Clin. Invest. (2013) 3(5), 425–427

CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Dual treatment approach may be the key to combating glioblastoma multiforme

By elucidating the mechanisms behind the aggressive recurrence of glioblastoma multiforme (GBM) after treatment with anti-angiogenic therapy, researchers may have discovered a new, effective method of treatment.

A team of researchers from the Mayo Clinic (AZ, USA) has highlighted a potential method of combating the recurrence of GBM after treatment with bevacizumab (Avastin™). In a study, published online in *PLOS ONE*, the team has discovered the underlying mechanism behind this recurrence and a potential method of treatment.

GBM is the leading cause of CNS tumor-related mortality. These poor clinical outcomes are associated with the powerful angiogenic activity of GBM and the ability to aggressively invade surrounding tissues. In recent years, antiangiogenic therapy has been the focus of the treatment of GBM. Significant therapeutic benefit has been observed in studies with the humanized monoclonal antibody bevacizumab, which targets the pro-angiogenic factor VEGF. However, after treatment with bevacizumab, tumor recurrence is often associated with increased invasiveness and rapid clinical deterioration. The mechanisms underlying this phenomenon were previously unknown.

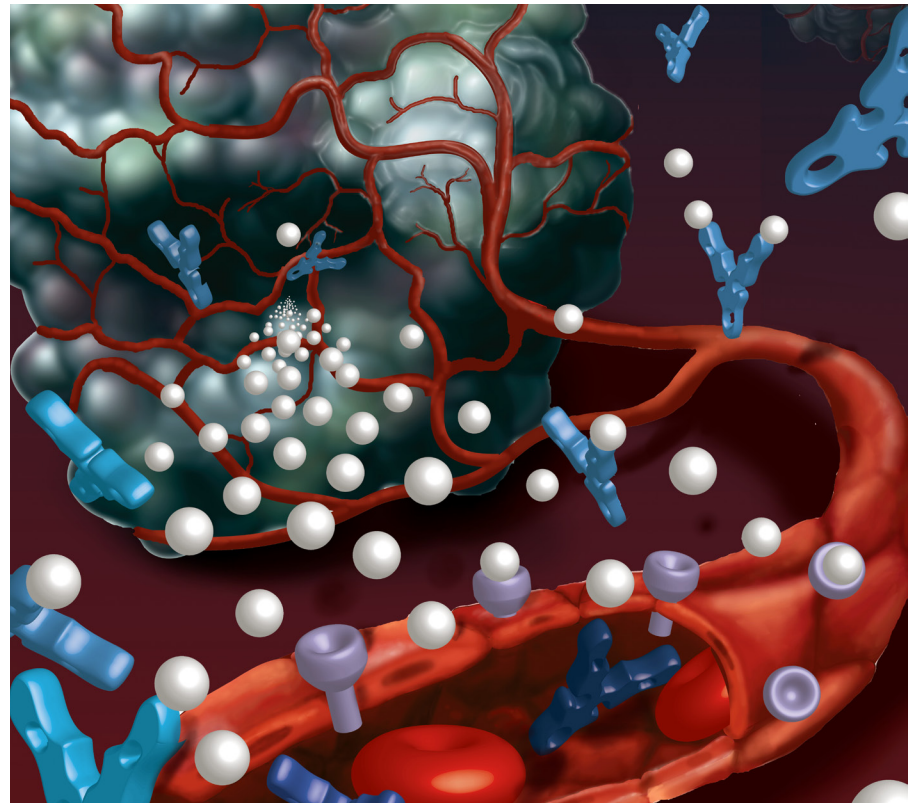
The team discovered that one possible mechanism responsible for this major impediment to the efficacy of antiangiogenic GBM therapy is the activation of Src family kinases. These then activate proteins at the edge of brain tumors that migrate to other parts of the brain to form new malignancies. Using an orthotopic xenograft model of GBM, the group demonstrated that Src family kinase activation and phosphorylation of downstream targets were upregulated at the leading edges of orthotopic glioma xenografts.

Dastinib is a drug that inhibits Src kinases. The team discovered that, while treatment with bevacizumab or dasatinib alone did not confer clinical benefit in mouse models of GBM, when used in combination, these drugs both shrank the tumors and prevented subsequent spread.

This study strongly suggests that Src family kinase activation underlies the tumor cell migration and invasion associated with GBM treated with bevacizumab. It also suggests that this impediment can be avoided by the dual treatment of GBM with bevicizumab and dasatinib (or other Src family kinase blockers). A Phase I clinical trial testing a combination of bevacizumab and dasatinib in GBM patients has already been conducted, with promising results. A Phase II trial of bevacizumab and dasatinib versus placebo in GBM patients is now being carried out.

Written by Caroline Telfer

Sources: Huveldt D, Lewis-Tuffin L, Carlson B *et al.* Targeting Src Family kinases inhibits bevacizumab-induced glioma cell invasion. *PLoS One* 8(2), e56505 (2013); Combo of avastin, second drug shows promise fighting brain cancer: www.sciencedaily.com/releases/2013/02/130214194111.htm



ISSN 2041-6792
10.4155/CLI.13.43 © 2013 Future Science Ltd

Rituximab chemotherapy regimens for treating advanced follicular lymphoma evaluated in new study

Clinical trial results, recently published in *Journal of Clinical Oncology* and lead by Massimo Federico at the University of Modena and Reggio Emilia (Italy), have shown important differences between common chemotherapy regimens for first-line treatment of follicular lymphoma (FL). These could be used to inform oncologists for their future decisions on chemotherapy treatments.

"These results will influence healthcare practitioner' decisions and may have important implications for the future treatment of implications for the future treatment of follicular lymphoma patients."

FL is an indolent cancer that accounts for 10–20% of all non-Hodgkin lymphomas in the Western world. The National Institute for Health and Care Excellence recommends the use of rituximab (R), a monoclonal antibody used for treating non-Hodgkin lymphomas, along with combinations of certain chemotherapies for the treatment of FL as standard. This type of treatment has been shown to produce higher response, overall- and progression-free-survival rates than chemotherapy alone. "When the study started in 2006, data from randomized trials confirmed that R added to any kind of chemotherapy improved treatment results" the team stated. However, less is known about the best type of chemotherapy regimen to use.

The team of scientists conducted an open-label, multicenter, randomized Phase III trial to compare different chemotherapy regimens in patients with previously untreated FL. They compared three common regimens, R-CHOP (R with cyclophosphamide, doxorubicin, vincristine and prednisone), R-CVP (R with cyclophosphamide, vincristine, and prednisone) and R-FM (R with fludarabine and mitoxantrone).

At the end of the therapy, all three arms had the same complete remission rates. However, R-CHOP and R-FM showed a significantly better time to treatment failure than R-CVP (62 and 59 vs 46%, respectively). The team stated that the "study concludes that both CHOP and FM given with R have the same antilymphoma profile and are both superior to R-CVP in terms of TTF." However it was also found that patients treated with R-FM had a higher incidence of toxicity.

The researchers concluded that, "the current standard therapy for patients with advanced FL should be R-CHOP followed by 2-year maintenance therapy with R for responding patients." These results will influence healthcare practitioners' decisions and may have important implications for the future treatment of FL patients.

Written by Georgina Askeland

Sources: Federico M, Luminari S, Dondi A *et al.* R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the fondazione italiana linfomi. *J. Clin. Oncol.* doi: 10.1200/JCO.2012.45.0866 (2013) (Epub ahead of print); Salles G, Seymour JF, Offner F *et al.* Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a Phase 3, randomised controlled trial. *Lancet* 377, 42–51 (2011).

Research asks whether a sufficient number of patients are studied before approval of new medicines

In a recent research article published in *PLOS Medicine,* a group of researchers explore whether the International Conference on Harmonization's E1 guideline recommendations are being upheld in the approval of new therapeutics by the European Medicines Agency. Their results suggest that for therapeutics against chronic conditions, the number of patients studied in clinical trials prior to approval is insufficient.

The researchers carried out their analysis on the European Commission's Community Register of Medicinal Products – including data from all medicines containing new molecular entities approved between 2000 and 2010. A total of 200 therapeutics were identified, which included orphan medicines. The main outcome measured was the total number of patients studied before the approval of such entities by the European Medicines Agency. In addition, data were analyzed for the number of patients studied at 6 or 12 months for chronic medication.

The researchers found that, on average, more patients were studied before the approval of medicines from chronic use, but that this number was still "insufficient to evaluate safety and long-term efficacy" when compared with the International Conference on Harmonization's E1 guideline recommendations. In total, 82.1 and 79.8% of medicines for chronic use "met guideline recommendations" in terms of patients studied for at least 6 and 12 months, respectively.

The authors suggest that a review of current study size and long-term data requirements is required, in particular for medicines intended for chronic use. In addition, they highlight the importance of post-approval safety and efficacy studies for new medicines.

Written by Alice O'Hare.

Source: Duijnhoven RG, Straus S, De Bruin ML, Raine JM, Hoes AW. Number of patients studied prior to approval of new medicines: a database analysis. *PLoS Med.* 10(3), e1001407 (2013).

New pretreatment options approved for the 8% capsaicin patch for the treatment of peripheral neuropathic pain

The European Commission has approved a patch label amendment for the 8% capsaicin patch. There are now extended options available for pretreatment before the use of the patch. Currently, prior to application of the patch, patients can ingest an oral analgesic or the area to be treated can be pretreated with topical analgesics.

The patch itself, named Qutenza® (Astellas Pharma Europe Ltd, Surrey, UK) is a cutaneous patch developed for the treatment of peripheral neuropathic pain. It is the first and only high concentration (8%) capsaicin patch licensed for the indication.

Peripheral neuropathic pain is a difficult-to-treat condition and has a negative effect on the sufferer's quality of life. It is most often caused by a disease or lesion to the peripheral somatosensory nervous system.

The 8% capsaicin patch has been approved for the treatment of peripheral neuropathic pain for use in non-diabetic adults and is approved for use in 21 countries in Europe.

The submission to the regulatory body was supported by LIFT study data – a study that aimed to investigate the use of an oral analgesic as a different option of pretreatment for the capsaicin patch.

The study comprised patients that were either randomized to receive tramadol tablets (oral analgesic) or an application of lidocaine cream (topical analgesic) before the 8% capsaicin patch was applied. Patients were treated with the patch for 60 min with a follow-up period of 7 days where tolerability and pain scores were monitored. The LIFT study defined the end point as a patient using the capsaicin patch for 90% of the duration that the patch was intended to be worn.

Written by Priti Nagda

Source: Astellas Pharma Europe Ltd newsroom: www.presseportal.de/pm/61801/2433374/european-commission-approves-new-pre-treatment-options-for-qutenza-tm-8-capsaicin-patch-in

Chicken pox may be a disease of the past

A new long-term effectiveness study, published in *Pediatrics*, has revealed that the vaccine for the childhood affliction chicken pox (*Varicella zoster*) has so far experienced great success.

The study, which followed 7585 children vaccinated with the varicella vaccine in 1995 over the subsequent 14 years, was designed to establish the long-term effectiveness of the vaccine.

Prior to a routine vaccination, established in 1995 in the USA, more than 90% of children and young adults experienced varicella infection before the age of 20. Remarkably, the study found that the overall vaccine effectiveness rate was approximately 90%. The incidence of varicella was nine- to ten-times lower in vaccinated children compared with children who did not receive the vaccine in the years before its introduction.

It has been made clear during this study that the varicella vaccine has been highly effective in limiting the contraction of the virus in children. "As with any vaccine, though, the rate of vaccination has a huge impact on effectiveness; the more children vaccinated, the more effective the vaccine is for the entire community," commented Randy Bergen, chief of outpatient pediatrics at Kaiser Permanente's Walnut Creek Medical Center (CA, USA).

Almost all breakthrough cases of varicella were classified as mild or moderate (<300 lesions), with only 28 out of 7585 children experiencing the severe symptoms (>300 lesions) most unvaccinated children experience. In addition, the incidence of varicella decreased over the study period owing to direct vaccine effectiveness and herd immunity.

Bergen concluded, "Keeping vaccination rates high confers benefit on the community as a whole because there are fewer children who can contract and spread the virus."

Written by Sophie Breeze

Sources: Kaiser Permanente National Press Release: http://xnet.kp.org/newscenter/pressreleases/nat/2013/040113-chicken-pox-vaccine-works.html; Baxter R, Ray P, Tran TN *et al.* Long-term effectiveness of varicella vaccine: a 14-year, prospective cohort study. *Pediatrics* doi:10.1542/peds.2012–3303 (Epub ahead of print) (2013).

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

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