# ASH Conference Review
## Haematology

Making Education Easy ASH, Florida, USA 2006

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## Welcome

**to ASH Conference Review, a locally focused summary of some of the most exciting clinical research on Haematology presented at the 48th annual meeting of the American Society of Haematology in December 2006.**

This independent review has been created to allow those unable to attend, but with a keen professional interest in haematology, to access a summary of significant clinical studies presented that are likely to affect current practice. Selection and review of the research has been carried out by Professor Peter Browett, who attended the ASH meeting in Florida..

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

Kind Regards

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## MabThera (rituximab) plus cyclophosphamide, vincristine and prednisone (CVP) chemotherapy improves survival in previously untreated patients with advanced follicular non-Hodgkin's lymphoma (NHL)

**Authors:** Marcus, R et al

**Summary:** This study demonstrated that the addition of rituximab to 8 cycles of cyclophosphamide, vincristine and prednisone (CVP) (R-CVP) chemotherapy improves outcomes in previously untreated patients with stage III/IV CD20-positive follicular non-Hodgkin's lymphoma (NHL), compared with CVP alone. Of a total of 321 patients, 83% in both arms had intermediate to high-risk disease, as defined by the Follicular Lymphoma International Prognostic Index (FLIPI, score 2-5). Median time to progression or death (TTP) in the R-CVP arm was 34 months, compared with 15 months in the CVP arm. This increase in TTP was observed in all FLIPI groups, with a risk ratio of 0.40 for good intermediate-risk patients and 0.51 for poor risk patients; overall the risk ratio was 0.44. In patients achieving a complete response or CR unconfirmed, disease-free survival (DFS) was significantly prolonged; the estimated 4-year DFS rate was 54% for patients receiving R-CVP compared with 17% for CVP. At the time of this analysis, 19% of patients in the R-CVP group had died, compared with 29% in the CVP group. Patients receiving R-CVP experienced significantly improved overall survival compared with CVP. The authors concluded that the addition of rituximab to first-line chemotherapy improves TTP and DFS, as well as overall survival in follicular NHL.

**Comment:** This is the long term follow up data on the previously published study of R-CVP versus CVP alone for patients with previously untreated follicular NHL. In addition to the improvement in response rate and disease free survival at 4 years, this study now shows a significant improvement in overall survival for the R-CVP arm. A similar survival benefit has reported in three other randomized trials, two in first line therapy and one in relapsed disease. Taken together, these data indicate that previously untreated patients with follicular lymphoma should receive Mabthera (Rituximab) plus combination chemotherapy as first line therapy.

**Reference:** *Blood* (ASH Annual Meeting Abstracts) 2006 108: Abstract 481
http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/481

## Long-term follow-up confirms the benefit of all-trans retinoic acid (ATRA) and arsenic trioxide (As2O3) as front line therapy for newly diagnosed acute promyelocytic leukemia (APL)

**Authors:** Liu, Y-F et al

**Summary:** This analysis of front-line use of all-trans retinoic acid (ATRA) combined with arsenic trioxide (As2O3) in patients with newly diagnosed acute promyelocytic leukemia (APL) confirmed a benefit regarding long-term survival. Two patient groups were analyzed: a current cohort of 60 patients enrolled since April 2001 and a historical cohort of 56 patients, enrolled from May 1998 to April 2001. For the current cohort of patients, all patients received 25 mg/m2 ATRA and 0.16 mg/kg As2O3 daily until complete remission (CR). Thereafter, they received 3 courses of consolidation chemotherapy and then 5 cycles of sequential treatment of ATRA, As2O3 and 6-MP/MTX. The historical group received ATRA either 25mg/m2 daily till CR, chemotherapy was added in case of leukocytosis. In the current group, 93.3% of patients achieved CR, and the median time to CR was 27 days. Compared with the historical group, the combined therapy induced an early haematological response. At a median 48 months' follow-up, estimated 4-year OS and EFS were 98.1% and 94.2%, respectively; corresponding values for the historical group after a median follow-up of 56 months were 83.4% and 45.6%, respectively. At last follow-up, all of the available event-free patients of the current group remain in molecular remission. The authors concluded that combined front-line therapy of ATRA and As2O3 confers a survival benefit in newly diagnosed APL.

**Comment:** Arsenic trioxide (ATO), often in combination with ATRA, is now second line therapy for patients with relapsed or refractory acute promyelocytic leukaemia (APML), and the ALLG are currently evaluating the role of this combination as first line therapy. These data from investigators in Shanghai are quite outstanding, with a high CR rate (93.3%) and 94% EFS and 98% OS at 4 years for patients treated with ATO and ATRA induction therapy, in this case followed by consolidation chemotherapy and maintenance ATO / ATRA and 6-MP/MTX. The results are similar to those recently reported from the Mathews et al (Blood 107: 2627, 2006) with single agent ATO alone, and suggest we may be moving to a time when ATO and ATRA is considered front line therapy in APML.

**Reference:** *Blood* (ASH Annual Meeting Abstracts) 2006 108: Abstract 565

http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/565

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## Correlation of pharmacokinetic data with cytogenetic and molecular response in newly diagnosed patients with chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib – an analysis of IRIS study data.

**Authors:** Larson, R et al

**Summary:** This study summarised the correlation of clinical responses with the steady-state trough plasma concentrations (Cmin) of imatinib and its major metabolite CGP74588, using data from 551 pts with newly diagnosed chronic myeloid leukaemia in chronic phase (CML-CP) who received imatinib 400 mg/day in the IRIS study. Estimated rates of complete cytogenetic response (CCyR 0% Ph+) and major molecular response (MMR - 3 log reduction in BCR-ABL/BCR ratio from a standardized baseline value for untreated patients) were given for the lower and upper quartiles (below Q1=25th percentile, above Q3=75th percentile) and the inter-quartile range of PK trough levels. At 4 weeks, the overall mean steady-state trough levels (Cmin) for imatinib and CGP74588 (n=351 pts) were 979 and 242 ng/mL, respectively. Times to CCyR and MMR within CCyR pts were significantly different between the three groups of imatinib plasma exposure (low/intermediate/high; p<0.025). Similar outcomes were observed for CGP74588, due to a high correlation between the parent drug and metabolite levels (0.77, Spearman correlation coefficient). Overall, the imatinib Cmin was significantly higher in patients who achieved CCyR. The estimated MMR rate among all patients was significantly lower in patients with low imatinib levels; this outcome persisted at 4 years.

**Comment:** The dose of most chemotherapy regimens is based on the weight or surface area of the patient; it was therefore surprising that Imatinib therapy in adult chronic myeloid leukaemia patients was a standard dose of 400mg/day. This study correlates Imatinib pharmacokinetic data with cytogenetic and molecular response rates in patients entered into the IRIS study. Trough levels at steady state (measure after 4 weeks in this study) correlated with cytogenetic and molecular response rates, which in the IRIS study have been clearly shown to predict for prolonged progression free survival. In optimizing CML therapy, it will be important to identify at an early stage of those patients who may not respond to standard dose Imatinib therapy, and may therefore benefit from higher dose Imatinib or a second generation abl kinase inhibitor). Although NZ clinicians do not have access to Imatinib drug levels at present, these results suggest that achieving and maintaining an adequate plasma level of Imatinib will be important in the achieving the best possible response for patients with CML.

**Reference:** *Blood* (ASH Annual Meeting Abstracts) 2006 108: Abstract 429

http://bloodjournal.hematologylibrary.org/search.dtl

## Front line combined immuno-chemotherapy (R-CHOP) significantly improves the time to treatment failure and overall survival in elderly patients with advanced stage follicular lymphoma – results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG)

**Authors:** Buske, C et al

**Summary:** This study reported that the addition of rituximab (R) to standard CHOP chemotherapy boosted overall response rates, prolonged time to treatment failure, and improved overall survival in older patients with follicular lymphoma. In this analysis of 221 patients aged >60 years who were part of a larger multicentre phase III study, those who were treated with the combination, R-CHOP, achieved higher overall response rates and had a median time-to-treatment failure of 5.0 years, compared with 2.1 years for patients treated with standard CHOP alone. The estimated 4-year progression-free survival was 62.2% for R-CHOP, versus 27.9% for CHOP alone ($p<0.0001$). In addition, rituximab added to CHOP as frontline therapy improved the estimated 4-year overall survival from 81% to 90%. A multivariate analysis identified the following risk factors that were independently associated with time-to-treatment failure: elevated serum lactate dehydrogenase levels, haemoglobin below 12 g/dL, more than four areas of nodal involvement, and CHOP alone (versus R-CHOP). Toxicities, including reduced haemoglobin, granulocytopenia, thrombocytopenia, infections and nausea, were similar in both groups. The authors concluded that the addition of rituximab to CHOP significantly improves the outcome of elderly patients with previously untreated advanced stage follicular lymphoma, without added toxicities.

**Comment:** The GELA study showed the benefit of the addition of Mabthera to CHOP21 (R-CHOP) chemotherapy for elderly patients with large cell lymphoma. The German B2 study showed a similar benefit of CHOP14 over CHOP21 in the same patient group. The final results of the German Ricover study show an improvement in CR/Cru, EFS and OS at 4 years for R-CHOP14 x 6 cycles when compared to R-CHOP14 x 8 cycles, and CHOP14 6 versus 8 cycles in patients aged 61 – 80 with large cell lymphoma. The data suggests that R-CHOP14 x 6 cycles should be standard of care for older patient with large cell lymphoma being treated with curative intent. This needs to be balanced against the difficulty of administering the regimen to a higher risk patient group. We have no data as to whether these results can be extrapolated to younger patients aged < 60 with large cell lymphoma.

**Reference:** *Blood* (ASH Annual Meeting Abstracts) 2006 108: Abstract 482
http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/482

## First analysis of the Australasian Leukaemia and Lymphoma Group (ALLG) Trial of thalidomide and alternate day prednisolone following autologous stem cell transplantation (ASCT) for patients with multiple myeloma (ALLG MM6)

**Authors:** Spencer, A et al

**Summary:** This study investigated the efficacy of thalidomide and maintenance alternate day prednisolone (AP) (ARM 1) versus AP (ARM 2) following autologous stem cell transplantation (ASCT) in 243 patients with multiple myeloma. Although high-dose chemotherapy with ASCT prolongs survival in multiple myeloma, relapse is inevitable. Evidence indicates that glucocorticoids maintain response following conventional chemotherapy. Thalidomide is effective in both de novo and relapsed multiple myeloma and synergizes with glucocorticoids at low doses without relevant myelotoxicity. At randomization, 9% versus 11% of patients in ARM 1 and 2, respectively, showed an immunofixation-negative complete remission. 64% of patients completed 12 months of thalidomide at a median dose of 100mg. Neurological toxicities occurred more frequently in ARM 1 but there were no differences in thromboembolic or renal toxicities. A significant association was observed between pre-ASCT B2microglobulin levels and progression-free survival. Post-ASCT, ARM 1 demonstrated superior progression-free survival at 1, 2 and 3 years and overall survival at 2 and 3 years. The authors concluded that consolidation with low-dose thalidomide plus alternate day prednisolone maintenance is an effective, well tolerated regimen that prolongs disease response duration following ASCT for multiple myeloma.

**Comment:** High dose therapy with ASCT is now part of standard therapy for patients aged < 65 – 70 with multiple myeloma, however all patients will eventually relapse and we need new strategies to reduce the risk of disease progression and improve overall survival. This ALLG study, which included many NZ patients, shows that maintenance therapy with thalidomide and alternate day prednisone is feasible post ASCT, although only 64% of patients randomized to thalidomide were able to complete the planned 12 months of therapy at a median dose of 100mg/day. Adverse event were also increased in the combination arm, including increased neurological toxicity (20% vs 0%) and an increased incidence of infection (20% vs 12%). The combination arm resulted in improved progression free survival (63% vs 36%) at 2 years, but as yet there has been no impact on overall survival. Larger, confirmatory studies are required; however maintenance therapy may be an option for those patients with residual disease burden post ASCT.

**Reference:** *Blood* (ASH Annual Meeting Abstracts) 2006 108: Abstract 58
http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/58

## The lack of survival differences in randomised trials in CLL may be related to the effect of second line therapies. A report from the LRF CLL4 Trial.

**Authors:** Catovsky, D et al

**Summary:** This study investigated the lack of survival differences in CLL4 (and in other CLL trials), despite better response rates and progression-free survival (PFS) with fludarabine plus cyclophosphamide (FC) than fludarabine or chlorambucil alone in patients with chronic lymphocytic leukaemia (CLL). CLL4 confirmed a correlation between survival in CLL and the quality of response and better survival among good responders to second-line treatment. Data were therefore analysed from 180 patients who received second-line treatments in CLL4. Patients in the chlorambucil arm received, as second-line therapy, mostly fludarabine alone or in combinations including FC+/-Rituximab (R) (70% of cases), cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), alemtuzumab, high-dose methylprednisolone and others. Patients from the fludarabine arm had CHOP (31%), FC+/-R (24%), or others. In the chlorambucil arm, the response rate to second-line treatment was higher than that seen after first-line chlorambucil. Median survival after progression was superior in the chlorambucil (42 months) and fludarabine arms (35 months) than the FC arm (8 months). The authors suggested that the lack of survival differences in CLL4 relates to the better responses and improved survival rates after second-line treatment in those receiving the less effective therapy first, i.e. chlorambucil in CLL4. They added that analyses of salvage protocols should account for the quality of the initial treatments and the mechanisms underlying resistance.

**Comment:** The UK CCL4 trial demonstrated an improved response rate and progression free survival at 5 years for previously untreated patients with CLL receiving combination fludarabine and cyclophosphamide when compared to fludarabine alone and chlorambucil. Similar results have been reported from The German CLL study group (Eichhorst et al Blood 107: 885, 2006) and the recently reported US Intergroup Trial (Flinn et al, JCO 25: 793, 2007), although the UK study has shown these results hold for all age groups, including those aged > 70. Despite these results no improvement in survival has been shown in these studies. This appears to be due to the improved survival seen in patients responding to second line therapy, particularly those receiving less effective therapy initially. For the clinician treating CLL, this raises the interesting question as to whether the aim of initial therapy is improved disease free survival or an increase in overall survival, which would impact in the choice of initial therapy. In a laboratory sub study of CLL4 also presented at the ASH 2006 meeting (Oscier et al, abstract 299), 17p loss (>20%), deletion 11q, non mutated VH genes, high CD38 (7% cut off), and high ZAP70 (10% cut off) correlated with disease progression or death on a univariate analysis. On multivariate analysis p53 loss (17p deletion), non mutated VH genes, deletion of 11q and male gender were independent risk factors for disease progression.

**Reference:** *Blood* (ASH Annual Meeting Abstracts) 2006 108: Abstract 304

http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/304

## Dexamethasone and cyclophosphamide: more convenient and as effective as VAD before high-dose melphalan and autologous transplantation in newly diagnosed multiple myeloma. Results of a randomized NMSG trial.

**Authors:** Mellqvist, U-H et al

**Summary:** This study reports the results of a simplified initial tumour-reducing therapy in patients scheduled for autologous stem cell transplantation (ASCT). The Nordic Myeloma Study Group compared conventional initial therapy of three 4-week courses of vincristine, doxorubicin (Adriamycin) and dexamethasone (VAD) with two 3-week courses of cyclophosphamide and dexamethasone (Cy-Dex). A total of 315 patients were enrolled. ASCT was performed sooner in the Cy-Dex group, 3.2 months versus 4.5 months for the VAD group. There were no significant between-treatment differences in the proportion of patients undergoing ASCT, response rates (both after the initial therapy and after ADCT), and survival data were identical with a median event-free survival time of 29 months and 75% overall survival at three years, calculated from start of therapy for both groups. The authors concluded that Cy-Dex apparently speeds up and simplifies initial treatment with an efficacy comparable to VAD. They suggest that Cy-Dex can be recommended as a safe alternative for initial therapy in patients scheduled for ASCT, and should be further studied in combination with novel agents, such as thalidomide, bortezomib and lenalidomide.

**Comment:** Some NZ centres are now using Cyclophosphamide and dexamethasone (Cy-Dex) as an alternative VAD as induction therapy in myeloma patients, given the difficulties associated with administration of VAD infusional therapy, and the lack of access to thalidomide as first line therapy. The results of this randomized trial of Cy-Dex versus VAD before high dose therapy and ASCT in newly diagnosed patients is reassuring, with similar response rates pre and post transplant in both arms of the study, no difference in the number of patients coming to transplant, and equivalent EFS and OS at 3 years. It is therefore reasonable to consider this regimen as an alternative to either VAD or Dex/Thal as upfront therapy in multiple myeloma.

**Reference:** *Blood* (ASH Annual Meeting Abstracts) 2006 108: Abstract 793

http://bloodjournal.hematologylibrary.org/search.dtl

## Dexamethasone +Thalidomide (Dex/Thal) compared to VAD as a pretransplant treatment in newly diagnosed multiple myeloma (MM): a randomized trial

**Authors:** Macro, M et al.

**Summary:** This study compared the efficacy of a fixed-dose dexamethasone plus thalidomide (Dex/Thal) regimen with that of a vincristine-doxorubicin (Adriamycin)-dexamethasone (VAD)-like regimen as pretransplant induction therapy in 204 patients with untreated active multiple myeloma. The primary objective was the achievement of at least a very good partial response (VGPR), defined as a decrease in serum and urine monoclonal immunoglobulin by ≥90%. In both arms, 91% of pts proceeded to peripheral blood stem cell (PBSC) mobilisation, PBSC harvests were similarly successful and 83% of pts received high-dose melphalan therapy (HDT) autotransplant. Prior to PBSC collection, and before HDT, VGPR rates were significantly higher in the Dex/Thal arm than in the VAD arm. VGPR rates were then comparable between the treatment groups at 6 months post-transplant. More cases of venous thrombosis or pulmonary embolism, as well as symptomatic peripheral neuropathy, were observed in the Dex/Thal arm than in the VAD arm; otherwise, toxicity profiles were similar between the groups. Before PBSC mobilisation, hospitalisation stay was shorter in the Dex/Thal arm than in the VAD arm. The authors concluded that oral Dex/Thal is an effective first-line treatment for symptomatic myeloma and may be preferable to infusional VAD as pretransplant induction therapy.

**Comment:** VAD induction prior to high dose therapy and autologous stem cell transplantation in patients with multiple myeloma frequently requires insertion of a central line and admission to hospital when the infusional regimen is used, and is associated with a risk of neutropenic infection. Phase II studies of dexamethasone and thalidomide (Dex/Thal), a recently published case control analysis (Cavo et al Blood 106:35, 2005) and the ECOG randomized trial of Dex/Thal compared with Thal alone (Rajkumar et al JCO 24:431, 2006) have lead many to suggest that Dex/Thal should replace VAD and similar regimens as upfront therapy in myeloma. This randomized trial of Dex/Thal versus VAD has shown an increased response rate pre transplant in the Dex/Thal arm, but with equivalent response rates, EFS and OS post transplant. This data supports the argument that Dex/Thal may be a suitable alternative to VAD as initial induction therapy in myeloma, although at present thalidomide is only funded for second line therapy. There are likely to be cost savings related to the ease of administration of this oral regimen, although this may be balanced by the increased risk of DVT (prophylaxis not given in this study) and neuropathy. In addition, although the initial response rate is higher with Dex/Thal, no improvement in overall survival has been shown, and although post transplant response rates correlate with outcome, this has not been shown for other surrogate markers such as pre transplant response rates.

**Reference:** *Blood* (ASH Annual Meeting Abstracts) 2006 108: Abstract 57
http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/57

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# In adults with standard-risk acute lymphoblastic leukemia (ALL) the greatest benefit is achieved from an allogeneic transplant in first complete remission (CR) and an autologous transplant is less effective than conventional consolidation/ maintenance chemotherapy: final results of the international ALL trial (MRC UKALL XII/ECOG E2993)

**Authors:** Rowe, J et al.

**Summary:** This study reports post-remission data from an international trial addressing the role of stem cell transplantation in adults with acute lymphoblastic leukaemia (ALL). Patients younger than 50 years (55 since 2004) in first complete remission (CR1) were assigned to allogeneic transplant if they had a matched sibling donor. The other patients were randomised to receive consolidation/ maintenance therapy (chemotherapy) or autologous transplant. The analysis was done for Philadelphia-negative patients. In a donor versus no-donor analysis, patients with a sibling donor had improved overall survival and event-free survival and the relapse rate post-allogeneic transplant was significantly lower than for autologous transplant or chemotherapy. However, this advantage was seen only in standard-risk patients; this overall advantage was not seen in high-risk patients, defined as age >35 years or high white blood cell counts of both T- and B-lineage. Although the relapse rate in high-risk patients with a donor was lower, 36% versus 63% of patients without a donor, a high transplant-related mortality of 39% abrogated its effect on the overall outcome. The authors concluded that matched sibling allogeneic transplantation for ALL patients in CR1 is the best treatment strategy for standard-risk patients. The evidence failed to support replacing chemotherapy with autologous transplantation in any risk group.

**Comment:** Many NZ centres enrolled patients into this important study which prospectively compared allogeneic transplant, autologous transplant and chemotherapy as post remission therapy in over 1980 adult patients with ALL. In contrast to previously published studies in which only high risk patients were considered for allogeneic transplant, standard and high risk patients age < 50 – 55 with a sibling donor were offered a transplant. The data demonstrates the potent anti-leukaemic effect of allogeneic transplant in CR1, with improved EFS and OS at 5 years due to a significant reduction in the relapse rate. The OS benefit is however confined to those patients in the standard risk group (age < 35, low white cell count), whereas in the high risk group the reduced relapse risk was abrogated by the high treatment related mortality. The data also suggest no additional benefit for autologous transplant over chemotherapy with inferior EFS in this group due primarily to a higher relapse rate. While we need to wait for the publication of this trial in a peer reviewed journal, will it change management of adult ALL patients in the NZ setting? Improvement in transplant care and future trials evaluating the role of reduced intensity conditioning regimens may reduce the TRM in high risk patients. For the young standard risk patient, the question now is whether allogeneic transplant will offer any benefit over more intensive paediatric and adolescent ALL protocols.

**Reference:** *Blood* (ASH Annual Meeting Abstracts) 2006 108: Abstract 2

http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/2

***Independent commentary by Professor Peter Browett***
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