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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

New hope for bendamustine in the treatment of non-Hodgkin lymphoma

A StiL NHL-1 study has published results showing that in patients with indolent non-Hodgkin lymphoma (iNHL) and mantle cell lymphoma (MCL), treatment with bendamustine plus rituximab (B–R) doubles the progression-free survival (PFS) when compared with usual treatment.

NHL is the tenth most common cancer worldwide, MCL represents 3–10% of all NHL subtypes and iNHL represents 40%. The standard treatment for iNHL, or in elderly patients with MCL, is usually cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus rituximab (CHOP-R).

"These results represent a significant breakthrough in cancer treatment for patients with iNHL and MCL..."

A prospective, multicenter, randomized, open-label, non-inferiority trial was carried out at 81 centers in Germany between 2003 and 2008. The trial enrolled patients with iNHL or MCL who were 18 years or older, and were randomly assigned patients to receive either CHOP (275 patients, 253 assessed) or intravenous bendamustine (274 patients, 261 assessed) for up to six cycles. On the first day of each cycle both groups received rituximab and PFS was the main endpoint. In the CHOP-R group, at the 45 month median follow-up, PFS was 31.2 months, compared with 69.5 months in the B–R group.

Lead investigator of the study, Mathias Rummel (Hospital of the Justus-Liebig-University, Giessen, Germany), told *Expert Review of Hematology*; "These results represent a significant breakthrough in cancer treatment for patients with iNHL and MCL, who in the past have had to endure particularly aggressive and toxic chemotherapy combinations. Our study showed bendamustine and rituximab offered a significant improvement in PFS, and that the combination was better tolerated than CHOP-R. This means that the regimen, if approved by the regulatory authorities, could become the new preferred first-line treatment, capable of extending the time patients battling these malignancies live free of disease."

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This study marks the first time that, in randomized trial, a superior complete response was reported in a treatment protocol compared with CHOP-R. A complete response was seen in 40% of patients in the B–R group compared with 30% in the CHOP-R group. Fewer side effects were also seen in the B–R group, for instance 29% of patients experienced myelosuppression, with severe neutropenia compared with 69% in the CHOP-R group. Furthermore, serious adverse events were only seen in 19% in the B–R group compared with 29% in the CHOP-R group. Surprisingly, no patients in the B–R group reported hair loss as a side effect, a frequently stated side effect of CHOP-R treatment.

John Gribben, (Barts and the London School of Medicine, London, UK) explains the findings; "The results of this study are very encouraging for iNHL patients … The fact that bendamustine and rituximab results in fewer adverse effects with significantly better efficacy than the traditional

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Favorable review of vascular dementia drug

A recent systematic review published in the Cochrane library examined data from six randomized controlled trials of Cerebrolysin, involving 597 people in total, and found that the drug significantly improved cognitive function.

"Our review suggests that Cerebrolysin can help improve cognitive and global function in patients with mild to moderate severity vascular dementia," explained researcher Li He, from the Department of Neurology at Sichuan University, China.

The trials differed in their designs, but all patients considered in the review were give intravenous Cerebrolysin daily over a time period of a few weeks up to three years. Daily concentrations of the drug differed between trials. Across all six trials, compared with placebo or standard care alone, Cerebrolysin was found to improve cognition as measured by scales testing recall, arithmetic, cognitive and cognitive abilities.

"This indicates to us that Cerebrolysin is safe and well tolerated by patients with vascular dementia," said He. "But the fact that it has to be given in regular intravenous infusions means it could be impractical for use on a large scale."

No serious side effects were reported and the likelihood of non-serious side effects was not raised in the group taking the drug compared with placebo.

"The results are promising but due to low numbers of trials, inconsistencies between trials, risk of bias in the way some of the trials were conducted and lack of long-term follow up, we cannot yet recommend Cerebrolysin as a routine treatment for vascular dementia," He explained.

Only two of the studies looked at long-term implications, although the Cochrane review did suggest a possible greater benefit with longer term treatment.

Written by Laura McGuinness

Source: Chen N, Yang M, Guo J, Zhou M, Zhu C, He L. Cerebrolysin for vascular dementia. *Cochrane Database Syst. Rev.* doi: 10.1002/14651858.CD008900.pub2 (2013) (Epub ahead of print).

CHOP-R treatment regimen indicates that this could be a new cornerstone in the treatment of NHL."

Fritz Offner, (University of Ghent, Ghent, Belgium) summarizes the importance of the study; "The treatment of iNHL has come a long way … The current study from the StiL-group represents a major advance in this field … it also comes with a doubling of PFS, unseen with any other chemotherapeutic modification of the standard treatment … It is a big step forward for patients to make cancer care better and less disruptive for daily life."

> "...this could be a new cornerstone in the treatment of NHL."

Further work in this area is planned, as Rummel expained to *Expert Review of Hematology*; "The StiL group are currently conducting a study called MAINTAIN to investigate the effect of treating iNHL and MCL patients who have responded to B–R with rituximab maintenance therapy. The group is also in the process of planning our next large randomized front-line study in this group of patients, which will examine the effect of adding a very novel targeted agent to the B–R cornerstone."

– Written by Sophie Wraight

Sources: Rummel MJ, Niederle N, Maschmeyer G *et al*; on behalf of the Study group indolent Lymphomas (StiL) Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, Phase 3 non-inferiority trial. *Lancet* doi:10.1016/S0140–6736(12)61763–2 (2013) (Epub ahead of print); PR newswire Press Release: www.prnewswire.co.uk/news-releases/phase-3-data-published-in-lancet-show-bendamustine-levact-plus-rituximab-doubles-progression-free-survival-in-patients-with-indolent-non-hodgkin-lymphoma-and-mantle-cell-lymphoma-compared-with-chop-r-191916731.html

Beta-blockers: a potential way to beat lung cancer?

A study published in *Annals of Oncology*, suggests that patients taking beta-blockers while having radiotherapy for non-small-cell lung cancer might live longer than those not taking the drug, with a longer time before distant metastases from the disease.

The study, from the University of Texas MD Anderson Cancer Center (TX, USA) retrospectively studied 722 patients who had received definitive radiotherapy for non-small-cell lung cancer. A total of 155 of these had concurrently been taking beta-blockers for other conditions, including heart disease.

Overall survival, distant metastasis-free survival and disease-free survival were all higher with beta-blocker intake, although there was no association found with locoregional progression-free survival. These associations remained after adjusting for a number of factors, including age, tumor stage, performance status, alternative treatments and radiation dose, among others.

Daniel Gomez (MD Anderson Cancer Center) discussed the findings with *Lung Cancer Management*; "We believe that this study is important because we found that patients taking beta blockers during radiation therapy for non-small-cell lung cancer lived longer, even when controlling for other factors such as the stage of disease and the treatment regimen." While Gomez mentions that; "These findings were the first to our knowledge demonstrating a survival benefit associated with the use of beta blockers and definitive radiation therapy for lung cancer," previous preclinical studies have provided evidence for the idea that inhibiting beta-adrenergic receptors

US FDA approves Kynamro™ to treat familial hypercholesterolemia

The drug Kynamro™ developed by Genzyme (Cambridge, MA, USA) has been approved for use in the treatment of familial hypercholesterolemia by the US FDA. The announcement on Kynamro came following a randomized double-blind, multi-center Phase III trial published in *The Lancet* in 2010. The drug also known as mipomersen sodium is an inhibitor of apolipoprotein B synthesis and is administered weekly as a subcutaneous injection.

Familial hypercholesterolemia, a rare genetic disorder which affects approximately one in every million people in the USA, occurs when both LDL-receptor alleles are defective. Patients suffering with this condition are likely to experience heart attacks and/or death before the age of 30.

The study upon which this recent FDA approval was based involved nine lipid clinics in seven different countries. Patients were aged 12 and over with a clinical diagnosis or genetic confirmation of homozygous familial hypercholesterolemia, and were already receiving a maximum dose of a lipid-lowering medication. The study found significant reductions in LDL cholesterol in the group receiving mipomersen sodium compared with the placebo group.

The study concluded that the inhibition of lipoprotein B synthesis by mipomersen sodium represented a significant effective additional therapy for patients suffering with familial hypercholesterolemia.

The FDA released a press announcement on 29th January 2013, following a Risk Evaluation and Mitigation Strategy approving the Kynamro injection as an add-on therapy to lipid-lowering medications and diet in the treatment of the rare homozygous familial hypercholesterolemia. The FDA cited its ability to help reduce LDL cholesterol, apolipoprotein B, total cholesterol and non HDL cholesterol as being behind the decision. However, the FDA also stated that they were requiring four postmarketing studies to assess the long term safety of Kynamro, as well as a pharmacovigilance program to monitor malignancy, hepatic abnormalities and immune-mediated reactions.

"The study concluded that the inhibition of lipoprotein B synthesis by mipomersen sodium represented a significant effective additional therapy for patients suffering with familial hypercholesterolemia."

– Written by Dominic Chamberlain

Sources: FDA press announcement: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm337195.htm; Raal FJ, Santos RD, Blom DJ *et al.* Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. *Lancet* 375(9719) 998–1006 (2010).

might reduce cell migration and so inhibit metastasis.

"We believe that this study is important because we found that patients taking beta blockers during radiation therapy for non-small-cell lung cancer lived longer."

However, Gomez feels that these results might mean more than this; "it may be the case that beta-adrenergic signaling can influence other processes that affect cancer progression, such as invasion or proliferation of cells. Therefore, the results imply that there may be another mechanism, largely unexplored, that could potentially reduce the rates of tumor spread in patients with this very aggressive disease."

The authors acknowledge that these results are not enough to change clinical practice, but hope that the results will be confirmed in further trials at other institutions and in the prospective setting. Gomez says that "we are also working to examine the role of the beta blocker receptor in disease progression through translational studies."

– Written by Alisa Crisp

Sources: Wang HM, Liao ZX, Komaki R *et al.* Improved survival outcomes with the incidental use of beta-blockers among patients with non-small-cell lung cancer treated with definitive radiation therapy. *Ann. Oncol.* doi: 10.1093/annonc/mds616 (2013) (Epub ahead of print); Oxford University Press Press Release: www.eurekalert.org/pub_releases/2013–01/esfm-lcp010713.php

Novel non-invasive treatment for emphysema is currently undergoing trials

Emphysema affects millions across the world; a recent survey indicated that approximately 4.7 million (2%) people in the USA alone are affected. Doctors believe that it is largely under diagnosed with the figure possibly rising to approximately 4–6% of males and 1–3% of females in the USA. Currently approved treatment for emphysema involves surgery to remove large parts of the affected regions of the lung in order to reduce the volume of the lungs. This allows the diaphragm to return to somewhat more normal functionality. Recently, the first patients from the USA have begun to take part in a trial for a novel treatment for emphysema, at the University of Alabama (Birmingham, AL, USA).

The new treatment, named the AeriSeal System (Aeris Therapeutics, MA, USA) is thought to be almost as effective as surgery; however, without the associated risk of fatality. The AeriSeal System uses a proprietary foam sealant polymer in order to close off the most damaged parts of the lung. The sealant itself is comprised of two liquids that when combined in air produces foam, this foam then hardens over time to produce a solid seal. By sealing off the most damaged regions of the lung this causes the deflation of the alveoli and a reduction in the size of the lung.

Known side effects include flu-like symptoms that generally pass after a few days. However, preliminary results from the University of Heidelberg (Germany), suggested that treatment with the AeriSeal system produced relatively few side effects; further study with a longer duration and a larger cohort of patients is required to fully assess this.

"We don't yet know the balance of risks and benefits for this procedure as well as we do for surgery," commented Mark Dransfield, lead investigator in the trials. "Certainly we hope the risk will be far lower, and preliminary data from Europe indicates this is true. I think having a safer option that is as effective or almost as effective as surgery will greatly improve our ability to take care of these folks."

Although still in the trial stages of treatment, the AeriSeal system does provide hope of an easy and effective treatment. However, the complications of such therapy are yet to be fully assessed.

– Written by Hamish McDougall

Source: University of Alabama at Birmingham Press Release: www.uab.edu/news/latest/item/3187-uab-first-in-us-to-test-new-emphysema-procedure

The editorial team welcomes suggestions for timely, relevant items for inclusion in the news. If you have newsworthy information, please contact:

Isaac Bruce,
Managing Commissioning Editor, *Clinical Investigation*
Future Science Group
Unitec House
2 Albert Place
London, N3 1QB, UK
t: +44 (0)20 8371 6090
e: i.bruce@futuremedicine.com
w: www.future-science-group.com

Campaign to further clinical data transparency

GlaxoSmithKline (GSK) recently announced its support for the AllTrials Campaign in a bid to increase clinical trial transparency. The campaign is driving for public disclosure of clinical trial results and clinical study reports (CSRs). This announcement goes hand-in-hand with GSK's recent aim to advance openness in R&D, which was stated in a press release in October 2012.

The company already publishes summary information about every clinical trial they commence, whether the end result is positive or negative. This recent commitment to the AllTrials campaign will also make CSRs accessible to the public. CSRs are formal study reports that include details of the design, methods and results of clinical trials. From now on, GSK will publish CSRs for all of its medicines once they have been approved or discontinued from development, meaning that the data can be reviewed by regulators and the scientific community.

Patrick Vallance, President, Pharmaceuticals R&D, at GSK, commented, "We are committed to being transparent with our clinical trial data to help advance scientific understanding and inform medical judgment. Our commitment also acknowledges the very great contribution made by the individuals who participate in clinical research."

GSK also intends to publish CSRs for all clinical outcomes trials dating back to the founding of the company, with priority publishing given to CSRs for its most commonly prescribed medicines. Over the next few years, a team specifically designed for this work will retrieve and examine each CSR from the GSK back catalogue and remove confidential patient information prior to publication.

– Written by Lisa Parks

Sources: GSK Press Releases: www.gsk.com/media/press-releases/2012/GSK-announces-further-initiatives-to-tackle-global-health-challenges.html; amd www.gsk.com/media/press-releases/2013/GSK-announces-support-forAll-Trials-campaign-for-clinical-data-transparency.html; Parks L. Increase in R&D openness to tackle disease in the developing world. *Future Med. Chem.* 4(18), 2237–2239 (2012).