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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in clinical investigation

New treatment option for delivering anticancer drugs demonstrated in clinical trial

First human trial shows 'minicells' are safe, well tolerated and can induce stable disease in cancer patients

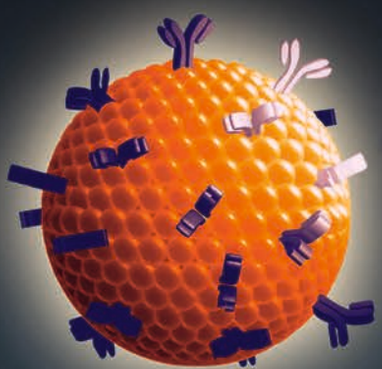
Research results of a Phase I clinical trial, recently presented at the 24th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (Dublin, Ireland), have shown 'minicells' can be safely given to patients with advanced, incurable cancers. In total, 28 patients were treated with the minicells at four centers in Australia. Ten patients had stable disease at 6 weeks and thus received more than one cycle of minicells.

The minicells, designed to deliver anticancer drugs directly to tumor cells, were developed by Himanshu Brahmbhatt and Jennifer MacDiarmid, founders of biotech company EnGeneIC (Sydney, Australia). The targeted delivery method aims to reduce toxicity side effects that are currently seen in the systemic delivery of chemotherapy, as well as to advance personalized treatment, specific to the genetic make-up of the tumor. Created from small bubbles of cell membrane pinched off the surface of mutant bacteria the minicells measure 400 nm in diameter, can be loaded with anticancer drugs and further coated with tumor-seeking antibodies that target surface receptors. Consequently, following delivery, cancer cells recognize the minicell, which is internalized, exposing the anticancer drug to the cancer cell nucleus.

Benjamin Solomon, principal investigator of the clinical trial and consultant medical oncologist at the Peter MaCallum Cancer Centre (Melbourne, Australia) explained the benefits of the larger size of the minicells over synthetic particles currently being developed: "This larger size means that the minicells preferentially fall out of the leaky blood vessels around the tumor and do not end up in the liver, gut and skin where they could cause nasty side effects like smaller particles do."

Solomon went on to describe the study protocol: "We loaded the cells with a cytotoxic chemotherapy drug (paclitaxel) and coated the minicells with an antibody targeting the loaded minicells to tumors expressing the EGF receptor – a protein that is found on the surface of many cancer cells. The study was then conducted in the way standard Phase I studies are conducted to determine the safety and toxicity of minicells by treating small groups of patients with progressively higher doses of minicells and closely monitoring safety and toxicity."

Noting that the key finding of the study was that minicells can be safely delivered to patients with advanced cancer forms, Solomon added: "Additionally, we showed that we could give multiple doses and one patient received 45 doses over 15 months. The major toxicity we observed was a mild self-limiting fever seen on the day of the infusion with little or no side effects seen in the remainder of the following week.



At higher doses we found that there were additional side effects, in particular changes in liver function tests, which, although asymptomatic, prevented us from raising the doses of the treatment higher."

Phase II trials of the minicells are now being planned, including a trial in patients with glioblastoma using minicells loaded with doxorubicin. Furthermore, the scientists are looking to develop imaging methods to track the minicells in patients.

– Written by James Potticary

Source: European Cancer Organisation press release: www.ecco-org.eu/Global/News/ENA-2012-PR/2012/11/9_11-First-trial-in-humans-of-minicells.aspx

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Alemtuzumab may be a new, superior treatment for relapsing multiple sclerosis

Two randomized controlled Phase III trials have been recently published in *The Lancet,* demonstrating that the monoclonal antibody, alemtuzumab, is more effective at reducing relapse rate in multiple sclerosis (MS) than IFN-β1a, one of the currently used treatments for the disease.

MS is an autoimmune disease in which the myelin sheaths around the axons of the brain and spinal cord are attacked by the immune system, leading to demyelination and a broad spectrum of symptoms. There are currently seven approved treatments for relapse-remitting MS, including IFN-β1a, IFN-β1b, glatiramer acetate, mitoxantrone, natalizumab, fingolimod and teriflunomide; these are modestly effective however each have their own profile of advantages and disadvantages. Alemtuzumab is a monoclonal antibody that is approved by the US FDA for the treatment of chronic lymphocytic leukemia and T-cell lymphoma.

One of the studies, lead by Jeffrey Cohen (Cleveland Clinic, OH, USA) and Alasdair Coles (University of Cambridge, Cambridge, UK) investigated alemtuzumab versus IFN-β1a as a first-line treatment for patients with relapsing-remitting MS. A total of 573 previously untreated patients aged 18–50 years were analyzed. The results were that 40% patients in the IFN-β1a group relapsed compared with 22% patients in the alemtuzumab group. In addition, 59% of patients in the IFN-B1a group were relapse-free at 2 years compared with 78% of patients in the alemtuzumab group. However, alemtuzumab treatment was associated with more adverse side effects than IFN-β1a, such as infection and development of other autoimmune diseases.

"Although other MS drugs have emerged over the last year – which is certainly good news for patients – none has shown superior effects on disability when compared with interferon except alemtuzumab. Additionally, no other treatment has led to improvements in disability," said Coles.

The other study, led by Coles, investigated alemtuzumab versus IFN-β1a after disease-modifying therapy for patients with relapsing-remitting MS. The participants were adults aged 18–55 years with relapsing-remitting MS and at least one relapse on IFN-β or glatiramer. A total of 628 participants were analyzed. The results were that 51% of patients in the IFN-β1a group relapsed compared with 35% patients in the alemtuzumab group. In addition, 47% of patients in the IFN-β1a group were relapse-free at 2 years compared with 65% of alemtuzumab-treated patients. As with the other study, alemtuzumab treatment was associated with more adverse side effects. Nevertheless, these results are encouraging for alemtuzumab as a potential drug of choice for relapsing-remitting MS.

> "Although other MS drugs have emerged over the last year ... none has shown superior effects on disability when compared with interferon except alemtuzumab."

"Our research shows the transformative effect that alemtuzumab can have for people with MS. Patients who continue to show disease activity while on their initial therapy are especially difficult to treat. Now, we have shown that alemtuzumab works where first-line drugs have already failed. It not only reduces the chances of disability associated with MS but may even result in long-term clinical improvements," said Alastair Compston (University of Cambridge, UK), principal investigator on both studies and chair of the steering committee that oversaw these and earlier clinical trials.

"Although alemtuzumab causes potentially serious side effects, these can be identified and treated provided a monitoring schedule is carefully followed," Coles stated, "additionally, we think that we can identify which patients are at risk of autoimmune disease after alemtuzumab, and we are currently recruiting for a clinical trial which will explore whether we can use a drug to reduce the risk of autoimmunity in those at highest risk."

The trials were supported by Genzyme (a Sanofi company) and Bayer Schering Pharma.

– Written by Jonny Patience

Sources: Cohen JA, Coles AJ, Arnold DL *et al.* Alemtuzumab versus IFN-β1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled Phase III trial. *Lancet* doi:10.1016/S0140–6736(12)61769–3 (2012) (Epub ahead of print); Coles AJ, Twyman CL, Arnold DL *et al.* Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled Phase III trial. *Lancet* doi:10.1016/S0140–6736(12)61768–1 (2012) (Epub ahead of print).

Ongoing results from the Phase III RTS,S malaria candidate vaccine trials show positive results for African infants

Results from the ongoing large-scale Phase III trial published in the *New England Journal of Medicine* have demonstrated that the RTS,S malaria vaccine candidate protected African infants against malaria. Infants vaccinated with RTS,S had one-third fewer episodes of malaria compared with infants immunized with a control vaccine.

Salim Abdulla, principle investigator at the Ifakara Health Institute (Tanzania) stated "We've made significant progress in recent years in our battle against malaria, but the disease still kills 655,000 people a year – mainly children under five in sub-Saharan Africa. An effective malaria vaccine would be a welcome addition to our tool kit, and we've been working toward this goal with this RTS,S trial. This study indicates that RTS,S can

help to protect young babies against malaria. Importantly, we observed that it provided this protection in addition to the widespread use of bed nets by the trial participants."

RTS,S was administered to 6537 infants (aged 6–12 weeks at first vaccination) along with standard childhood vaccines. The study found that over a period of 12 months – and following the third vaccine dose – the efficacy of the RTS,S vaccine was 31% and 37% against clinical and severe malaria respectively. About 86% of participants continued to use existing malaria control interventions such as insecticide-treated bed nets, demonstrating that the efficacy of RTS,S vaccination shown in this trial was in addition to existing interventions.

The RTS,S vaccine is able to prevent the parasite from infecting, maturing and multiplying in the liver. This stops the parasite re-entering the bloodstream, which would lead to the infection of red blood cells and disease symptoms. A previously published study into the efficacy of RTS,S in children aged 5–17 months of age against clinical and severe malaria was 55 and 47%, respectively. Researches are keen to analyze the difference in efficacy between the two age groups studied.

RTS,S was also seen to demonstrate an acceptable safety and tolerability profile. Abdulla remarked "We were also glad to see that the study indicated that RTS,S could be administered to young infants along with standard childhood vaccines and that side effects were similar to what we would see with those vaccines."

> "This study indicates that RTS,S can help to protect young babies against malaria."

RTS,S malaria vaccine candidate immunized infants were reported to have no additional serious adverse events compared with the infants in the control group who were immunized with a comparator vaccine. Local injection site reactions were less frequent following RTS,S vaccinations, however, fever was reported to be slightly more common than in the control vaccine group.

"This is an important scientific milestone and needs more study," said Bill Gates, cofounder of the Bill & Melinda Gates Foundation, which partially funds the project. "The efficacy came back lower than we had hoped, but developing a vaccine against a parasite is a very hard thing to do. The trial is continuing and we look forward to getting more data to help determine whether and how to deploy this vaccine."

Research centers across seven African countries are continuing the trial. Results for longer-term efficacy and the impact of a booster dose are expected before the end of 2014. The WHO has indicated that positive results could lead to a policy recommendation for the RTS,S malaria vaccine candidate in 2015.

– Written by Sophie Breeze

Sources: GlaxoSmithKline press release: www.gsk.com/media/press-releases/2012/RTS-vaccine-candidate-reduces-malaria-by-one-third-in-infants.html; The RTS,S Clinical Trials Partnership. A Phase III Trial of RTS,S/AS01 Malaria Vaccine in African Infants. *N. Engl. J. Med.* doi:10.1056/NEJMoa1208394 (2012) (Epub ahead of print).

Liraglutide versus exenatide: which is the superior drug?

Type 2 diabetics are sometimes prescribed glucagon-like peptide-1 receptor agonists in order to improve their glycemic control while decreasing body weight. Such drugs include exenatide and liraglutide. To determine the safety and efficacy of these drugs, Guntram Schernthaner (Rudolfstiftung Hospital, Vienna, Austria) and colleagues conducted a study aimed at comparing the impact of once-daily liraglutide with once-weekly exenatide in individuals with Type 2 diabetes.

The research, published in *The Lancet,* involved a trial that took place in 19 different countries between 11th January 2010 and 17 January 2011. The investigators selected 912 participants who had Type 2 diabetes, were older than 18 years and were undergoing treatment with oral antihyperglycemia medication and lifestyle intervention. The participants were randomly assigned into groups, in which they would receive injections of 1.8 mg liraglutide once per day or 2 mg exenatide once per week. The group stated that "the primary endpoint was change in glycated hemoglobin from baseline to week 26" and they analyzed the findings by treatment intentions.

All but one of the participants were incorporated into the intention-to-treat analysis. The researchers claim that the levels of glycated hemoglobin were subject to more change in those treated with liraglutide compared with those treated with exenatide. Furthermore, it appeared that adverse effects including diarrhea and nausea were more common among the liraglutide group; however, in both groups, these adverse events decreased in prevalence with time.

> "...the group concluded that both liraglutide and exenatide were associated with improved glycemic control."

After analyzing the results, the group concluded that both liraglutide and exenatide were associated with improved glycemic control. They further claim that greater reductions were observed among those being administered liraglutide. The investigators state that their findings, in addition to injection-related factors such as frequency, could potentially aid healthcare advisors to decide which treatment option to prescribe Type 2 diabetics.

– Written by Hannah Branch

Source: Buse JB, Nauck M, Forst T *et al.* Exenatide once weekly versus liraglutide once daily in patients with Type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* doi:10.1016/S0140–6736(12)61267–7 (2012) (Epub ahead of print).

Mesothelioma sufferers with an inactive *NF2* gene display encouraging results to new drug

The first trial for the mesothelioma drug, GSK2256098, was presented recently at the 24th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (Dublin, Ireland). The findings showed encouraging results for all those who participated in the trial but especially the patients who possessed an inactive *NF2* gene.

Mesothelioma, a rare form of cancer caused by exposure to asbestos, is a fatal condition with a survival rate of approximately 9–17 months after diagnosis. Currently, no substantial treatment has been developed.

Merlin, a protein expressed by the *NF2* gene, negatively regulates focal adhesion kinase (FAK); however, in 50% of mesotheliomas, the *NF2* gene is inactivated so merlin does not inhibit FAK, leading to increased proliferation and metastasis of mesothelioma cells.

Jean-Charles Soria, Professor of Medicine and Medical Oncology at South Paris University and Head of early drug development at the Institut Gustave Roussy (Paris, France), explained how the new drug works, saying "This suggested that if we could inhibit FAK in mesothelioma patients, it might slow or stop the spread of the disease. Preclinical work has shown that an agent, currently known as GSK2256098, is a potent and specific inhibitor of FAK." Soria continued, "A patient with mesothelioma, who had progressed quickly on prior therapies, had prolonged stable disease while on GSK2256098, which is suggestive of clinical activity."

> "Mesothelioma is a deadly disease without many treatment options, and therefore identification of novel and effective therapies is needed."

Patients treated with GSK2256098 showed an improved response with no sign of disease progression for an average of 17 weeks; however individuals who had an inactive *NF2* gene displayed an increased average of 24 weeks before the cancer progressed. This was over double the length of patients with an active *NF2* gene, who had an average of 11 weeks.

Describing the results, Soria said "These findings are important but preliminary, they show that merlin is a potential biomarker in mesothelioma that may enable us to identify a subset of patients who could benefit from GSK2256098 and have longer, progression-free survival."

The GSK2256098 Phase I trial enrolled 29 patients in July 2010 from nine centers in the UK, France and Australia and is still ongoing with larger clinical trials being planned to confirm these results. Soria concluded "Mesothelioma is a deadly disease without many treatment options, and therefore identification of novel and effective therapies is needed."

– Written by Theo Bond

Source: Conference News: http://ecancer.org/news/3548

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