Chronic Lymphocytic Leukaemia Highlights of the 50th Annual American Society of Hematology Congress

December 2008

The 50th American Society of Hematology (ASH) meeting was held in San Francisco where the latest research in haematological diseases was presented with over 21,000 attendees able to see more than 380 abstracts relating to CLL.

Presentations on CLL were focussed into two main areas:

- Biology and pathophysiology of CLL
- Therapy of CLL

Some of the CLL highlights of the meeting are described below. For more information the full abstracts can be accessed at the ASH website - www.hematology.org.

Biology of CLL - Murine models of CLL (Link to session website)

In the past it has been a challenge to replicate CLL to produce pre-clinical models of the disease that act in a similar way to CLL in humans. In a fascinating session, three groups reported major progress in this area.

(i) In a follow-up to previously presented work, the Dalla-Favera group (abstract 25) described the results of studies in which varying portions of the DLEU2 gene were deleted in transgenic mice. Previously it had been shown that removal of the entire locus resulted in development of a CLL-like disease, however, since two known microRNAs (miR-15A and miR-16-1) are contained within intronic portions of DLEU2, it was unclear which of these 3 elements are involved. The studies presented during this session convincingly showed that it is the microRNAs, rather than DLEU2 as a whole, that are involved in the pathogenesis of CLL.

(ii) Unlike other disorders such as acute myeloid leukaemia, it has so far not been possible to reliably engraft human CLL in immunodeficient mice. The Chiorazzi group (abstract 26) presented data showing that a human haemopoietic microenvironment, provided by umbilical cord derived CD34+ cells and bone marrow mesenchymal stem cells, allows engraftment of CLL in SCID-NODγc^{null} mice. These experiments emphasise the critical role of the microenvironment in the development of CLL and will be a useful tool for further analysis of the cell types and signalling pathways involved.

(iii) It is rare to hear data presented that challenges basic concepts, however, Kikushige and colleagues (abstract 29) did exactly that. They transferred highly purified CD34+ve/ CD38-ve haemopoietic stem cells from normal or CLL bone marrow into immunodeficient mice. Remarkably, clonal B cell proliferations developed in mice transplanted with bone marrow stem cells from CLL patients but not normals. These CLL-like clones were entirely distinct from those originally present in the patient in that they used different immunoglobulin variable genes and different cytogenetic abnormalities. If correct, this data would suggest that CLL is in fact a disease of the haemopoietic stem cell and not a mature B cell disorder. Independent confirmation of these intriguing data is clearly required.

Therapy of CLL (Link to session website)

The highlights of the session covering advances in the therapy of CLL were two presentations of large Phase III studies looking at the efficacy of the anti CD20 antibody rituximab (R) added to existing therapy of fludarabine plus cyclophosphamde (FC). The R-FC regimen was studied in previously untreated patients in the German CLL8 study and in patients with relapsed or refractory CLL in the REACH study.

CLL8 (abstract 325)

Michael Hallek from Germany presented the overall results of the CLL8 study. This trial included over 800 patients randomised to receive either 6 cycles of FC (F 25 mg/m^2 i.v. d1–3 and C 250 mg/m^2 i.v. d1–3 every 28 days) +/- rituximab (500 mg/m^2 d1 cycles 2–6, 375 mg/m^2 cycle 1). The median age of patients included was 61 years with 64% of patients having Binet stage B disease and 32% Binet stage C. Incidence of cytogenetic abnormalities were not significantly different between treatment arms, with 11q and 17p deletions present in 25% and 8% of patients respectively. The median observation time was 25.5 months. The key results showed significant benefit with R-FC compared with FC in terms of:

- Overall response rate (ORR) – 95% vs. 88% (p=0.001)
- Complete response (CR) rate – 52% vs. 27% (p<0.0001)
- Progression-free survival (PFS) at 2 years – 76.6% vs. 62.3% (p<0.0001).

R-FC treatment was more frequently associated with grade 3 and 4 adverse events, in particular with respect to haematological toxicity although there was no associated increase in severe infections.

Further analyses of the CLL8 data were presented and confirmed the relationship of minimal residual disease (MRD) and outcome for patients (abstract 326). Lower MRD levels at the end of therapy were associated with longer PFS - irrespective of which treatment they received - although more patients were MRD negative after R-FC than after FC.

Stephan Stilgenbauer presented an analysis of the relationship between genomic alterations and V_H mutational status and outcome in patients from the CLL8 trial (abstract 781). Patients with 11q deletions showed particular benefit from the R-FC combination whilst unmutated V_H status and 17p deletions remain independent prognostic factors for a worse response to therapy.

REACH study (abstract LBA-1)

Similar to CLL8, the REACH trial examined the effects of R-FC vs. FC alone but this time in patients with relapsed or refractory CLL. Again, R-FC was significantly better than FC:

- PFS was significantly prolonged by 10 months – 30.6 months vs. 20.6 months (p =0.0002)
- ORR – 70% vs. 58% (p=0.0034)
- CR rate – 24% vs. 13% (p=0.0007).

New therapeutic options

Data on a number of newer therapies were also presented and reflect the increasing numbers of potential new drug candidates being developed in CLL. These include:

Ofatumumab (abstract 328)

This is fully humanised anti CD20 antibody directed against an epitope close to the cell surface that exhibits increased complement dependent lysis compared with rituximab. It was tested in a study of monotherapy in patients who were refractory to both alemtuzumab and fludarabine (double refractory - DR) or had fludarabine refractory CLL with bulky disease (BR). Patients received 8 x weekly infusions of ofatumumab followed by 4 x monthly infusions (Dose 1, 300 mg; Doses 2–12, 2000 mg). There was an overall response rate of 51% in DR patients and 44% in BR patients, including 1 complete response in the BR group, suggesting that this drug has activity in these patients with difficult to treat disease.

Bendamustine (abstract 330)

Another study assessed the combination of bendamustine and rituximab in patients with relapsed CLL. The ORR was 77.4% with CR achieved in 14.5%. This combination is being tested in a further Phase III study comparing to R-FC.

Lenalidomide

Lenalidomide is an immunomodulatory compound that down-regulates VEGF and TNFa expression and stimulates production of inhibitory cytokines. Two oral presentations showed preliminary activity in patients with untreated CLL. In the first study (abstract 44) the drug was initially given at a dose of 10 mg twice daily. After 2 serious events of tumour lysis, the study was modified to reduce the dose escalation. Initial results show a partial response (PR) in 11 out of 17 patients and a median tolerated dose of 10 mg/day. Similar activity was seen in a study of patients >70 years old (abstract 45). Myelosupression, infections and tumour flare were the main complications of therapy.

Flavopiridol (abstract 46)

Given as an initial bolus and then as a continuous IV infusion, this study demonstrated ORRs in nearly 50% of heavily pre-treated patients. Some of those responding were able to have sufficient reduction of their disease to undergo reduced intensity conditioned stem cell transplant.

Summary

As was demonstrated by the plenary presentation on fostamatinib disodium in CLL and DLBCL (abstract 3), and through the advances in pre-clinical medicine, more and more targets are being identified leading to more and more molecules being tested in CLL. This is rapidly advancing therapy and leading us nearer to the goal of tailored therapy for patients with CLL.

In the immediate future, data presented at this congress will allow us to develop a better understanding of CLL, through new pre-clinical models. In the very near future these data will change the way we treat CLL, from FC to R-FC and other combinations.

The 51st ASH congress takes place in New Orleans in December (5th-8th), 2009…