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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

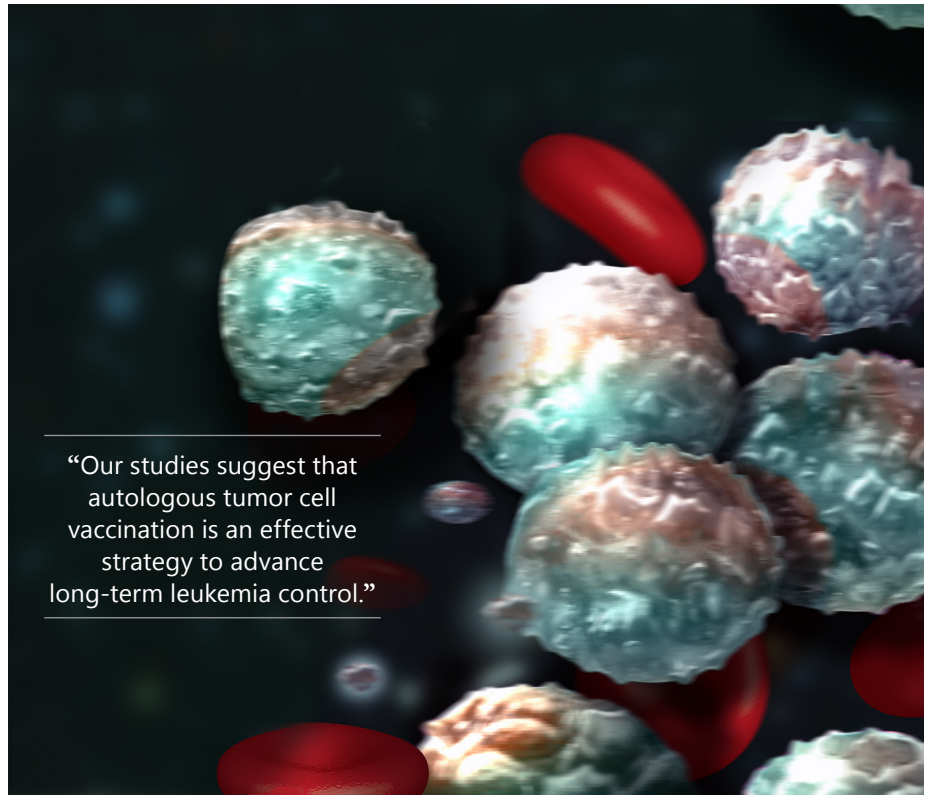
Novel vaccine technique shows promise in Phase I trial of advanced chronic lymphocytic leukemia

Scientists from Dana-Farber Cancer Institute (MA, USA) have recently reported the results of a Phase I trial examining the effect of an experimental vaccine strategy that they hope may have a significant place in the future treatment of advanced chronic lymphocytic leukemia (CLL). Their results have recently been published in the *Journal of Clinical Investigation*.

Transplantation of hematopoietic stem cells is currently often used as a treatment for advanced CLL, with the intention of restarting the patient's own immune system to combat the disease; however, there is a high rate of relapse in these patients and potentially serious complications, including graft-versus-host disease (GVHD). In their study, the Dana-Faber team has identified a potentially useful strategy whereby, following stem cell transplantation, patients receive a tumor vaccine comprising a patient's own inactivated leukemia cells in combination with the immuno-stimulant GM-CSF. The results of the experimental treatment suggest that the strategy may be useful in the long-term treatment of CLL. Discussing the trial, senior author Catherine Wu, from Dana-Farber, said, "Our studies suggest that autologous tumor cell vaccination is an effective strategy to advance long-term leukemia control … Although this was a Phase I study and not powered to look at questions of clinical efficacy, we did see promising clinical activity." To produce their vaccine, the research team took the patient's irradiated leukemia cells and mixed them with GM-CSF-producing cells. This was then injected back into the patient. The combination vaccine was found to greatly stimulate patients' own T cells, which became sensitized to the antigens present on the leukemia cells. This then directs the T cells to specifically attack the other leukemia cells present in the body.

In total, 22 patients were enrolled in the study, four developed GVHD from the stem-cell transplant and so did not continue the treatment. The remaining 18 received up to six vaccinations between 30 and 45 days following stem-cell transplantation. Seven out of the 18 patients receiving the leukemia cells plus GM-CSF vaccine in the trial developed GVHD and so stopped receiving further vaccine.

The median follow-up time for patients was 2.9 years; the estimated 2-year progression-free survival and overall survival rates were 82 and 88%, respectively. The study authors noted that while the vaccination seemed to only have limited impact on recovering the number of T cells in a patient's bodies, they found that CD8+ T cells recovered from vaccinated patients reacted consistently against autologous tumors.



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The authors noted that further trials that are randomized and carried out in a larger number of patients are needed to properly asses potential clinical efficacy; however, in their article they were able to conclude that, "Our studies suggest that autologous tumor cell vaccination is an effective strategy to advance long-term leukemia control following allogeneic hematopoietic stem cell transplantation."

– Written by Sean Fitzpatrick

Sources: Burkhardt UE, Hainz U, Stevenson K *et al.* Autologous CLL cell vaccination early after transplant induces leukemia-specific T cells. *J. Clin. Invest.* doi:10.1172/JCI69098 (2013) (Epub ahead of print); Dana-Farber Cancer Institute: www.dana-farber.org/Newsroom/News-Releases/vaccine-stirs-immune-activity-against-advanced-hard-to-treat-leukemia.aspx

Pretreating diffuse large B-cell lymphoma could improve chemotherapy outcome

In a proof-of-concept study published in *Cancer Discovery*, researchers demonstrated how low doses of azacitidine prior to chemotherapy treatment can cause an impressive level of chemosensitization.

Patients with diffuse large B-cell lymphoma (DLBCL), a particularly aggressive lymphoma, often experience relapses and have a fairly high mortality rate, with many patients dying within 2 years of their diagnoses. However, in a new study led by Peter Martin at Weill Cornell Medical College (NY, USA) and New York-Presbyterian Hospital (NY, USA), 11 out of 12 patients with high-risk DLBCL achieved cancer remission, of which ten remained disease free for up to 28 months following the administration of azacitidine.

Azacitidine is a drug that restarts molecular mechanisms that trigger cell death but are usually switched off as cancers, such as lymphoma, progress. It acts by removing methyl groups, which work as silencing chemicals, thereby allowing chemotherapy drugs to activate cell-death inducing genes, making chemotherapy more effective and causing tumor cells to die. The research team theorized that through pretreatment of DLBCL patients with azacitidine, they could turn the 'cell-death signal' back on and trigger it with subsequent chemotherapy treatment.

"To have any hope for helping patients with aggressive lymphoma, we need to make this resistant cancer sensitive to treatment," explained Leandro Cerchietti, the senior investigator of the study and assistant professor of medicine at Weill Cornell Medical College. "We found we could do this by reprogramming the cancer to a more benign disease, which can then respond to chemotherapy."

In their Phase III study, 12 patients were given low doses of azacitidine for 5 days before chemotherapy. Eleven out of 12 high-risk DLBCL patients achieved a complete remission of their cancer, with ten remaining cancer free for up to 28 months.

"By pretreating patients with a low dose of azacitidine – a targeted drug approved for use in myelodysplastic syndrome – we achieved a profound and stable degree of reprogramming and chemosensitization that was very surprising to us," commented Cerchietti. "Oncologists have long believed that using high doses of an anti-cancer drug is the best strategy. Our study shows that is not the case in this kind of lymphoma, and suggests this new approach can potentially be translated to other tumor types."

An expansion of the work will look at additional DLBCL patients in a multicenter clinical trial. Researchers are also keen to study their pretreatment strategy in additional types of lymphomas. They hope that the strategy could have the potential to change how patients with DLBCL and other tumors are treated in the future.

Cerchietti concluded, "The worse the disease is, the higher the degree of aberrant methylation. In about 20–30% of patients, this aberrant methylation is associated with chemoresistance. Our pretreatment strategy reversed it. We are in the process of tailoring treatments to achieve a more personalized treatment, and we are very excited about the potential to help make chemotherapy and other treatments more beneficial for cancer patients."

– Written by Sophie Breeze

Sources: Weill Cornell Medical College press release: http://weill.cornell.edu/news/releases/wcmc/wcmc_2013/08_16_13.shtml; Clozel T, Yang SN, Elstrom RL *et al.* Mechanism-based epigenetic chemosensitization therapy of diffuse large B-cell lymphoma. *Cancer Discov.* doi:10.1158/2159-8290 (2013) (Epub ahead of print).

Different efficacy for afatinib in non-small-cell lung cancer cases with EGF receptor mutations

New results of a Phase III trial evaluating the use of afatinib, an irreversible tyrosine kinase inhibitor (TKI), in patients with non-small-cell lung cancer have been published by James Chih-Hsin Yang and colleagues from the National University of Taiwan (Taiwan) in the *Journal of Clinical Oncology*.

This study is part of a larger project, the LUX-Lung clinical trial program, which is investigating the use of afatinib in patients with non-small-cell lung cancer harboring EGFR mutations. The focus of this specific study was to compare the effect of afatinib on tumor growth, disease-related symptoms and quality of life with standard chemotherapy. In direct correspondence, Yang reported that, "This is the only global study comparing EGFR TKI to combination chemotherapy in EGFR mutation positive patients and the only study

that used the best and most commonly used regimen (pemetrexed/cisplatin) as a comparator".

"Irreversible EGFR TKI, afatinib can be recommended as the front-line treatment of EGFR mutation-positive patients."

The authors considered 345 patients who received either afatinib 40 mg per day or up to six cycles of cisplatin/pemetrexed. Their cancer-related symptoms and health-related quality of life was assessed every 21 days until progression using two different questionnaires, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and Lung Cancer-13 questionnaire.

Afatinib delayed the time to deterioration for cough and dyspnea but it did not have the same effect on pain. The patients receiving this TKI also scored better in terms of general health status and cognitive and physical functioning, although they demonstrated worse scores for diarrhea and dysphagia. Patients receiving afatinib also showed the longest progression-free survival, 13.6 months, among those receiving EGFR TKI in the whole program.

In conclusion, considering all these results, Yang concludes that the "irreversible EGFR TKI, afatinib can be recommended as the front-line treatment of EGFR mutation-positive patients."

– Written by Marco De Ambrogi

Source: Yang JC, Hirsh V, Schuler M *et al.* Symptom control and quality of life in LUX-Lung 3: a Phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. *J. Clin. Oncol.* doi:10.1200/JCO.2012.46.1764 (2013) (Epub ahead of print).

The potential benefits of administering chemotherapy with radiotherapy in testicular cancer sufferers shown in study

A new study has demonstrated the potential effectiveness of administering men diagnosed with testicular cancer a single dose of chemotherapy along with radiotherapy, in an effort to both reduce the long-term adverse effects of treatment, as well as to improve treatment effectiveness. Approximately 96% of men diagnosed with testicular cancer survive, at minimum, 10 years from diagnosis; however, the more serious and advanced forms require treatment with combination chemotherapy. This form of treatment can give rise to serious long-term complications.

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Researchers from The Royal Marsden NHS Foundation Trust (London, UK) and The Institute of Cancer Research (London, UK) have been looking into treatment options that would decrease the chances of relapse occurring after initial treatment and therefore lessening the number of men that would need combination chemotherapy.

The pilot study was tested in men with stage IIA and IIB testicular seminoma – a form of cancer that spreads to the lymph nodes within the abdomen. The results demonstrated that administering carboplatin prior to radiotherapy had the potential to decrease the relapse rate than when compared to just administering radiotherapy alone. This not only meant radiation doses could be reduced but also that the number of men that would normally require follow-up treatment was lowered.

A total of 51 men with stage IIA and IIB testicular seminoma were administered one cycle of carboplatin. This was followed, after 3–4 weeks, by radiotherapy. The average age of men enrolled in the study was below 50 years, with a range spanning 18–73.

The incorporation of carboplatin into the treatment regime meant that, for most men in the study, doctors could administer a lower dose of radiation over a smaller area of the body. Approximately 39 men experienced a reduction in their prescription of radiation from 35 Gy (the standard amount) to 30 Gy – to a smaller section of the abdomen. In the follow up, which was 4.5 years on average, there were no relapses of cancer in comparison to the 5–11% relapse rate posed by radiotherapy only. The adverse effects were mild and lasted for a short time.

"The incorporation of carboplatin into the treatment regime meant that, for most men in the study, doctors could administer a lower dose of radiation over a smaller area of the body."

Robert Huddart (Institute of Cancer Research, London, UK) led the study and explained that, "The results of this study show great promise. Men who have this stage of testicular seminoma are normally treated with just radiotherapy, or in some countries with intensive combination chemotherapy, where several anticancer drugs are given at once. Relapse occurs in 5–11% of men after radiotherapy alone, and these recurrences have to be treated with combination chemotherapy, which is associated with a risk of serious long-term complications such as cardiovascular disease or second cancers."

– Written by Priti Nagda

Sources: Horwich A, Dearnaley DP, Sohaib A, Pennert K, Huddart RA. Neoadjuvant carboplatin before radiotherapy in stage IIA and IIB seminoma. *Ann. Oncol.* 24(8), 2104–2107 (2013); The Institute of Cancer Research press release archive: www.icr.ac.uk/press/press_archive/press_releases_2013/23947.shtml

Early-phase trial of multiple myeloma drug suggests experimental treatment may help to treat patients resistant to other therapies

The pharmaceutical company Patrys Limited (Melbourne, Australia), has recently announced data from the first six patients in the Phase I/IIa clinical trial of multiple myeloma patients treated with PAT-SM6. The six patients were treated as the second and third cohorts in its ongoing trial of PAT-SM6 in multiple myeloma. Patrys is taking the positive results as support for the fourth cohort of its clinical trial. The six patients had end-stage multiple myeloma; the patients had received, on average, five lines of therapy previously, including autologous stem cell transplantation, as well as bortezomib and lenalidomide. Patients that have received numerous treatments normally have very few therapeutic options, with a median survival of approximately 9 months.

The patients in the second cohort each received PAT-SM6 1 mg/kg, intravenously, four times over a 2-week period. Patients in the third cohort received four doses at 3 mg/kg over 2 weeks. All of the patients were then followed for a period of 36 days.

PAT-SM6 was found to be well tolerated with no drug-related serious adverse events and on dose-limiting toxicities. It was based on these safety data that the Drug Safety Monitoring Board for the trial approved Patrys progressing to the fourth study cohort. In the fourth cohort, patients will be dosed at 6 mg/kg.

Of the six patients treated in the study, two demonstrated stable disease. Following the completion of the study cohorts, five of the six patients received further therapy. Of interest to the study, two of these five patients responded positively to drugs that they had previously demonstrated resistance to. Patrys believes that the use of PAT-SM6 may be having a positive influence on the cancer cells, converting them from resistant to treatment, to susceptible. Patrys hopes that these early positive trial results are indicative of further success in the program and the continued development of the drug.

– Written by Sean Fitzpatrick

Source: Patrys Limited: www.patrys.com/patrys-news-room/media-releases

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