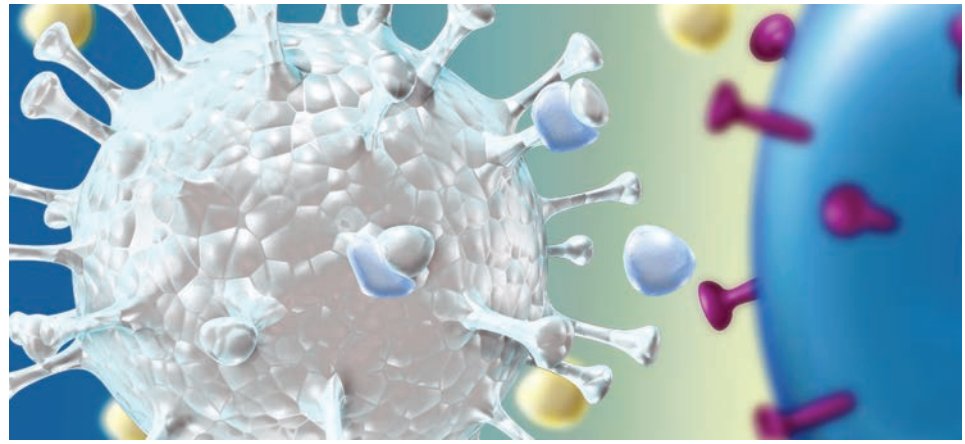
News & Views in ...
CLINICAL INVESTIGATION
Highlighting the latest news in clinical investigation

Effectiveness of Tamiflu during swine flu pandemic assessed



Study suggests that Tamiflu reduced the risk of death by 25% in adults hospitalized with H1N1 pandemic influenza

During the 2009–2010 influenza A H1N1 pandemic, neuraminidase inhibitors (NAIs), such as Tamiflu, were commonly used. However, it was unknown how effective they were at reducing mortality.

Jonathan Nguyen-Van-Tam (University of Nottingham, UK) and lead author of the study, explained: "There has been a lot of previous controversy about whether NAIs work in reducing serious complications and deaths due to influenza. Many countries stockpiled NAIs in readiness for a future pandemic. But it's fair to say that when the 2009 pandemic actually started we did not know if these drugs would reduce deaths – governments around the world had simply made a best estimate that this would probably be so."

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The large meta-analysis, published recently in *The Lancet Respiratory Medicine*, tried to address this by assessing if NAI treatment affected mortality in patients hospitalized with confirmed or suspected H1N1 infection between January 2009 and March 2011. In total, 29,234 patients from 38 countries were included in the study. It was found that irrespective of timing, NAI treatment reduced mortality risk when compared with no treatment (adjusted odds ratio [OR] 0.81; 95% CI: 0.70–0.93; p = 0.0024) and early treatment reduced mortality risk when compared with late treatment (adjusted OR 0.48; 95% CI: 0.41–0.56; p < 0·0001). However, it was observed that these findings were non-significant in children.

"We did our best to assemble and combine all the data we could identify from around the entire globe and to perform the cleanest analysis possible, given the fact that it's unethical to do clinical trials during a pandemic," added Nguyen-Van-Tam. "From our results, it seems that in 2009, among patients hospitalized with the pandemic virus, the chances of dying could be reduced by roughly

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one half if an NAI was given with 48 h of illness onset compared with no treatment. In my view, these data suggest that NAIs are a likely to be important in the fight against both seasonal and pandemic influenza."

Consequently, the authors conclude that NAI treatment should be used as soon as possible after the onset of flu symptoms in adults, particularly in hospitalized adults.

– Written by Natasha Leeson

Sources: University of Nottingham press release: www.nottingham.ac.uk/news/pressreleases/2014/march/tamiflu-saved-lives-during-swine-flu-pandemic,-international-study-finds.aspx; Muthuri SG, Venkatesan S, Myles PR et al. *Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data.* Lancet Respir. *doi:10.1016/S2213-2600(14)70041-4 (2014) (Epub ahead of print).*

Stubborn blood cancers: is idelalisib ideal?

A recently published set of three studies suggest that a pill that suppresses a key regulator of cancer growth may provide hope for relapsed leukemia and lymphoma patients running out of treatment options.

Blood cancer patients are typically administered a combination of chemotherapy and immunotherapy. Owing to the harmful side effects of chemotherapy and the fact that patients typically develop resistance, researchers have been prompted to investigate new targeted therapies that may be able to block the production of cancer cells while leaving normal cells unharmed.

Taken as a pill, idelalisib first targets and blocks the expression of the delta isoform of the PI3K enzyme, critical for the activation and survival of cancerous B cells. Idelalisib's narrow targeting of the PI3K delta make it an attractive potential therapy for patients with cancers that form in the B-cell pathway such as chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphoma (iNHL) and mantle cell lymphoma (MCL).

Discussing the drug, Jennifer Brown (Dana-Farber Cancer Institute, MA, USA), one of the study's authors commented "Idelalisib is a part of a revolutionary new class of treatments that can hone in on a specific target without causing the wide range of side effects seen with chemotherapy."

In the three studies the investigators present data from a large Phase I study evaluating the safety and efficacy of idelalisib in > 150 patients with CLL, iNHL and MCL. Prior to joining the trial, all patients had received several previous treatments (some as many as 14) that either failed to destroy the disease or provided only temporary reprieve. After an initial study involving all trial participants, patients were separated into CLL, iNHL and MCL disease cohorts and received varied doses of idelalisib. The study results suggest that the therapy appeared to be effective, as patients suffered few side effects and demonstrated promising response rates, with 72% of CLL patients, 47% of iNHL patients and 40% of MCL patients achieving either a complete or partial response.

Another one of the authors, Ian Flinn (Sarah Cannon Research Institute, TN, USA) noted, "Considering the high number of previous therapies that these patients had received, higher than we sometimes see in comparable studies, the efficacy of idelalisib that we observed was remarkable," adding that "It was this initial excitement that has inspired further studies of this therapy in patients with treatment-resistant blood cancers."

In the studies, while patients in the CLL and iNHL cohorts experienced significant and prolonged reduction of disease activity, the authors note that patients with MCL experienced less favorable responses. Despite MCL patients' high overall response rate of 40% to idelalisib, the duration of their response to the drug was not as impressive; only a small fraction (22%) enjoying prolonged benefits. Despite the modest duration of survival facilitated by idelalisib in the MCL group, the strong response rate suggests that investigators have identified a key regulator of cancer growth; however, more research is needed to further understand the potential of this therapy in MCL patients.

Coauthor Brad S Kahl (University of Wisconsin, WI, USA) opined "While idelalisib is unlikely to receive designation as a single-agent therapy in mantle cell lymphoma due to the short duration of response, the path forward will likely include administering it in combination with other agents or developing second-generation PI3K inhibitors. This study offers a strong foundation for future research on idelalisib in this disease."

– Written by Dominic Chamberlain

Source: *American Society of Hematology press release: www.hematology.org/News/2014/12509.aspx; This story is also featured on: www.oncology-central.com*

New targeted cancer therapy for resistant gynecologic cancers

Mutations in the infamous *BRCA* gene are synonymous with breast cancer and in addition woman who carry a *BRCA* mutation also have a high risk of developing gynecologic cancers. A recent Phase II study, presented at the Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer (FL, USA), has shown that gynecologic cancer cells that have a *BRCA* mutation appear to be sensitive to veliparib.

This drug works by targeting an enzyme called PARP, which is essential in enabling cancer cells to repair themselves after DNA damage. As such veliparib has been effective when combined with chemotherapy but it had not be identified if the drug is effective when used as a single agent, until this recent trial.

Robert Coleman, lead author of the study and professor and vice chair of clinical research at the University of Texas MD Anderson Cancer Center (TX, USA), explained that "One criticism of the PARP drugs is they are not active in patients who have developed resistance to other therapies, but we found veliparib appears to be effective in some platinum-resistant patients with recurrent or persistent disease." Coleman continued "Most of these patients have run out of treatment options, and it is very hopeful to potentially have another therapy to offer them."

A twice daily dose of veliparib was given to 50 patients with *BRCA* gene mutations. Disease was stabilized for more than four months in over half of the patients (26) and overall 26% of patients responded positively to the treatment, with their tumors reducing in size. In addition, tumors in two patients completely disappeared.

Coleman concluded "Patient recruitment can be a problem for many clinical trials, however, this one filled up very quickly, which reflects that women and their doctors understand that PARP inhibitors hold real promise."

– Written by Theo Bond

Source: *The Society of Gynecologic Oncology Press release: www.sgo.org/newsroom/news-releases/targeted-cancer-therapy-may-treat-resistant-gynecologic-cancers; This story is also featured on: www.oncology-central.com*

Stem cells show promise in the treatment of failing hearts

New research presented by a team from Rigshospitalet University Hospital Copenhagen (Copenhagen, Denmark) at the American College of Cardiology's 63rd Annual Scientific Session suggests that heart failure patients may benefit from a new treatment in which stem cells derived from bone marrow are injected into the heart.

Heart failure is a leading cause of mortality and morbidity. Treatments are available but many patients are still dramatically debilitated by the disease. This study is the largest placebo-controlled double-blind randomized trial to use mesenchymal stromal cells injected directly into the heart muscle to treat patients with chronic ishemic heart failure. Previous studies have demonstrated that mesenchymal stromal cells can stimulate repair in various tissues, including heart muscle.

A total of 59 patients with chronic ischemic heart disease and heart failure were included in the study. A small amount of bone marrow was extracted from each patient and the mesenchymal stromal cells were then isolated and induced to self-replicate. Patients were then given an injection containing either a saline placebo or their own cultured mesenchymal stromal cells directly into the heart muscle via a catheter inserted in the groin; a procedure requiring only local anesthesia.

After 6 months, treated patients showed an 8.2 ml decrease in end systolic volume, the study's primary end point and a key measure of the heart's pumping ability. An increase in end systolic volume of 6ml was observed in patients in the placebo group.

These results support previous findings from smaller studies that demonstrated reduced scar tissue in the heart in patients treated with stem cells. Researchers will now continue to monitor these patients in order to evaluate the long-term outcomes. A larger, Phase III clinical trial is now required in order to progress towards the acceptance of this treatment for widespread use in patients with ischemic heart failure.

– Written by Caroline Telfer

Source: *www.sciencedaily.com/releases/2014/03/140331130858.htm*

Mood stabilizing drug linked to reduced risk of head and neck cancer

Johann Christoph Brandes of Emory University (GA, USA) recently led an investigation into the anticancer potential of the mood stabilizing drug valproic acid. Valproic acid is able to inhibit the action of histone acetyl transferase enzymes, which assist in the regulation of gene expression by orchestrating epigenetic changes to DNA. Such changes are known to play a major part in the carcinogenesis of tobacco-related cancers. The results of the study, published online ahead of print in *Cancer*, indicate that use of valproic acid is associated with a lower risk of developing head and neck cancers.

Utilizing a data set linked to the Veterans Affairs Central Cancer Registry, the authors conducted a retrospective cohort study to evaluate the effect of valproic acid treatment on the risk of developing cancers of the head and neck, prostate, bladder, colon and lung. Overall, they evaluated this potential anticancer effect in 439,628 veterans aged >40 years, 26,911 off whom were receiving valproic acid for the treatment of bipolar disorder, post-traumatic stress disorder, migraines and seizures.

Hazard models indicated that those who took valproic acid for at least one year were associated with a 34% decreased risk of head & neck cancer, compared with those who did not receive the treatment. Additional benefit was noted with higher doses and longer duration of treatment. However, no differences in incidence were observed in the other malignancies investigated.

"A 34 percent risk reduction for the development of head and neck cancer with valproic acid use could result in the prevention of up to approximately 16,000 new cases and 3000 to 4000 annual deaths in the US alone," commented Brandes. "Head and neck cancer is an important global health crisis, and low cost and low toxicity prevention strategies like valproic acid use have a high potential impact on pain, suffering, costs, and mortality associated with this disease."

– Written by Emily Brown

Sources: *Kang H, Gillespie TW, Goodman M* et al. *Long-term use of valproic acid in US veterans is associated with a reduced risk of smoking-related cases of head and neck cancer. Cancer doi:10.1002/cncr.28479 (2014) (Epub ahead of print); Wiley press release: http://eu.wiley.com/WileyCDA/PressRelease/pressReleaseId-110490.html;*
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