle) with 20mg dexamethasone or a flat dose of 40 or 60mg selinexor (21-day cycle). Selinexor alone was shown to have a moderate clinical benefit with 4% of patients having a partial response (PR). Objective response rate (ORR>PR) was observed in 22% of combination selinexor/dexamethasone treated patients with all responses coming from the 45mg/m^2 combination group (50% ORR). It was concluded that 45mg/m^2 selinexor plus 20mg dexamethasone was the recommended phase 2 dose with advantages seen in less weight loss, fewer dose reductions, more of target dose received and improved tolerability than the higher dose. Median time to response was 1 month and median duration of response 5 months.

Comment: Exportin 1 (XPO1) is a member of the mammalian karyopherins family, responsible for the extrusion of numerous tumour suppressor proteins from the cell nucleus allowing tumour cells to evade genomic surveillance and cell-cycle regulation. XPO1 is overexpressed in MM as well as many other cancer cells and selinexor is a first-in-class oral selective inhibitor of XPO1-mediated nuclear export. Although selinexor appears to have limited activity as a single agent, when combined with dexamethasone the agent has significant clinical activity and the combination is now being evaluated in quad- and penta-refractory MM patients. Selinexor also shows promise in combination with other backbone MM agents and is being tested in other combinations. Targeting the nuclear export mechanism looks to be another potentially useful strategy in RRMM and worthy of further study.

Reference: Blood 2018;131(8):855-63
Abstract

Syndecan-1 promotes Wnt/β-catenin signaling in multiple myeloma by presenting Wnts and R-spondins

Authors: Ren C et al.

Summary: This pre-clinical Dutch study proposed heparin sulfate (HS) proteoglycan syndecan-1 as a potential therapeutic target for MM treatment. Using CRISPR/Cas9-mediated knockout and doxycycline-inducible short hairpin RNA–mediated knockdown of EXT1 (an enzyme critical for HS polymerisation) they showed that MM cell proliferation can be blocked by targeting HS proteoglycan syndecan-1 through the Wnt/β-catenin pathway.

Comment: In RRMM, therapeutic approaches that overcome microenvironmental sources of drug resistance continue to be explored and developed. Syndecan-1 is a membrane-bound heparin sulphate (HS) proteoglycan that binds to and regulates the activity of a number of soluble protein ligands involved in cell signal regulation and growth, survival and proliferation. Proteins called R-spondins are secreted by osteoclasts and collaborate with HS/Sydecan-1 to activate the Wnt-β-catenin signalling pathway which activates key downstream mediators of MM cell growth and survival including c-Myc and cyclin D1. This elegant study from a Dutch group used gene-editing technology (CRISPR/Cas9) to knockdown HS and their results suggest this approach may represent a unique and novel therapeutic strategy in MM. In an accompanying editorial by Steven Grant from Virginia, discussion centred on the pivotal role of this pathway in stem cell maintenance across a number of haematological malignancies including MM and the potential activity of this strategy against MM progenitors. This study supports the importance of this pathway in mediating microenvironment-related MM resistance and a potential therapeutic target.

Reference: Blood 2018;131(9):982-94
Abstract

