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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Oncology studies tend to be smaller and less robust

Compared to other diseases, studies for oncology studies tend to be smaller and less robust. This is in part due to the fact that there is more inclination to speed up newer treatments for patients suffering from cancer.

However, this does raise questions as to how cancer therapies derived from these studies will actually work in practice. Researchers at Duke Medicine (NC, USA) have published an analysis of nearly 9000 cancer clinical research studies that were registered between 2007 and 2010 on the clinicaltrials.gov website. This analysis was the result of a public-private partnership between the US FDA and Duke university as a means to both identify and encourage practices that will lead to improved clinical research.

> "Unfortunately, the high prevalence of small studies that lack rigor limits the ability to assess the evidence supporting specific treatments."

Bradford Hirsch (Duke University, NC, USA) was the lead author of the study and explains the study's aims, "We need to understand the strengths and weaknesses of the clinical studies in oncology. There are a lot of reasons for why cancer studies are different than those for other illnesses – cancer is a very grave disease and for a long time there weren't a lot of treatment options. But what we're trying to understand is if those differences justify differences in the clinical research being conducted."

Hirsh, along with his research team found that in the case of oncology clinical research studies, they were predominately small. These early phase trials usually evaluated a single treatment without comparing it with other therapies. The more rigorous and larger trials randomly assign patients to various treatments, double blinding both patients and doctors from acknowledging who has received the therapy that is being investigated, thus eliminating bias.

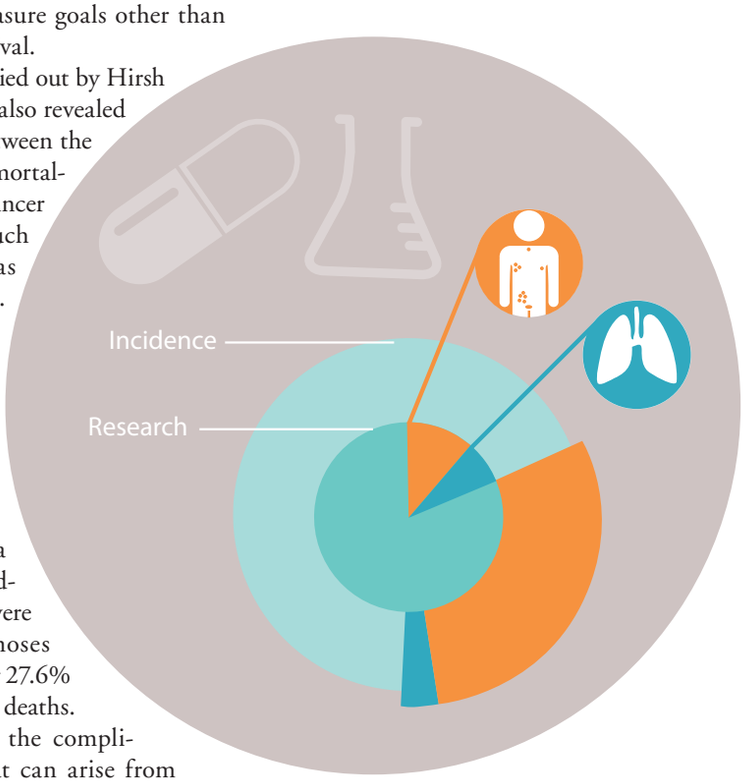
The orientation to a less robust clinical study design is in significant contrast with other areas of medicine. The move can be, in part, explained by the accelerated approval process that the FDA has adopted since 1992 in order to improve access to treatments for grave life-threatening conditions such as cancer. Therefore, early-phase studies usually measure goals other than just extending survival.

The analysis carried out by Hirsh and his researchers also revealed some disparities between the inci-dence and the mortality of some of the cancer types and how much clinical research as being carried out. This can be highlighted by looking at data for lung cancer which revealed that although it has the highest occurrence it is the focus of a mere 9.2% of studies. In 2010 there were 14.5% new diagnoses and it accounted for 27.6% of all cancer-related deaths.

Hisrch explains the complicated situation that can arise from these smaller studies, "An inherent tension arises between the desire to use new, life-saving treatments and the imperative to develop the evidence that patients, clinicians, regulatory agencies, and advocacy groups need to make sound decisions. Unfortunately, the high prevalence of small studies that lack rigor limits the ability to assess the evidence supporting specific treatments."

Written by Priti Nagda

Sources: Duke University Medical Center News: www.dukehealth.org/health_library/news/cancer-studies-often-lack-necessary-rigor-to-answer-key-questions



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Enzalutamide recommended for EU approval in advanced prostate cancer

Following application from Astellas Pharma Europe, Ltd. (Chertsey, UK), Xtandi™ (enzalutamide; 40 mg; soft capsule) has received a positive opinion from the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) to be recommended for European Commission approval for the treatment of adults with metastatic castration-resistant prostate cancer (mCRPC) following disease progression during or after docetaxel therapy.

Enzalutamide, developed by Medivation, Inc. (CA, USA), is a once-daily androgen receptor signaling inhibitor that was approved by the US FDA in August 2012 for the treatment of patients with mCRPC who have previously received docetaxel. The positive opinion from the CHMP follows results from the Phase III AFFIRM trial, which evaluated 160 mg/day enzalutamide versus placebo in 1199 mCRPC patients who had previously received docetaxel-based chemotherapy. The AFFIRM trial demonstrated a statistically significant improvement in overall survival in patients receiving enzalutamide compared with placebo, and indicated that it was well tolerated. The positive recommendation from the CHMP will now be reviewed by the European Commission.

Written by Francesca Lake

Sources: Committee for Medicinal Products for Human Use (CHMP). Summary of opinion (initial authorisation). Xtandi: www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002639/WC500142493.pdf; Press release: Positive CHMP opinion for XTANDI™ (enzalutamide) in advanced prostate cancer. 26th April, 2013.

Phase I trial data show promise for antibody immunotherapy in cancer treatment

Recent Phase I trial results have been presented at the AACR Annual Meeting 2013, held in Washington, DC (USA), on the 6–10 April 2013, which demonstrated that the engineered antibody MPDL3280A was safe and effective for several cancers. Michael Gordon (Pinnacle Oncology Hematology, Scottsdale, AZ, USA) presented the findings.

The engineered antibody, MPDL3280A, targets and blocks PD-L1, a protein found on the surface of several types of cancer cell, which is believed to suppress the ability of the immune system to fight such cells by binding to its receptor PD-1, found on immune cells.

"PD-L1 is essentially a plug, which inserts into an outlet (PD-1) on the surface of the immune T cells," Gordon said. "As the T cells come close to the tumor, for example, they are engaged by PD-L1, which inserts into the outlet on the surface of the T cell. That starts a signal inside the T cell that blocks the T cell's ability to kill the cancer cell."

"The PD-L1 antibody differs most significantly (from anti-PD-1 antibodies) in that it binds PD-L1, the tumor-expressed ligand for PD-1, as opposed to the PD-1 receptor itself," said Gordon. "One key difference is that the anti-PD-L1 antibody does not affect the interaction between the PD-L2 protein expressed in lung tissue and the PD-1 receptor. This may provide an additional safety benefit by reducing the risk of pneumonitis and pulmonary toxicity."

Pneumonitis has been shown to be a very rare, but seriously toxic complication of antibodies against PD-1; hence reduction of this is an important goal for antibodies targeting this PD-1 interaction. The fact the MPDL3280A does not affect PD-L2 may help to achieve this goal.

"Our PD-L1 antibody was well tolerated, and there were no limiting toxicities," stated Gordon, "It was active with antitumor activity across a broad range of cancers, and we have developed biomarker tools that we are testing, which may allow us to optimize patient selection for this novel therapy."

Thirty patients were treated with escalating doses of the antibody from 0.01–20 mg/kg every 3 weeks. Patients had a variety of locally advanced or metastatic solid tumors and had previously received a median of two prior therapies and received a median of 5.5 doses of the antibody.

"We were able to escalate to the top dose without being limited by any serious side effects," Gordon said.

"From a therapeutic standpoint, we were able to identify a number of patients with a broad range of diseases, including lung cancer, kidney cancer, colon cancer and stomach cancer, who responded to the treatment."

It is likely that anti-PD-L1 antibodies will be active against a range of tumor types, provided the tumor expresses the PD-L1 protein on its cell surface and that PD-L/PD-L1 signaling is important for the tumor's growth. Although these are preliminary results, they show promise for a novel treatment for a range of cancers.

"One would anticipate, compared with drugs being developed to specifically block the T-cell outlet (PD-1) and, therefore, block the relationship between the outlet and both PD-L1 and PD-L2, that we might see less lung or pulmonary toxicity with MPDL3280A. But we need to conduct larger studies to confirm this."

"In terms of antitumor activity, all of [these immune checkpoint targeting] agents seem to have exciting activity in patients with metastatic solid tumors," said Gordon. "The remaining question is whether some of these outstanding responses will be long-lasting."

Written by Jonny Patience

Sources: American Association for Cancer Research press release: engineered antibody demonstrated safety, efficacy in wide range of advanced tumors. www.newswise.com/articles/engineered-antibody-demonstrated-safety-efficacy-in-wide-range-of-advanced-tumors; Azvolinsky A. AACR: Immunotherapy Antibody Has Activity in Range of Solid Tumors. *Cancer Network*. www.cancernetwork.com/conference-reports/aacr2013/content/article/10165/2137210

Promising Phase II results for reduced radiation in therapy for lymphoma patients

A recent single-arm Phase II trial, conducted by Wyndham Wilson and colleagues at the National Cancer Institute (Bethesda, MD, USA), demonstrated that a new regimen of lymphoma treatment was effective at curing primary mediastinal B-cell lymphoma without using radiation. The study was recently published in *The New England Journal of Medicine*.

Primary mediastinal B-cell lymphoma mainly affects people from their teenage years to their early 30s. Although most patients are cured with a combination of chemotherapy and radiation therapy, about one-fifth of patients see their disease progress. Patients who undergo radiotherapy receive radiation to their chest, which can cause new cancers and damage the heart. This is also a particular problem for women, in whom primary mediastinal B-cell lymphoma is more common, as it increases their chances of developing breast cancer.

The trial followed 51 patients with untreated primary mediastinal B-cell lymphoma for a period of between 10 months and 14 years. Every patient received infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) and filgrastim without radiotherapy.

After follow up, all but two patients achieved a complete remission when treated with DA-EPOCH-R. The two patients who did not achieve a complete remission underwent radiotherapy and were disease-free at follow-up. No evidence of other diseases or cardiotoxic effects developing subsequently was detected.

"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," said Wilson.

A retrospective analysis at another center (Stanford University Medical Center, Stanford, CA, USA), tested this regimen to treat 16 patients with primary mediastinal B-cell lymphoma. This study demonstrated similar results, verifying these findings.

"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," stated Kieron Dunleavy (National Cancer Institute) and first author on the study. "Based on our results, an international Phase II trial of DA-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."

Written by Jonny Patience

Sources: National Cancer Institute press release: NIH trial shows promising results in treating a lymphoma in young people: www.cancer.gov/newscenter/newsfromnci/2013/DA-EPOCHlymphoma; 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).

Topical arthritis treament shows promise in dry eye disease

New research has demonstrated the benefits of using an approved rheumatoid arthritis drug in the treatment of dry eye disease. The results of the clinical trial are published online in *JAMA Ophthalmology*.

Researchers from the Massachusetts Eye and Ear Infirmary (MA, USA), Harvard Medical School (MA, USA) and the Brigham and Women's Hospital (MA, USA) set out to evaluate the safety and efficacy of treatment with topical anakinra, a recombinant version of human IL-1Ra. The data suggest that IL-1 antagonists, like anakinra, may provide a novel therapeutic option for patients with dry eye.

The research team performed a randomized, double-masked and vehicle-controlled clinical trial. A total of 75 patients were recruited over the 12 week study and randomly allocated to receive either eye lubricant, 2.5 or 5% anakinra. Akinra was well tolerated and no reports of serious adverse reactions were attributed to the therapy.

Anakinra 2.5% was fourtimes more likely than the eye lubricant to bilaterally eliminate corneal staining; one of the primary outcomes being measured. Furthermore, topical akinra significantly reduced dry eye symptoms sixtimes more effectively than the eye lubricant. When akinra administration was stopped, patients reported an increase in dry eye symptoms.

Senior author, Reza Dana (Harvard Medical School) comments on the findings of the trial: "This clinical trial was a significant milestone in our research. The results clearly show us not only that we can possibly help the millions of people affected by dry eye disease worldwide, but that biologics such as this have the potential to provide targeted therapies for other ocular ailments, as well."

"We have never seen results such as this before in a trial to treat dry eye disease. We possibly have found a safe, well tolerated eye drop that can treat the underlying cause of dry eye rather than just temporarily mask the symptoms. We are excited about the positive results we saw in the data and with our patients who found relief in their symptoms and were able to return to some of their normal daily activities."

Dry eye disease is one of the most common ophthalmic conditions and is incompletely understood. With an estimated nine million sufferers in the USA alone, there is significant need for effective and long-term treatment of the condition which causes discomfort and visual disturbances.

Written by Jitesh Patel

Sources: Amparo F, Dastjerdi MH, Okanobo A *et al.* Topical Interleukin 1 Receptor Antagonist for Treatment of Dry Eye Disease: A Randomized Clinical Trial. *JAMA Ophthalmol.* doi: 10.1001/jamaophthalmol.2013.195 (2013) (Epub ahead of print). Massachusetts Eye and Ear Infirmary Press release: www.eurekalert.org/pub_releases/2013–04/meae-tuo041813.php

Positive reports from Phase I H5N1 vaccine clinical trial

A Phase I clinical trial for an H5N1 avian influenza virus-like particle (VLP) vaccine candidate has shown promising results.

Researchers from the Infectious Disease Research Institute (IDRI; WA, USA), and Medicago Inc. (NC, USA) have recently announced that their Phase I clinical trial has demonstrated positive interim results. Not only has the H5N1 vaccine been found to induce a solid immune response exceeding the European Medicines Agency Committee for Medicinal Products for Human Use immunogenicity criteria but the vaccine was also found to be safe and well tolerated. The results were revealed at the World Vaccine Congress (16–18 April 2013) in Washington, DC (USA).

H5N1 causes avian influenza, a highly infectious, severe respiratory disease in birds. Human cases occur occasionally and although the WHO reports that it is difficult to transmit the infection from person to person, when infected, the mortality rate is approximately 60%. As pandemic flu is highly unpredictable, efforts are currently being made to create and stockpile a vaccine to combat H5N1 that reduces the amount of vaccine needed per person and can be easily administered. Due to the unpredictability of pandemic flu, efforts are being made to create and stockpile a vaccine to combat H5N1 that reduces the amount of vaccine needed per person and can be easily administered.

Andy Sheldon, President of Medicago, comments on the findings; "These positive US clinical trial results confirm that our H5N1 vaccine candidate is the best in class in our opinion, positioning Medicago as a significant player in the global pandemic market. The robustness of our H5N1 vaccine coupled with our rapid speed of production, offers a vastly improved solution in preparing for and managing potential pandemics. We also believe that our H5N1 vaccine with alum is the only alum-adjuvanted pandemic vaccine to achieve the three CHMP immunogenicity criteria."

The vaccine was tested in three different configurations: using IDRI's Glucopyranosyl Lipid A (GLA) formulated adjuvant, given both intramuscularly and intradermally, and using alum intramuscularly. The trial started in September 2012 enrolling 100 healthy adult volunteers between the ages of 18–49 years. The trial focused on evaluating the safety and immunogenicity of the H5N1 vaccine in combination with IDRI's GLA adjuvant. Two doses of a given formulation of the vaccine were administered intramuscularly or intradermally to each participant. The route of administration was also measured to test previous indications that microneedle devices (US FDA licensed device, MicronJet600®, NanoPass Technologies, Israel) allow significant dose sparing. This study is among the first to test intradermal adjuvants and is the first time GLA has been tested intradermally. Currently. the H5N1 vaccine candidate has been tested in over 300 volunteers, with no serious adverse reactions. All three configurations of adjuvant and route of administration for the H5N1 vaccine candidate induced a solid immune response against the H5N1 viral strain.

Medicago's H5N1 vaccine candidate was formulated to protect against the Indonesian influenza virus and is manufactured in the plant *Nicotiana benthamiana*, using the Company's VLP technology. This technology only requires the genetic sequence of a viral strain rather than the live influenza virus, allowing vaccines to be manufactured within four weeks of obtaining the genetic sequence of a pandemic strain. This is much improved on the current manufacturing technologies that can only deliver a vaccine 6 months after a pandemic is declared as they rely on strain adaptation. Brian Ward (McGill University, QC, Canada) member of Medicago's scientific advisory committee comments on the results "This H5N1 vaccine candidate represents the next generation of flu vaccines, combining our adjuvant technology with Medicago's rapid VLP technology and the intradermal delivery device from NanoPass."

Speaking on the relevance of their results, Andy Sheldon, remarks "The combination of our vaccine candidate with IDRI's adjuvant generated a robust immune response. In the case of a pandemic, governments will require the rapid development of an effective vaccine within their borders to conquer the spread of the virus, with our cost-effective and capital inexpensive system we are perfectly poised to obtain this objective." The group plan to further investigate the use of alum and formulated GLA in a Phase II trial with results expected in late 2013.

Written by Jenaid Rees

Sources: Infectious Disease Research Institute press release: www.idri.org/ress-04–17–13.php; WHO. H5N1: page: www.who.int/nfluenza/human_animal_interface/avian_influenza/h5n1_research/faqs/en/

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