December 10, 2017 • Volume 39, Number 23

oncology-times.com

ONCOLOGY TIMES

Independent News on HEMATOLOGY / ONCOLOGY

Maintenance Therapy in Advanced Small Cell Lung Cancer

BY RICHARD SIMONEAUX

Extensive small cell lung cancer (SCLC) is a particularly aggressive malignancy, with patients often having overall survival (OS) times of only 9-11 months. This disease is often characterized by a high response rate in patients to the first-line chemotherapy followed by a limited period of stable disease in those showing response to the initial therapy. Additionally, there have been few new therapies developed for the treatment of this disease in the past 2-3 decades. As a result, there is a considerable unmet need for patients with SCLC.

CME Article

One method for increasing the length of the stable disease period in SCLC responders after their first-line chemotherapy may be the activation of the patient's immune system. Lefitolimod is a chemically unmodified, non-coding

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Breast Cancer Survivors Find Strength in Dragon Boat Racing

BY BRANDON MAY

Breast cancer treatment, although effective for many patients, carries with it a physical, mental, and emotional toll that can substantially impact a patient's quality of life. Often, treatment for breast cancer can reduce physical strength as well as lung capacity, resulting in a decreased motivation and ability to engage in physical activity (*In Vivo* 2009;23(5):867-871, *Breast Care (Basel)* 2013;8(5):330-334).

Many women who undergo treatment for breast cancer and subsequently enter remission may experience depression and a period of uncertainty, especially in regard to the fear of disease recurrence (*Eur J Oncol Nurs* 2015;19(2):113-119). In this sense, the use of the term "cancer-related weakness" may refer to these patients' loss of strength encompassing the physical, mental, and emotional domains.

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Pharmacoscopy Improves Therapy for Relapsed Blood Cancer

Researchers at CeMM and the Medical University of Vienna presented a preliminary report in *Lancet Hematology* on the clinical impact of an integrated ex vivo approach termed pharmacoscopy (2017; doi:http://dx.doi.org/10.1016/S2352-3026(17)30208-9). The procedures measure single-cell drug responses of millions of individual cells to hundreds of possible treatments in small biopsies from cancer patients.

The interim analysis of the first-ever clinical trial with the approach highlights the potential of the method: 88.2 percent of patients receiving pharmacoscopy-guided treatment achieved partial or complete remission, compared to 23.5 percent to their own previous treatment. Further, the median progression-free survival increased fourfold. Retrospectively, pharmacoscopy also predicted the response of acute myeloid leukemia patients to first-line treatment with 90 percent accuracy. These results show that pharmacoscopy can assist decision-making of the responsible clinicians effectively and thus represent a powerful tool for practical precise and personalized medicine.

Pharmacoscopy Defined

Patients suffering from refractory and relapsed blood cancers often have few treatment options and short survival times. At this stage, identifying effective therapies can be challenging for doctors. Even state-of-the-art genetic analyses, due to the high heterogeneity of cancer cells and the impact of

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PERIODICALS

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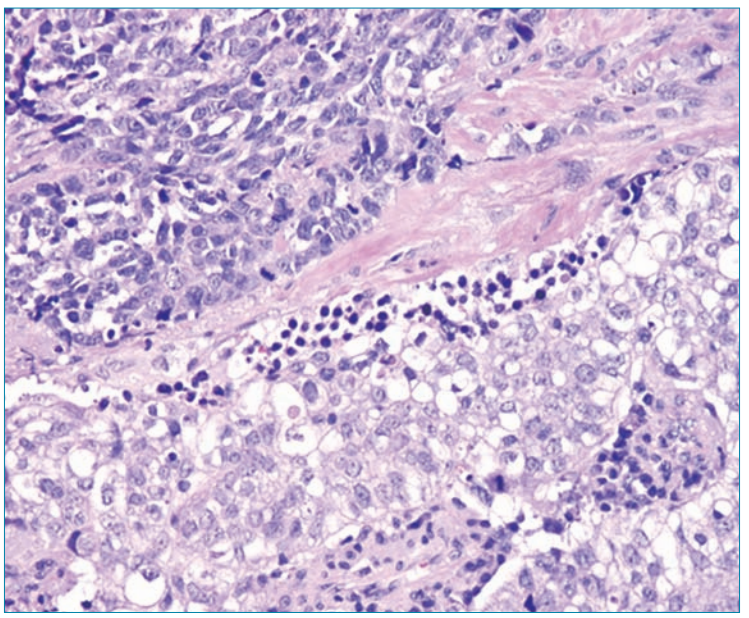
DNA molecule consisting of two single-stranded loops connected by a double-stranded stem. This compound functions as an agonist for the toll-like receptor 9 (TLR9), an important receptor that is expressed in many immune system cells, including natural killer cells, macrophages, dendritic cells, and other antigen-presenting cells. TLR9 binds preferentially to viral or bacterial DNA present, initiating a signaling cascade, resulting in the release of cytokines and, ultimately, a pro-inflammatory response. TLR9 expression and activation can be altered by conditions such as infection, tissue damage, and cancer.

To gauge the efficacy of this DNA-based therapy, the phase II IMPULSE trial was undertaken by Michael Thomas, MD, Head of the Department of Thoracic Oncology and Internal Medicine, Thoraxklinik, Heidelberg University Hospital, and colleagues. This trial evaluated the use of lefitolimod as maintenance therapy in advanced SCLC patients who had undergone standard first-line platinum-based chemotherapy. This was an international study which drew participants from Austria, Belgium, Germany, and Spain. Data from this trial was reported by Thomas at the ESMO 2017 Congress in Madrid (*Abstract 15270*).

Clinical Trial Design

Prior to randomization, prospective participants with advanced SCLC underwent four rounds of standard platinum-based chemotherapy. Those that were considered responders (i.e., showed partial response (PR) or complete response (CR)) were screened and then randomized in a 3:2 ratio to either the experimental arm (n = 61) or the control arm (n = 41).



After randomization, during the maintenance phase of the trial, the control group received their fifth and sixth rounds of chemotherapy followed by the established practices of the region. Participants in the experimental arm also received their fifth and sixth cycles of standard platinum-based chemotherapy followed by 60 mg lefitolimod subcutaneously twice weekly. No other medications were provided as maintenance therapy for the experimental arm.

The primary endpoint for this study was OS in the intent-to-treat (ITT) population. Among some of the secondary endpoints were progression-free survival; best objective response rate; safety profile for investigational drug; pharmacodynamics (PD) response to gauge *in vivo* efficacy for lefitolimod; pre-planned subgroup analysis using both a lefitolimod-associated parameter (e.g., immunological biomarker, activated B cells); and indication-specific parameter (e.g., COPD).

When discussing the PD parameters for gauging the investigational drug's efficacy, Thomas noted, "With lefitolimod dosing *in vivo*, we should see an increase in the activation of monocytes; additionally, we should also see an increase in the secretion of IP-10 (interferon-gamma-induced protein 10). Both of these parameters could be easily measured from a patient's blood sample quickly and efficiently; flow cytometry could be used to detect monocytes present and IP-10 levels could be determined using a multiplex assay. Comparison of levels prior to and after a period of lefitolimod dosing (typically 4 weeks) should give a reasonable idea if the compound is doing what it should be *in vivo*.

This study included extensive disease SCLC patients who had completed four cycles of first-line platinum-based chemotherapy. Additionally, only those patients who had a documented response (i.e., PR or CR) after the first four chemotherapy cycles and those who had an ECOG performance status (PS) of 0 or 1 were randomized for inclusion in this trial. Patients were excluded if they met any of the following conditions: current or previous SCLC-associated paraneoplastic syndrome; a history of immune deficiency or autoimmune disease; or the use of systemic steroid therapy.

In the experimental arm (n = 61), the mean age was 63.9 years (range: 49-80 years), 64 percent were male, 98 percent had smoking histories, and all were white. Of these patients, 70 percent had an ECOG PS of 1 and 30 percent had a PS of 0. Brain metastases were present in 80 percent of this arm and 26 percent had COPD.

The patients in the control arm had a mean age of 64.6 years (range: 51-82 years), 100 percent were white, 71 percent were male, and 95 percent had smoking histories. Eighty-three percent of patients in this arm had brain metastases while 22 percent had COPD. ECOG PS scores of 0 and 1 were noted in 46 percent and 54 percent of the participants in this arm, respectively.

Patient enrollment was initiated in April 2014 and completed in October 2015. Top-line results were obtained in April 2017. Follow-up for survival and other data are currently ongoing.

Study Results

OS was assessed in the ITT population for each investigational arm. Median OS values of 279 days (95% CI: 233-320 days) and 272 days (95% CI: 231-434 days) for the experimental and control arms, respectively. These figures gave a hazard ratio (HR) of 1.27 (95% CI: 0.80-2.01; p = 0.57).

Patients in the experimental arm had a median duration of lefitolimod therapy of 72 days, while the mean duration of lefitolimod therapy was 113.1 days.

PD evaluations of patients' blood samples were performed at a central location. In some of these analyses, flow cytometry was utilized to assess the presence of $CD169^+$ monocytes. Additionally, IP-10 serum

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Learning Objective for This Month's CME Activity: After participating in this CME activity, readers should be able to discuss the findings of a study designed to evaluate the use of Lefitolimod as maintenance therapy in advanced small cell lung cancer (SCLC) patients who had undergone standard first-line platinum-based chemotherapy.

Pharmacoscopy Improves Therapy for Relapsed Blood Cancer

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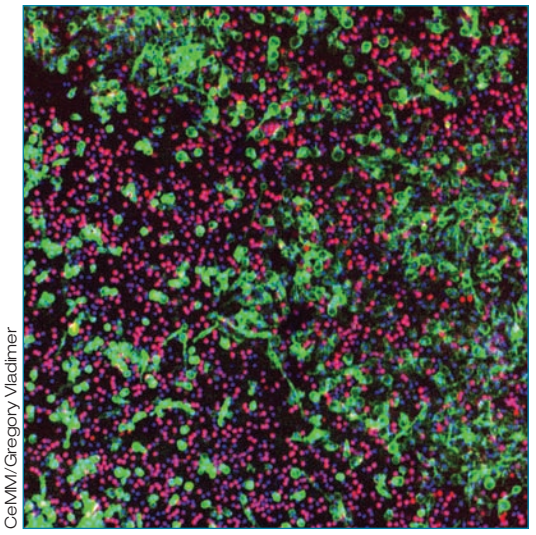
the various mutations on their drug response, often do not suffice to instruct personalized treatments.

Pharmacoscopy, a technology developed by scientists at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences and tested for its clinical efficacy by clinicians of the Medical University of Vienna, offers a functional approach: hundreds of drug options can be quickly pre-tested ex vivo in small liquid biopsy samples collected from individual patients.



CeMM/Gregory Vladimer

The effects of each drug on the individual cells are quantified using high-throughput and high-content automated confocal microscopy. In combination with specially developed analysis methods and machine learning and other unique algorithms, pharmacoscopy allows quantification of never-before visualized phenotypes. The method was first presented in *Nature Chemical Biology* (2017; doi:10.1038/nchembio.2360).

The multidisciplinary team publishing the current study is spearheaded by Giulio Superti-Furga, PhD, Scientific Director of CeMM and Professor at the Center for Physiology and Pharmacology of Medical University of Vienna together with Philip Staber, MD, PhD, Program Director for Lymphoma, Chronic Lymphatic Leukemia, and T-cell Lymphoma of the Medical University of Vienna.

While the clinical study is still recruiting, interim analysis of the program showed that 88.2 percent of the patients recruited (15 out of 17) who received pharmacoscopy-monitored personalized therapies achieved partial or complete remission, while only 23.5 percent (four out of 17) responded similarly well to their previous respective treatments.

In addition, the median progression-free survival of patients who were treated in accordance to pharmacoscopy-guided therapy increased from 5.7 weeks to 22.6 weeks compared to their last line of treatment. Further, a retrospective study organized to specifically determine the ability of the method to stratify responding and non-responding newly diagnosed patients with acute myeloid leukemia resulted in 90 percent accuracy. Before, such accuracy in prediction of treatment outcome was unachievable, with or without genetic assays.

"Having a robust, fast, and reliable predictive test at our disposal during the patient treatment process, especially at the time of relapse where a new intervention must be selected quickly, will change how medical doctors prioritize drugs to use for late-stage patients," noted Staber, principal investigator of the clinical trial.

"Evidence that the pharmacoscopy approach is helpful for clinical evaluation of therapy is wonderful. Single-cell functional analysis of primary material gives unprecedented resolution and precision that we are sure to further develop in the future to address yet more diseases," added Superti-Furga, whose goal at the beginning of activities of the Research Center for Molecular Medicine 10 years ago was to create scientific advancements able to positively impact medical practice. OT

SMALL CELL LUNG CANCER

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levels were determined using a multiplex assay. In the experimental arm, there were 59 patients who had paired blood samples, while 33 participants in the control arm had matched samples that were utilized for these PD analyses.

At baseline, patients in the experimental arm showed a mean level of 8.4 percent $CD169^+$ monocytes; however, after 4 weeks or more of lefitolimod therapy, their mean maximum levels were found to be 86.1 percent, a 10.3-fold increase ($p < 0.0001$). For the control arm, the mean baseline and maximum $CD169^+$ monocyte levels were found to be 7.7 percent and 16.1 percent, respectively ($p = 0.14$), a 2.1-fold increase. "The large increase of these monocytes in the experimental arm participants' blood samples confirmed lefitolimod's mode of action," Thomas noted.

Serum samples for the experimental arm showed mean baseline and maximum levels of 221.0 and 724.6 pg/mL, respectively, a 3.3-fold increase ($p < 0.0001$). In the control arm, the mean baseline and maximum values were 238.3 and 334.6 pg/mL, a 1.4-fold increase ($p = 0.03$). "These data, as with the flow cytometry data, also confirmed lefitolimod's action *in vivo*," Thomas added.

Subgroup Analyses

When performing subgroup analyses, the presence of COPD at baseline was utilized as an indication-specific parameter. In this OS analysis, 25 patients were included from the ITT population (16 for the experimental arm and nine for the control arm). Median OS values of 316 days (95% CI: 277-422 days) and 246 days (95% CI: 133 days-n.a.) were obtained respectively for the experimental and control arms.

"Clearly, these data are for a small number of patients; to further explore the potential survival differences noted in this patient subset, a more thorough study in a larger group of patients should be undertaken with a more concise and objective definition of COPD than investigator assessment only," Thomas commented.

Subgroup analyses were also performed using a lefitolimod-associated biomarker. "For these analyses, the levels of activated B cells were defined as the proportion of $CD86^+$-staining $CD19^+$ B cells in these patients," Thomas explained. Samples for these analyses were available for 88 of the patients. These patients were then separated into those having high (greater than 15.4%) and low (15.4% or less) levels of activated B cells. Of the 88 patients having samples available, 38 had low levels of B cells present (23 in the experimental arm and 15 in the control arm). OS evaluation was performed in this subgroup of patients.

Patients at or below the 15.4 percent activated B cell threshold in the experimental arm ($n = 23$) displayed a median OS of 284 days (95% CI: 188-423 days), while those in the control arm had a median OS of 231.5 days (95% CI: 171-272 days), affording a HR of 0.59 (95% CI: 0.29-1.21). Concerning these results, Thomas noted, "There was a strong OS signal in patients with low numbers of activated B cells."

No grade 4 or 5 adverse events (AEs) were recorded in this study. Among the grade 3 AEs observed in the experimental arm were cough (25%), headache (21.7%), and erythema (18.3%). The most common grade 3 AEs observed in the control arm were nausea (20.5%) and asthenia (17.9%). When asked to summarize the safety results for this study, Thomas noted "limited add-on toxicity in the combination of lefitolimod with chemotherapy."

Conclusions

"Evaluation of OS within the ITT population showed that there was no significant difference between the treatment arms," Thomas stated. "Additionally, a favorable safety profile was obtained in the experimental arm," he noted. When discussing the PD parameters evaluated in this study, Thomas stated, "We were able to confirm the mode of action for lefitolimod *in vivo*, as both the monocyte counts and the IP-10 levels obtained from matched blood samples taken before beginning and after 4 weeks of therapy showed statistically significant increases."

Regarding the data for the B cell subgroup, Thomas commented, "Despite the fact that these data were from a very small number of patients, there was clearly a strong signal in OS for patients with low B-cell counts. It is thought that perhaps the lower levels of B cells, which can be regulatory and immunosuppressive at higher counts, may be allowing the responding patients to mount a more vigorous immunological response to their tumors," he explained. "More studies definitely need to be done to gain a better understanding of just how these B-cell counts are affecting outcomes with lefitolimod. This could be accomplished by assessing the effect in cancers with low levels of B cells.

"One particularly elegant aspect of this study was that much useful information was gleaned from patients' blood samples using relatively simple and quick analyses like flow cytometry," Thomas concluded. "In the future, we may be able to rapidly screen patients to select those for whom certain therapies may be more appropriate." OT

Richard Simoneaux is a contributing writer.