American Society of Haematology Conference Review

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In this issue:

Welcome

to the American Society of Haematology Conference Review, a locally focused summary of some of the latest and most exciting developments in haematology research presented at the ASH conference.

This Review has been created to allow those unable to attend, but with a keen professional interest in haematology research, to access a summary of significant clinical studies presented that are likely to affect current practice. Selection and review of the research is carried out independently by Dr Nigel Patton, Specialist Haematologist at the Institute of Medical and Veterinary Science, Adelaide, South Australia, who attended the American Society of Hematology 49th Annual Meeting held in Atlanta, Georgia, USA.

I hope you find the conference review stimulating and I look forward to your feedback

Kind Regards

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Mantle cell lymphoma can be cured by intensive immunochemotherapy with in-vivo purged stem-cell support; final report of the Nordic Lymphoma Group MCL2 study

Authors: Geisler CH et al

Summary: This is the final report of the Nordic Lymphoma Group MCL2 study, which enrolled 159 untreated patients aged <66 years with mantle cell lymphoma for 6 cycles of intensive induction immunochemotherapy with alternating cycles of rituximab (R) + maxi-CHOP and R + high-dose AraC; 153 responders (CR in 55% and PR in 41%) then received BEAM/BEAC with *in vivo* purged (R) autologous stem cell (ASC) support. Five-year event-free (EFS) and overall survival (OAS) rates were 63% and 74%, respectively; there was a 5-year response duration in 72% of the 144 responders who completed treatment. Six treatment-related deaths occurred (3.8%). Of 77 patients with available primers, 90% had become PCR-negative two months post-transplant; a longer clinical response duration was seen patients who remained PCR-negative at >1 year post-transplant compared with patients who did not. Of 42 stem-cell products assessed, 88% were PCR-negative. Multivariate analysis identified international prognostic index (IPI) and Ki-67 proliferation index as independent predictors of EFS and response duration, respectively; independent predictors of OAS included IPI and cytological variants.

Comment: The Nordic Lymphoma Group has presented longer term follow up data of their combined modality phase II approach for the treatment of younger patients with MCL. The logic of the combined modality approach has taken time to develop, building upon the results of earlier partial combination studies conducted by various groups. Their results are certainly extremely impressive and the data would support their conclusion that this approach may cure mantle cell lymphoma in younger patients. The incidence of secondary MDS (significant in the MDACC studies of R-hyperCVAD) was not mentioned and is of interest. Additional caveats include the phase II design but perhaps the greatest question is the applicability of this approach or alternative therapies to the significant numbers of patients with MCL aged > 65 years.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Late Breaking Abstr 1

About the reviewer - Dr Nigel Patton BSc(Hons), MD, FRCPA, FRACP

Nigel Patton is currently a Specialist Haematologist at the Institute of Medical and Veterinary Science, Adelaide. He undertook Haematology training in the West Midlands working as research fellow and university lecturer in the Departments of Immunology and Haematology, University of Birmingham and was subsequently appointed consultant at the Queen Elizabeth Hospital. He then spent time at Christchurch Hospital. His interests include diagnosis and management of haematological malignancies, stem cell transplantation, infection in immuno-compromised patients and iron overload.

Oral rivaroxaban compared with subcutaneous enoxaparin for extended thromboprophylaxis after total hip arthroplasty: The RECORD1 trial

Authors: Eriksson BI et al

Summary: 4541 patients undergoing total hip arthroplasty received either an oral 10mg fixed dose of the direct Factor Xa inhibitor rivaroxaban commencing 6–8 hours after surgery and once daily thereafter, or SC enoxaparin 40mg once daily commencing the evening before surgery and restarting 6–8 hours after surgery. Therapy continued for 5 weeks, after which patients underwent mandatory, bilateral venography. The primary efficacy endpoint was the composite of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and all-cause mortality. In the modified intention-to-treat population (n=3153), the incidence of the primary efficacy endpoint was significantly reduced in the rivaroxaban group compared with the enoxaparin group (1.1% vs 3.7%), as was the incidence of major VTE (0.2% vs 2.0%, respectively). No differences in bleeding rates were seen between the two groups (major bleeding: 0.3% for rivaroxaban and 0.1% for enoxaparin; non-major bleeding: 5.8% for rivaroxaban and 5.8% for enoxaparin).

Comment: This is the first presentation of a phase III clinical study of an oral anti-Xa inhibitor in comparison with a low molecular weight heparin, in the setting of extended surgical prophylaxis against deep vein thrombosis. Potential advantages of an agent such as this include its fixed-dose oral administration, lack of requirement for patient monitoring and safety. It seems that anti-Xa inhibitors may have advantages over the direct anti-thrombin inhibitors as new anti-coagulants especially in view of more advanced clinical trial development and the hepatotoxicity concerns raised in the previous study using ximelagatran. This is a early result for anti-Xa inhibitors and there are still unanswered questions such as their role in acute DVT. Although such therapies are likely to be expensive and perhaps not immediately available in NZ, it is a portent of things to come. Other agents are also in development and this should encourage our continued participation in clinical trials of new therapies offering such potentially significant advantages.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 6

GA101, a novel humanized type II CD20 antibody with glycoengineered Fc and enhanced cell death induction, exhibits superior anti-tumor efficacy and superior tissue B cell depletion in vivo

Authors: Umana P et al

Summary: Results are reported from a series of experiments involving GA101, a novel monoclonal antibody of IgG1 type which binds with high affinity and selectivity to the extracellular domain of the human CD20 antigen on B cells. GA101 showed increased affinity for the low and high affinity FcγRIIIa receptor expressed on natural killer cells, macrophages and monocytes, thereby mediating a 5- to 50-fold enhanced induction of effector cell mediated antibody-dependent cellular cytotoxicity. In B cell depletion assays with whole blood from healthy donors, GA101 showed greater potency and efficacy than rituximab in B cell depletion. In cynomolgus monkeys, GA101 induced complete, rapid and long-lasting B cell depletion both in peripheral blood and in lymphoid tissue e.g. spleen and lymph nodes. Following 2 IV doses administered on days 0 and 7, GA101 (10 and 30 mg/kg) resulted in statistically superior depletion of total B cells from lymph nodes compared to rituximab (10 mg/kg) from day 9 to 35 onwards, with a decrease in B cell numbers of >95%.

Comment: There is no doubt that rituximab has been a major advance in improving the survival of patients with B cell lymphoproliferative disorders, however, limitations to its efficacy have lead to the development of second (e.g. ofatumumab, ocrelizumab) and third generation (e.g. GA101) monoclonal antibodies directed against CD20 and other B cell antigens. Rituximab, ofatumumab and ocrelizumab are directed against the type 1 CD20 epitope. Ofatumumab (HuMax-CD20) has similar antibody dependent cytotoxicity (ADCC) but enhanced complement dependent cytotoxicity CDC in comparison to rituximab and seems more active versus cells with low expression of CD20 such as B-CLL. Ocrelizumab demonstrates enhanced binding to the low affinity variant FcγR(F158) and has both increased ADCC and CDC in comparison to rituximab. GA101 is directed versus the type II epitope of CD20 which results in markedly enhanced direct non-caspase dependent cell death induction but concomitant reduction in CDC, a feature of the type I epitope. The Fc–region has also been glycoengineered to increase binding affinity to both the low and high affinity FcγR with significant increases in ADCC versus rituximab. Posters 2338 and 2348 describe preliminary data with GA101 in comparison with rituximab including use in NHL xenograft models and first in vivo administration in primates. There is every reason to hope that these new generation monoclonal antibodies, especially GA101, will be even more effective in treating CD20 positive B cell lymphoproliferative disease.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 2348

FDG-PET guided consolidative radiotherapy in patients with advanced stage Hodgkin's lymphoma with residual abnormalities on post chemotherapy CT scan

Authors: Savage KJ et al

Summary: This study investigated the need for consolidative radiotherapy in advanced-stage Hodgkin's lymphoma with bulky disease at diagnosis or for residual abnormalities on post-chemotherapy CT imaging when the residual mass is FDG-PET-negative (PET-neg) following chemotherapy. Outcomes are reported from 52 cases of advanced-stage Hodgkin's lymphoma, identified in the British Columbia Lymphoid Cancer Database. Patients were treated with 6 cycles of ABVD followed by a PET scan for residual abnomalities ≥2 cm. Median follow-up was 19 months. Prior to this treatment schedule commencing in July 2005, post-treatment PET scans were obtained in some individuals by self-pay. Radiotherapy was administered if the PET scan was positive, otherwise, patients were observed. A total of 40 scans were PET-neg and 12 were PET-pos. Two-year progression-free survival was better for PET-neg patients compared to PET-pos patients (91% vs 26%). Five of 10 PET-pos patients administered the planned radiotherapy have relapsed. Two-year progression-free survival did not differ between PET-neg patients with bulky (n=17) or non-bulky disease (n=20) (86% vs 94%).

Comment: There is an increasing evidence base for the use of PET scanning in the management of cancer patients. This may be of greatest value in assessing the role of surgery for solid tumour patients but it is also of value in malignant lymphoma, especially Hodgkin's disease for both initial staging and in assessing treatment response where the results guide treatment decisions. Indeed, the recently revised response criteria for malignant lymphoma (JCO 2007:25:579) recommend the use of PET scanning in these circumstances. This study, from a centre of excellence at the British Columbia Cancer Agency, provides further evidence for the value of PET scanning in Hodgkin's patients and should help argue the case for access to such technology in NZ. Data from the German HD15 study in abstract 212 confims the high negative predictive value of post-treatment PET in advanced HD and its ability to reduce the numbers of patients receiving additional XRT. The Vancouver group, on the basis of their NCIC HD6 trial, are also utlising PET scanning to manage early stage favourable HD patients: e.g. after 2 cycles of ABVD if PET scan is negative such patients go on to receive 2 further cycles of ABVD and avoid any potentially harmful XRT. If the PET scan is positive they receive involved field XRT 30Gy. The current German Hodgkin's disease HD16 study offers PET scans to such patients after 2 cycles of ABVD and if negative no further therapy, whereas postive patients go on to receive IF XRT. Their current HD18 study in advanced HD offers randomisation options for either positive or negative PET scans after two initial cycles of escalated BEACOPP.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 213

Positive impact of iron chelation therapy (CT) on survival in regularly transfused MDS patients. A prospective analysis by the GFM

Authors: Rose C et al

Summary: Survival data as at May 15, 2005 are presented for 165 patients with myelodysplastic syndrome referred for red blood cell (RBC) transfusion between May 15 and June 15, 2005 to 18 French Groupe Francophone des Myélodysplasies centres. Median overall survival (OS) from diagnosis was significantly better for chelated versus non-chelated patients (115 months vs 51 months), even after adjusting for prognostic variables. In International Prognostic Scoring System (IPSS) 0 patients, median OS was not reached in chelated patients and was 69 months in non-chelated patients. In IPSS 0–1 patients, median OS was 115 months in chelated patients and 50 months in non-chelated patients. Median OS was prolonged with "standard" chelation (continuous iron chelation therapy with deferoxamine, deferiprone or deferasirox; 12 months) versus "low" chelation (SC bolus deferoxamine or IV deferoxamine once after each RBC transfusion).

Comment: This is certainly a topical and controversial issue given the frequency of red cell transfusion in MDS and the availability of new options for iron chelator therapy, however, there are some key questions that need to be addressed. These include: *1) Does iron overload cause significant harm in MDS? 2) How can any potential harmful effects from iron overload be assessed in MDS patients? 3) What is the mechanism of any potential harmful effect from iron overload in MDS? 4) Does iron chelation benefit MDS patients and if so what subsets might benefit? 5) Would any benefit be cost effective?* Although the benefit of iron chelation is well proven in thalassaemia, it remains unproven in MDS but it is certainly a hypothesis worthy of investigation. Can we design studies to address these questions? How relevant to the MDS population at large would be such a study population? Is such a study possible given the registration of deferasirox? Reasonable consensus guidelines on the use of iron chelation in MDS have been produced but it is my preference that the international community attempt to address the problem. A randomised trial may be possible in countries where iron chelation is unlikely to be funded.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 249

Phase 1/2 study of AMG 531 in thrombocytopenic patients with low-risk myelodysplastic syndrome (MDS): Update including extended treatment

Authors: Kantarjian H et al

Summary: Data are reported from an ongoing phase I/II study evaluating the safety and efficacy of AMG 531 in 44 low-risk myelodysplastic syndrome patients with severe thrombocytopaenia receiving 3 weekly SC injections of AMG 531 in each of 4 sequential dose cohorts (300, 700, 1000, and 1500µg). At week 4 evaluation, patients could continue AMG 531 in an optional treatment extension at their assigned dose or escalate to a responding dose. Forty patients entered the extension; 16 continue treatment. Overall, 18 patients (41%) achieved a durable platelet response of ≥8 consecutive weeks; responses occurred in 12 patients with a baseline count of ≥20x109/L, and in 6 patients with a baseline count of <20x109/L. The mean duration of the platelet response was 22.8 weeks. Of a total of 104 platelet transfusions given to 17/44 patients, 7 were given to 3 patients with a durable response. Seventeen patients reported treatment-related AEs. There were 2 confirmed cases of transformation to AML. Of 6 patients with blast cell increases, blast cell counts had fallen upon follow-up assessments within 7 weeks after treatment discontinuation.

Comment: Recombinant growth factors for granulopoiesis and erythropoiesis have been available for some time but the prospect of thrombopoietic growth factors for clinical use, despite a great need, has been much more elusive. Initial studies with first generation recombinant thrombopoietins (rhTPO, Peg-rHuMGDF) were abandoned as the latter induced neutralising antibodies in a significant percentage of patients and IL-11 has not proved overly useful. New approaches have resulted in second generation novel peptide and non-peptide (oral) c-MPL ligands with exciting potential such as AMG 531 and eltrombopag. The efficacy of these agents in ITP has been recently demonstrated (see also plenary abs 2) but this abstract describes the early phase I/II experience of the parenteral agent AMG 531 (a dimeric TPO agonist peptide linked to a carrier Fc fragment) in low-risk MDS patients with severe thrombocytopaenia. The oral presentation stated a response rate of 54%, a result of major significance. Of concern was the documentation of two cases of AML transformation and of temporarily increased blast cells in 6 patients who all had the higher doses of 1000 and 1500μg but whose counts fell again after treatment discontinuation. One of these patients was retreated at a lower dose of 700μg without a subsequent increase in blast cells. Marrow fibrosis has been seen with high doses in ITP patients. These results, although preliminary, are extremely encouraging and suggest that this agent may be very effective in low risk MDS with severe thrombocytopaenia/bleeding especially at doses <1000μg. The prospects may be even better in combination with active anti-MDS drugs such as the DMTIs and/or lenalidomide. An oral agent would have more appeal in MDS. The current huge expense of platelet transfusion support and possible availability of competing agents would help mitigate against the expected high costs of such new therapies.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 250

VELCADE/dexamethasone (Vel/D) versus VAD as induction treatment prior to autologous stem cell transplantion (ASCT) in newly diagnosed multiple myeloma (MM): Updated results of the IFM 2005/01 trial

Authors: Harousseau JL et al

Summary: This is an interim analysis of 222 of the 482 patients with newly diagnosed multiple myeloma enrolled in the IFM 2005/01 trial comparing the CR rate obtained with the Velcade® (bortezomib)/dexamethasone combination or VAD prior to stem cell transplantation (ASCT). ASCT was performed in 92% of evaluable patients in the Vel/D combination and in 94% of the VAD regimen. Rates of serious adverse events and grade 3–4 adverse events were comparable between the treatment arms. However, a higher proportion of patients had neurological symptoms (all grades) during induction treatment with Vel/D than with VAD (36% vs 11%). According to intention-to-treat analyses, post-induction CR, CR+VGPR, and PR rates were respectively 22%, 50% and 89% with Vel/D and 9%, 24% and 71% with VAD; corresponding post-ASCT rates were respectively 38%, 66% and 87% with Vel/D and 28%, 50% and 88% with VAD. Consolidation therapy with 2 cycles of DCEP did not increase the CR rate (16% pre-ASCT in both treatment arms with and without DCEP). One-year progression-free survival and overall survival rates are respectively 90% for VAD and 95% for VAD+DECP, 93% for Vel/D and 97% for Vel/D+DCEP.

Comment: This was one of many presentations of phase III studies of novel agents in newly diagnosed myeloma patients. See also abstracts 73–78, a session too full for me to attend, for other important studies in mainly non-transplant eligible patients. The attainment of complete response is considered a surrogate endpoint for improved survival in multiple myeloma. As with non transplant eligible patients the addition of novel agents to the induction regimen improves response rates but it has been a moot point as to whether this increased response rate pre-SCT will increase CR rates post SCT and further improve survival. There is also the potential for the novel agents to be combined or used in sequence in other treatment phases such as transplant conditioning, consolidation or maintenance. In this study, using bortezomib and dexamethasone in induction v VAD, the response rates were higher before and after ASCT with the new agent with fewer patients proceeding to second ASCT in the bortezomib arm. Data on PFS and OS are to be presented next year. Haematological toxicity is reduced versus VAD but bortezomib is associated with a low but increased risk of VZV reactivation, increased neuropathy and an in increased number of patients requiring a second mobilisation. Abstract 73 compared velcade/thal/dex with thal/dex induction pre double ASCT. The data are less mature but the results after first ASCT seem similar to those reported in IFM 2005/01. There is certainly a degree of frustration in accessing these agents in first-line therapy although it seems that thalidomide is likely to be the first one available in NZ.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 450

Nonmyeloablative allogeneic transplantation (NMT) for relapsed follicular lymphoma (FL): continuous complete remission with longer follow-up

Authors: Khouri IF et al

Summary: This study enrolled 47 patients with relapsed follicular lymphoma after prior chemotherapy and autologous transplantation, 29 of whom were in Partial response (PR) and 18 in Complete response (CR), who underwent a conditioning regimen then an HLA-matched haematopoietic cell infusion and graft-versus-host disease (GVHD) prophylaxis, prior to nonmyeloblative allogeneic transplantation (NMT). All attained CR after NMT. Two relapses occurred; one at 18 months responded to donor lymphocyte infusions with a continuous CR at 24+ months. The other relapsed at 20 months after NMT, responded to rituximab and remains in CR at last follow-up 4 years later. Of 100 bone marrow post-treatment PCR samples, 98 were PCR-negative at a median 45 months after NMT. Two samples were PCR-positive early after transplant and became PCR-negative 3 months later. Estimated 6-year overall survival (OS) and current progression-free survival rates were 85% and 83%, respectively. Acute grade II–IV GVHD and chronic extensive and limited GVHD rates were 11% and 51%, respectively. Twenty-eight patients developed chronic GVHD; 20 were de novo. The median onset time for chronic GVHD was 262 days post-NMT, and at a median 67-month follow-up, the OS of patients with chronic GVHD was 89%. At last follow-up, only 5/47 patients still receive immunosuppressants.

Comment: This was one of several abstracts on the potential benefits of reduced intensity allogeneic (RIC) SCT in low grade B cell LPD. Others of interest were abs 484 on MCL, abs 486 on FL/CLL, abs 619 on Waldenström's macroglobulinaemia and abs 47 on 17pdel CLL. In this study, the results are very impressive and it is unclear whether this is partly related to possible selection bias, an MDACC centre of excellence effect or their modified conditioning therapy which includes high-dose rituximab. All patients were reported as chemosensitive. Treatment options for patients with relapsed follicular lymphoma are complex but there is no doubt that RIC sibling allogeneic SCT should be actively considered for such patients. The US BMT Clinical Trials Network is developing a phase II RIC protocol (0701) for use in relapsed follicular NHL which is likely to be based on the MDACC approach, using conditioning with fludarabine/cyclophosphamide/rituximab.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 485

INCB018424, an oral, selective JAK2 inhibitor, shows significant clinical activity in a phase I/II study in patients with primary myelofibrosis (PMF) and post polycythemia vera/essential thrombocythemia myelofibrosis (post-PV/ET MF)

Authors: Verstovsek S et al

Summary: This phase I/II trial investigated treatment responses to INCB018424 (a potent, orally bioavailable selective Janus tyrosine kinase 2 gene inhibitor) in patients with primary myelofibrosis and post polycythaemia vera/essential thrombocythaemia myelofibrosis. The first 3 patients started therapy at a twice-daily oral dose of 25mg and experienced a rapid, marked reduction in splenomegaly; spleen sizes of 25, 22, and 7cm below the left costal margin decreased to 8, 10, and 0cm in the first month of therapy. At 2 months' follow-up, spleen size had decreased to 2cm from 22cm at baseline in one patient. The patients also had significant symptomatic improvement. The second cohort of 3 patients started therapy at 50mg twice daily and after one week, spleen size had decreased in the initial two patients (one JAK2 wild type, one JAK2 V617F) from 22cm to 17cm and from 22cm to 16cm, respectively. No significant toxicity was observed. INCB018424 markedly suppressed phosphorylated STAT3 (a substrate of JAK2) in whole blood cells. In the first cohort of patients, baseline percentages of blood cells with JAK2 V617F mutation were 79%, 49% and 91%; corresponding values one month later were 59%, 48% and 78%, respectively.

Comment: The presentation of preliminary phase I/II clinical studies of selective JAK2 inhibitors within 2 years of publication of the role of JAK2 in myeloproliferative disease (MPD) is truly remarkable. Patient treatment with another agent was also presented, although not listed, in abstract 553 and abstracts 556 and 557 reported data with other agents in animal models of MPD. The results presented in this abstract are extremely encouraging. There is no doubt that more effective treatment options are required in patients with higher risk MPDs such as primary myelofibrosis although it remains to be seen what effect such therapies will have on the natural history of the disease.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 558

The KIT tyrosine kinase inhibitor midostaurine (PKC412) exhibits a high response rate in aggressive systemic mastocytosis (ASM): Interim results of a phase II trial

Authors: Gotlib J et al

Summary: This is an interim analysis of an ongoing phase II study involving 15 patients with aggressive systemic mastocytosis receiving oral midostaurine 100mg twice daily as continuous 28-day cycles until progression/intolerable toxicity. The overall response rate was 73%; 5 patients achieved a MR (all incomplete remissions) and 6 patients a PR (5 good, 1 minor). Four patients were stopped after 2 cycles (2 stable disease, 2 progressive disease [PD]). Among responders, findings included marked reduction in pleural effusion (n=2), reversion of weight loss, and improvement in cutaneous mastocytosis lesions. Nausea and/or vomiting (N/V) was the most frequent non-haematologic toxicity. Grade 1 tremor, grade 1–2 diarrhoea, fatigue, and headache (HA) were less common. Possibly related haematological toxicity consisted of worsening anaemia in 2 patients (grade 3), and recurrent grade 3 thrombocytopenia despite dose reduction to 50mg twice daily. After dose reduction in 4 additional patients (N/V, n=2; HA, n=1; recurrent pleural effusion, n=1), re-escalation to 100mg twice daily was feasible in 3 of these 4 patients. Midostaurine was discontinued after 4 cycles for grade 3 fatigue (n=1) and grade 2 N/V (n=1), and after cycles 8 and 15 for PD (n=2).

Comment: PKC 412 or midostaurine is an oral small molecule investigational TK inhibitor under development. It has activity versus FLT3, PDGFRA, PKC, FGFR1/3 and KIT receptor tyrosine kinases. Current studies include AML and this study of aggressive systemic mastocytosis where the D816V KIT mutation is known to be resistant to imatinib and difficult to treat. The responses, although incomplete, and the tolerability to treatment are encouraging given the lack of alternative options. At this point they don't know whether response is correlated with the D816V KIT mutation. It is hoped that the company may expand access to this phase II protocol. This agent may also be of value in the rare very poor prognosis 8p11 (FGFR1) rearranged MPD syndrome on the basis of 1 previous case report.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 3536

A phase III, multicenter, randomized, double-blind, placebo controlled, comparative trial of AMD3100 (plerixafor)+G-CSF vs. placebo+G-CSF in non-Hodgkin's lymphoma (NHL) patients for autologous hematopoietic stem cell (AHSC) transplantation

Authors: DiPersio JF et al

Summary: This phase III trial compared the safety and efficacy of plerixafor (AMD3100) + G-CSF (A+G) with placebo + G-CSF (P+G) in 298 adult patients with non-Hodgkin's lymphoma requiring an autologous haematopoietic stem cell (aHSC) transplant, in first or second CR or PR. At 100 days' follow-up, intention-to-treat analyses revealed that the primary endpoint (the percentage of patients who achieved ≥5 x 106 CD34+cells/kg in ≤4 aphereses days) was achieved by significantly more patients in the A+G group versus the P+G group (59% vs 20%). In addition, significantly more patients in the A+G group than in the P+G group collected ≥2 x 106 CD34+cells/kg in ≤4 aphereses days (87% vs 47%). A+G rescue (for patients failing to mobilize ≥2 x 106 CD34+cells/kg) was successful in 33/52 rescue patients in the P+G group and 4/10 rescue patients in the A+G group. Transplantation was performed in 90% of the A+G group and 55% of the P+G group. More GI effects (mild to moderate) and injection site erythaema occurred in the A+G group than in the P+G group. Two drug-related serious adverse events occurred in the A+G group and 1 in the P+G group.

Comment: Abstracts 445 and 601 were presentations of the phase III studies of the new stem cell mobilising agent AMD3100 used in combination with G-CSF in myeloma and NHL respectively. The results were similar in both studies although the myeloma patients were much less likely to fail to mobilise with G-CSF alone than the NHL patients. The combination showed enhanced stem cell mobilisation potential both in terms of reaching a target threshold more quickly and in being more likely to achieve sufficient cells to support an autologous transplant. Engraftment seemed durable and the agent was well tolerated. In the NHL study a much higher percentage of patients mobilised with AMD3100 underwent initial transplant. Similar to the compassionate use CUP study, a significant percentage of NHL patients (60%) who failed mobilisation with G-CSF alone could be rescued with repeat mobilisation with G-CSF and AMD3100 and be able to proceed to ASCT with durable engraftment. A 40% success rate was even seen with repeat mobilisation with the combination in patients who had received the combination initially (abstract 602). Autologous transplants are likely to used for some time to come in myeloma and lymphoma. Although AMD3100 may not be used as first-line in NZ, especially in myeloma, it is likely to be used as a second-line mobilising agent as it would seem superior to either a bone marrow harvest or the use of G-CSF/SCF. The potential of AMD3100, through its inhibition of the stromal CXCR4/CXCL12 interaction, to prime myeloma or leukaemia cells to the effects of chemotherapy is also an area of interest at the present time.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 601

Azacitidine (AZA) treatment prolongs overall survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): Results of the AZA-001 phase III study

Authors: Fenaux P et al

Summary: This multinational phase III trial aimed to show the superiority of azacitidine plus best supportive care (BSC) over conventional care regimens (CCR) plus BSC for prolonging overall survival (OS) in 358 patients with higher-risk myelodysplastic syndrome. Prior to randomisation, patients were assigned to 1 of 3 CCR: BSC only (transfusions, antibiotics, and G-CSF for neutropenic infection); low-dose ara-C (LDAC, 20 mg/m^2/d x 14d, every 28 days); or standard chemotherapy (Std CT: conventional induction/consolidation). At a median 21.1 months' follow-up, OS was significantly prolonged by azacitidine compared with CCR (24.4 months vs 15 months). The hazard ratio was 0.58 (95% CI, 0.43 to 0.77) for a 74% OS improvement. At 2 years, azacitidine had a 2-fold OS advantage (51% vs 26% for CCR). Differences in OS Kaplan-Meier medians between AZA and BSC, LDAC, and Std CT, respectively, were 12.9 months, 9.1 months, and 8.7 months. Median OS values per IPSS cytogenetic subgroup were similarly significantly better for azacitibine compared with CCR. The 1-, 2-, and 3-month survival rates did not differ between AZA and BSC only (p>0.20). AZA was well tolerated.

Comment: This study is hugely significant in that it has demonstrated the first therapy, the DNA methyltransferase inhibitor, azacitidine, to improve survival, albeit limited, in high-risk MDS. It has confirmed the provisional findings of the previous CALGB phase III trial whose crossover design limitation impacted on its ability to demonstrate significantly improved survival these patients. The study was complex in view of the 79 sites for 358 patients and choice of 3 possible comparative conventional care regimens. Significantly improved survival was seen across all MDS subgroups, whether categorised by IPSS/WHO or FAB classification systems but this improved survival was not significant in comparison with the group treated with standard AML induction chemotherapy who paradoxically demonstrated an increased CR rate but reduced survival (HR = 0.69; p = 0.19). Most if not all secondary endpoints were also significantly improved with azacytidine. In keeping with previous experience the drug was well tolerated. In the absence of haematological response one major benefit with azacytidine may be the continuation of stable disease and the delay in transformation to AML. Problems limiting its widespread adoption would include the requirement for parenteral use and continuous therapy, high cost and its essentially palliative benefits but these limitations should not diminish the significance of this study. An oral formulation is in development. Azacytidine seems to have a current advantage over decitabine for which the data are much more limited.

Reference: Blood (ASH Annual Meeting Abstracts) 2007;110: Abstr 817

To view the full abstracts in this Review please go to http://www.abstracts2view.com/hem07/

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