Two new studies suggest ibrutinib can be safe and effective in the treatment of chronic lymphocytic leukemia and mantle cell lymphoma

“The results from two clinical studies investigating ibrutinib have suggested that this innovative Bruton’s tyrosine kinase inhibitor may be a potentially safe and effective treatment for both of these cancers.”

In two studies carried out by the Ohio State University Comprehensive Cancer Center (OSUCCC; OH, USA) and MD Anderson Cancer Center (TX, USA), researchers have demonstrated that ibrutinib has the ability to significantly prolong survival in patients with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL).

CLL is the most common form of leukemia, affecting approximately 15,000 people in the USA every year, and yet, it is currently an incurable cancer. Similarly MCL, a rarer but more aggressive blood cancer, is also incurable. Scientists worldwide are keen to develop effective treatments for these lethal diseases. The results from two clinical studies investigating ibrutinib have suggested that this innovative Bruton’s tyrosine kinase inhibitor may be a potentially safe and effective treatment for both of these cancers.

CLL affects B cells, adversely affecting the patient’s immune system. As ibrutinib can selectively disrupt a protein that is essential in the B-cell receptor pathway, it is able to

halt tumor cell growth and inhibit cell survival while still leaving healthy T cells intact and functional. The results from the Phase Ib/II trial in 85 relapsed CLL patients demonstrated this ability through a range of promising results, such as an overall response rate of 71%, progression-free survival rate of 75% and overall survival rate of 83%.

“Essentially all CLL patients respond well to ibrutinib, which lacks many of the side effects of chemotherapy and frequently produces long-lasting remissions even in patients with high-risk genetic lesions,” comments John Byrd, co-leader of the study and director of the division of hematology at the OSUCCC.

Similar to CLL, MCL also affects B lymphocytes. At present, available treatments include stem cell transplantation, combination chemotherapy and chemotherapy plus immunotherapy. In the MCL Phase II trial, carried out in 111 patients with relapsed or refractory MCL, an overall

News & Views

News

Journal Watch

response rate of 68% was observed. Additionally, 21% achieved a complete response while 47% achieved a partial response.

Encouragingly, the overall survival in this MCL trial was 58%. “This is remarkable because the last agent approved by the FDA for MCL had a 30% response rate,” commented senior author Kristie Blum, associate professor of medicine at the OSUCCC.

These studies provide hope that an alternative treatment for these blood cancers may be available sooner rather than later, potentially improving the therapy options available for patients.

Sources: Byrd JC, Furman RR, Coutre SE *et al.* Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N. Engl. J. Med.* 369(1), 32–42 (2013); Wang ML, Rule S, Martin P *et al.* Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N. Engl. J. Med.* doi:10.1056/NEJMoa1306220 (2013) (Epub ahead of print); Foà R, Guarini A. A mechanism-driven treatment for chronic lymphocytic leukemia? *N. Engl. J. Med.* doi:10.1056/NEJMoa1215637 (2013) (Epub ahead of print); The Ohio State University news release: <http://cancer.osu.edu/mediaroom/releases/Pages/Drug-Shows-Potential-as-Safe-and-Effective-for-Chronic-Leukemia-Mantle-Cell-Lymphoma.aspx>

Researchers have revealed the cancer-treating potential of SALL4

Scientists from the Harvard Stem Cell Institute (HSCI; MA, USA) have demonstrated the therapeutic potential of targeting *SALL4*, a gene that is known to enable continued stem cell division and prevent stem cell maturation.

SALL4 is usually only expressed during embryonic development, and controls embryonic stem cell self-renewal. However, it has also been implicated in tumor formation as it is expressed in some of the most aggressive forms of cancer, including almost all cases of acute myeloid leukemia, and in 10–30% of gastric, ovarian, breast, endometrial, liver and lung cancers.

“*SALL4* is a marker, so if we had a small-molecule drug blocking *SALL4* function, we could also predict which patients would be responsive.”

Traditionally, transcription factors have been unconventional targets in cancer research owing to the difficulties associated with developing drugs for genetic targets, and so recent research has mainly focused on targeting kinases. However, researchers at the HSCI were not content to be limited by this, and were eager to target the previously ‘undruggable’ *SALL4* protein, which is responsible for turning off a tumor suppressor gene.

Researchers at the HSCI found that they could treat mouse liver tumors by using an inhibitor of the *SALL4* protein.

Daniel Tenen, the HSCI Blood Diseases Program leader, was keen to emphasize the potential therapeutic impact of the research, “Our paper is about liver cancer, but it is likely true about lung cancer, breast cancer, ovarian cancer, many, many cancers. *SALL4* is a marker, so if we had a small-molecule drug blocking *SALL4* function, we could also predict which patients would be responsive.”

In fact, a coauthor of the recent paper and assistant professor at the Harvard Medical School (MA, USA), Li Chai, has previously reported how a *SALL4* inhibitor has shown the same therapeutic potential in leukemia cells. In this research, blood samples from patients with acute myeloid leukemia were treated with a *SALL4* protein inhibitor, which caused a gradual regression of the cancer when transplanted into mice.

Chai and Tenen hope to work on future cancer treatments, exploiting *SALL4* expression. “I think as academics, we seek to engage drug companies because they can do these types of things better than we can,” Tenen concludes. “But, also as an academic, I want to go after the important biologic targets that are not being sought after by the typical drug company – because if we do not, who will?”

Sources: Yong KJ, Gao C, Lim JS *et al.* Oncofetal gene *SALL4* in aggressive hepatocellular carcinoma. *N. Engl. J. Med.* 368(24), 2266–2276 (2013); Harvard Gazette press release: <http://news.harvard.edu/gazette/story/2013/06/developing-cancer-drugs>

Lenalidomide receives European approval for the treatment of a rare blood disease

The European Commission has recently announced that lenalidomide (Revlimid®; Celgene, Uxbridge, UK) has been approved for the treatment of transfusion-dependent anemia caused by myelodysplastic syndrome (MDS).

In MDS, a rare type of blood cancer, the bone marrow is unable to produce a healthy number of blood cells and platelets. This can cause the development of anemia, bleeding and infections. Out of approximately 2000 people affected by this cancer each year in the

UK, approximately 50% will experience a chromosome abnormality, one of the most common being the 5q deletion. There is generally a poor prognosis associated with the 5q deletion abnormality, with patients being at risk of developing acute myeloid leukemia.

Patients with low or intermediate-1 risk MDS associated with a 5q deletion chromosomal abnormality are liable to develop transfusion-dependent anemia. Although there are some treatment options currently available for these patients, the recent approval of lenalidomide is especially welcome for those who have found other treatments to be insufficient or inadequate.

“Historically, the standard of care for MDS has been red blood cell transfusions, which can help control the disease but pose a tremendous burden to patients, particularly the elderly ones who make up the majority of MDS patients,” explains Ghulam Mufti, Professor of Hematological Oncology at King’s College London (London, UK). “Today’s decision from the European Commission offers new hope to patients with MDS isolated del (5q) by enabling them to access lenalidomide, an effective and possibly targeted treatment option.”

The approval has come on the heels of a positive Committee for Medicinal Products for Human Use opinion in April 2013,

and follows the positive benefit-to-risk ratio results of Phase III trials in MDS patients. In particular, the MDS-004 trial was a multicenter, double-blind, randomized, placebo-controlled study that demonstrated that a statistically significant larger number of patients were able to achieve transfusion independence compared with those on placebo (55.1 vs 6.0%, respectively).

“Today’s announcement is the result of many years of development and ongoing collaboration with the European regulatory authorities to bring an important and targeted treatment option to people with MDS throughout Europe who have an isolated del (5q) cytogenetic abnormality,” concludes the President of Celgene EMEA, Alan Colowick. “Celgene has pursued an indication for this rare disease for nearly 7 years, and after much perseverance, we are proud to now be able to start the important work of partnering with our many stakeholders to ensure patients have access to lenalidomide for MDS isolated del (5q).”

Sources: Virgo HEALTH press release: Lenalidomide receives European approval for the treatment of a rare blood disease; Celgene press release: <http://ir.celgene.com/phoenix.zhtml?c=111960&p=irol-newsArticle&ID=1811727&highlight=>

Researchers develop method for producing patient-specific progenitor cells for cell-replacement therapy

A new method of producing precursor cells similar to hematopoietic cells developed by scientists at Icahn School of Medicine at Mount Sinai (NY, USA) may be the first step towards producing patient-specific blood products for use in cell-replacement therapy.

There is a shortage of donors that are suitable for blood stem cell transplants for the treatment of hematologic malignancies. Currently, donors remain the only way in which patients with blood diseases such as lymphoma, leukemia and multiple myeloma are able to undergo cell-replacement therapy. It is in the interest of improving treatment options and patient outcomes that the programming of hematopoietic stem cells is developed as an alternative to the current reliance on donors.

In this new study, four transcription factors (Gata2, Gfi1b, cFos and ETV6) were chosen by scientists at the Icahn School of Medicine from a screening of 18 genetic factors known to induce blood-forming activity. In the novel study, the scientists found that by transferring these four genes into mouse fibroblast cells they were able to produce cells resembling hematopoietic stem cells, which are responsible for producing new blood cells.

Carlos Filipe Pereira, first author of the study and Postdoctoral Fellow of Developmental and Regenerative Biology at the

Icahn School of Medicine commented that, “The cells that we grew in a petri dish are identical in gene expression to those found in the mouse embryo and could eventually generate colonies of mature blood cells.”

The cells produced by the group, after finding the right combination of genetic factors, appeared to express a human CD34 reporter, Sca1 and Prominin1. There was some surprise that the combination of factors used was able to replicate these hematopoietic stem cells so accurately, with other investigators having encountered many problems and failed in the past.

This discovery is hoped to be the platform for future development of patient-specific progenitor cells and blood products for use in cell-replacement therapy. Dennis Charney, Executive Vice President for Academic Affairs at The Mount Sinai Medical Center (NY, USA), concludes, “This discovery is just the beginning of something new and exciting and can hopefully be used to identify a treatment for blood disorders.”

Source: Pereira CF, Chang B, Qiu J *et al.* Induction of a hemogenic program in mouse fibroblasts. *Cell Stem Cell* pii, S1934-5909(13)00217-8 (2013); Mount Sinai Hospital news release: www.mountsinai.org/about-us/newsroom/press-releases/mount-sinai-researchers-succeed-in-programming-blood-forming-stem-cells

New approach for treating primary mediastinal B-cell lymphoma demonstrates positive outcomes

A recent trial conducted by the NIH (MD, USA) has shown promising outcomes for young patients with primary mediastinal B-cell lymphoma who are treated with infusions of chemotherapy without undergoing radiation therapy to an area of the thorax known as the mediastinum.

Primary mediastinal B-cell lymphoma is a cancer that predominantly affects people aged between 15 and 35 years. While many patients with this disease can be cured through a combination of chemotherapy and radiation therapy, approximately 20% of patients are not cured and experience disease progression.

The main concern of researchers at the National Cancer Institute (NCI; MD, USA) was that when patients undergo radiation therapy to the chest area (a common practice in the treatment of this condition), patients are liable to develop new cancers or experience damage to their heart. These long-term toxic side effects, and the subsequent development of breast cancer in young women in particular, is a major concern for these patients.

In this long-term study, during which some patients were followed for up to 14 years, patients received a combination

chemotherapy regimen consisting of etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and rituximab (also known as dose-adjusted EPOCH-R). Out of a study group of 51 patients, all but two achieved a complete remission following the dose-adjusted EPOCH-R therapy, with none of these patients developing a recurrent lymphoma. A positive outcome from this regimen appears to be that there is no evidence of cardiac toxic effects or the development of other cancers.

“While many patients with this disease can be cured through a combination of chemotherapy and radiation therapy, approximately 20% of patients are not cured and experience disease progression.”

“The high success of this regimen in greatly reducing the need for radiation and improving the cure rate in this disease may relate to specialized dosing and continuous infusion delivery of the EPOCH-R agents,” remarked Wyndham Wilson, head of NCI’s Lymphoma Therapeutics Section.

Correspondingly, investigators at Stanford University (CA, USA) carried out an experiment using dose-adjusted EPOCH-R in 16 patients with primary mediastinal B-cell lymphoma, achieving similar results. Both of these studies indicate that dose-intense regimens are effective, and that radiation therapy can be avoided to reduce the possibility of long-term toxic side effects.

“For me, these results are exciting and demonstrate that, using this approach, almost all patients appear to be cured and very few patients require radiation,” explained first author on the study, Kieron Dunleavy, from the NCI. “Based on our results, an international Phase II trial of dose-adjusted EPOCH-R in pediatric patients with primary mediastinal B-cell lymphoma is ongoing to confirm these findings, and we hope this international trial will have a similarly positive outcome.”

Sources: Dunleavy K, Pittaluga S, Maeda LS *et al.* Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N. Engl. J. Med.* 368(15), 1408–1416 (2013); NIH news release: www.cancer.gov/newscenter/newsfromnci/2013/DA-EPOCHlymphoma

– All stories written by Sophie Breeze

About the News

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