

Conference Scene: Recent developments in the understanding and treatment of hematological malignancies

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Published Online: 8 Oct 2013 | <https://doi.org/10.2217/ijh.13.52>

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Abstract

The 18th Congress of the European Hematology Association, Stockholm, Sweden, 13–16 June 2013

The European Hematology Association (EHA) is a nonprofit scientific organization created in 1992, whose aim is to provide a forum for European medical professionals to unite and share research, develop education and promote excellence within the clinic. Today, the EHA has over 3000 members from various countries throughout the world, governed by an executive board and councilors elected by members. The multidisciplinary nature of the Annual Congress of the EHA is an opportunity for medical professionals with an interest in hematology to exchange information on various topics from novel therapeutics to best clinical practice, such as the ethical issues involved in biobanking. Here we have outlined some of the research that was of most interest at this meeting.

Role of Bruton's tyrosine kinase in B-cell malignancies

Bruton's tyrosine kinase (BTK) is a key component of the B-cell receptor (BCR) signaling pathway and has been indicated to play a role in the interaction between B cells and the tumor microenvironment [1]. This is an important aspect of B-cell malignancies since factors found on the

surface of malignant B cells encourage the cells to stay in proliferative centers like the lymph nodes, allowing chemoresistance to occur [2].

BTK inhibitors have been found to have great efficacy in the clinic, in particular Pharmacyclics (CA, USA) has had astonishing results with their first-in-class BTK inhibitor ibrutinib (PCI-32765) against chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL) and the activated B-cell (ABC) subtype of diffuse large B-cell lymphoma (DLBCL). A Phase II study of the activity of ibrutinib against ABC DLBCL was presented at this meeting. The aim of the study was to find an overall response rate (ORR) to this single agent in relapsed/refractory ABC DLBCL [3]. Seventy patients were enrolled in this study with a median age of 64 years. In ABC patients, responses were observed in 12 out of 29 patients, giving an ORR of 41%, whereas in the germinal center B-cell patients, a response was seen in only one out of 20 patients, giving an ORR of 5%. This agent also demonstrated a very favorable safety profile and these results confirm the hypothesis that a greater response would be shown in the ABC subtype due to its reliance on chronic BCR signaling compared with germinal center B-cell DLBCL, which arises from B cells found in secondary lymphoid organs and do not have a BCR signaling component.

The results of an interim study of an international, multicenter Phase II study of ibrutinib against relapsed/refractory MCL were also reported [4]. MCL is an aggressive subtype of non-Hodgkin lymphoma and many patients are prone to relapse. The patients enrolled in this study were either bortezomib-naïve or -exposed, relapsed/refractory MCL patients. Bortezomib is the licensed treatment for MCL. Ibrutinib 560 mg per os every day (q.d.) was administered until disease progression occurred and responses were measured every 2 months. One hundred and fifteen patients were enrolled with a median age of 68 years and the median number of prior treatments was three. Treatment-related adverse effects were found in less than 20% of patients, the median time on the study was 9.2 months and 47% of patients remain on therapy. Interestingly, it was found that the longer a patient followed the treatment, the faster the observed response rate, and data of longer follow-up periods showed how durable the response to ibrutinib could be. In addition, no significant difference was observed between the response in the patients that were bortezomib-naïve or -exposed. Further studies have been started as a result.

Results from a Phase I study of another highly selective BTK inhibitor, CC-292, which was recently acquired by Celgene (NJ, USA) were presented [5]. The aim of this study was to identify dose-limiting toxicities and to assess the clinical activity of this molecule in patients suffering from CLL or B-cell non-Hodgkin lymphoma (B-NHL). Cohorts of 3–12 patients who had more than one prior treatment for CLL or B-NHL were given doses of the drug from 125, 250, 400, 625, 750 and 1000 mg q.d. or 375 and 500 mg twice daily (b.i.d.). An expansion cohort of 750 mg q.d. for CLL patients was also

included. All patients underwent continual dosing in 28-day cycles until progressive disease or intolerable toxicity occurred. Eighty six patients were enrolled in this study and many had high risk factors (e.g., unmutated *IGHV* or deletion of 11q22). The median time on this therapy was 144 days, however, the minimum toxic dose was not reached and the most frequent adverse effects were fatigue and diarrhea, which were found in less than 10% of patients. This study demonstrated how well tolerated this agent is with minimal adverse events seen over the full dose range. Seventeen CLL patients and one B-NHL patient achieved partial remission at doses of 750 mg q.d., 1000 mg q.d., 375 mg b.i.d. and 500 mg b.i.d.. A trend towards improving responses as the dose increased was observed. The half-life of CC-292 is 2 h and BTK resynthesis occurs after 12 h, therefore b.i.d. dosing maintains BTK inhibition. The results of this study will determine the conditions for the Phase II study on this agent. As with other BTK inhibitors, a significant reduction in the size of lymph nodes was noted, as well as an increase in peripheral lymphocytosis, further strengthening the notion that BTK has an important role in maintaining the tumor microenvironment and encouraging malignant B cells to stay in proliferative centers such as secondary lymphoid organs. Further evidence to support the existence of this poorly understood interaction between B cells and the lymphoid microenvironment, combined with the exciting results of BTK inhibitors in the clinic, has made BTK a hot topic at the European Hematology Association (EHA) congress this year.

'Sleeping Beauty' system to generate CD19⁺ T cells

This novel research described the use of the 'Sleeping Beauty' system of gene transfer to create both autologous and allogenic T cells expressing a CD19-specific chimeric antigen receptor (CAR) [6], conferring a new antigen specificity on the T cell, which can be manipulated to target malignant cells. In this case, the CAR was created against CD19, which is found on the surface of normal and malignant B cells and is a popular target for gene therapy treatments against B-cell cancers. In addition it has been suggested that CD19 causes the upregulation of the MYC oncoprotein through the PAX5 transcription factor [7]. In this study, 11 patients received the T cells, all had shown relapses of acute lymphoblastic leukemia (ALL; n = 4) or B-cell lymphoma (n = 7) after autologous (n = 3), allogenic (n = 3) or cord blood (n = 1) hematopoietic stem cell transplantation. When patients were dosed with 10⁶ T cells/m², a prolonged persistence of CAR⁺ T cells was not observed and these patients relapsed. Subsequently, two patients with ALL received an increased dose of 10⁷ T cells/m², one patient relapsed, however the other obtained complete remission with continued expression of CAR⁺ T cells 4 months after the infusion. This new approach to treating B-cell malignancies has an impressive safety profile with no adverse effects due to treatment experienced by any patient enrolled on the study, which gives it an advantage over the current chemotherapy regimen available for patients. This could be the next upcoming treatment for maintaining remission in CD19⁺ lymphoid cancers.

Ongoing debate on *Notch*: oncogene or tumor suppressor?

The *Notch* gene was first discovered in *Drosophila* and is responsible for the Notched wing phenotype. Now, *Notch* has been found to have multiple functions within multicellular organisms from the maintenance of stem cell populations and influencing cell fate decisions to tumorigenesis. The ongoing debate in oncology is whether *Notch* genes are oncogenes or tumor suppressors. Freddy Radtke's research (Ecole Polytechnique Federale de Lausanne, Life Sciences Switzerland) showed that the best example of Notch acting as a tumor suppressor is in the skin, where it is normally expressed within the basal layer and is involved in cell differentiation [8]. When this expression is inactivated, mice develop tumors within 1 year. Interestingly, when all Notch signaling in the skin is blocked, the mice develop a severe form of inflammation similar to atopic dermatitis, indicating this gene's role in controlling the immune system. Jon Aster (Brigham and Womens Hospital, MA, USA) reported that frequent loss-of-function mutations in the *Notch1* gene are found in T-cell ALL (T-ALL), CLL and squamous cell carcinoma [9]. Radtke's group also worked to investigate the role of *Notch1* as an oncogene by knocking out Dicer in an early onset T-ALL mouse model. Dicer is an endoribonuclease, which is absolutely essential for Notch signaling in hematopoietic cell lineages. All control animals died within 90 days whereas the Dicer knockouts survived. In addition, primary T-ALL patient samples were treated with Notch inhibitors and all patients whose cells expressed the NCID Notch1 biomarker showed a positive result. These data imply that Notch1 signaling has a role to play in T-ALL. Notch signaling in oncology is not yet well understood but it has the potential to become an important therapeutic target in the future.

BKT140 in the treatment of chronic myeloid leukemia

Tyrosine kinase inhibitors have revolutionized the treatment of chronic myeloid leukemia (CML); however, drug resistance and relapse are common with this myeloproliferative disorder. The reason for relapse is believed to be due to the presence of leukemic stem cells in the bone marrow, where the chemokine-rich bone marrow microenvironment lends protection to the leukemic stem cells. The CXCR4 receptor and its ligand CXCL12 are thought to be involved in the maintenance of these cells within the bone marrow, making CXCR4 an attractive target. Katia Beider (Sheba Medical Center, Tel HaShomer, Israel) presented the findings of her study on the role of CXCR4 in CML and the effect of the CXCR4 antagonist BKT140 on CML cell survival and sensitivity to imatinib [10]. BKT140 is a unique CXCR4 antagonist that binds with high affinity and induces cell death. The results showed that BKT140 inhibited CML cell proliferation by 40–60%. When a coculture system was set up using CML cells and primary human bone marrow stromal cells, increased levels of imatinib resistance were observed; however, when BKT140 was added in combination with imatinib the amount of proliferation was reduced and an apoptotic effect was observed.

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Conclusion

This brief overview is a summary of some of the presentations that were of most interest and does not encompass the vast amount of research and clinical data presented at the 18th Congress of the EHA. Many other interesting reports were presented at both plenary and poster sessions alike. This meeting of European oncology professionals provided the opportunity for the presentation of excellent translational research and clinical data, as well as education sessions, which gave in-depth information into the biology of disease progression.

Financial & competing interests disclosure

S Brumskill is an Associate Scientist at Redx Oncology, V Walker is a Senior Pharmacologist at Redx Oncology and M-A Campbell is Head of Pharmacology at Redx Oncology. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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