EDITORIAL

Immunomodulatory effect of stereotactic ablative radiotherapy in lung cancer

Joanna Domagała-Kulawik

Department of Internal Diseases, Pneumonology and Allergology, Medical University of Warsaw, Warsaw, Poland

There are several methods of lung cancer therapy, depending mainly on the histology of the primary tumor and the stage of the disease. For non-small cell lung cancer (NSCLC), the predominating histological type, tumor resection or radiotherapy belongs to the most effective radical therapeutic options. Recently, immunotherapy has been introduced for the treatment of patients with advanced stages of NSCLC, with promising results. The aim of this immunomodulatory treatment is the blockade of suppressive molecules, which is known as immune checkpoint blockade. The examples of these molecules include cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the programmed death-ligand 1 and 2 (PD-L1–PD-L2) pathway.[1] As the effects of tumor resection or radiotherapy are predictable, the results of immunotherapy are generally good but vary between individual patients. Patients treated with checkpoint inhibitors can survive as long as 36 months.

No predictive factors for lung cancer immunotherapy have been found to date except the PD-L1 expression on cancer cells, which is somewhat controversial.[2] Therefore, the candidates for valuable biomarkers before immunomodulatory treatment are being widely investigated. Such a biomarker may be a precise description of the immune status of the patient. Similarly to other solid tumors, lung cancer is characterized by so called immunoscoring, that is, "a multiparametric biomarker conveying quantitative and spatial information on the immunological tumor infiltrate."[3] However, the availability of lung tumors with the surrounding microenviroment composed by immune cells is very low because of a low resection rate (less than 25%). Therefore, peripheral blood cell analysis remains the only method for defining the immune status in the majority of patients with lung cancer.

Since the immunotherapy of solid tumors was successfully introduced into clinical practice, the number of studies investigating host immunity has rapidly increased.[4-6] There is a growing body of evidence that the balance between cytotoxicity and immunosuppression sets a direction for immune response, and it was established that the mechanisms of suppression are generally prevalent in malignancy. Lymphocytes are the main cells that are active in cancer immunity, and the population of cytotoxic cells ($CD8^+$ and $CD4^+$ lymphocytes, natural killer [NK] cells, and NKT cells) dominates in the first stages of tumor progression. In the majority of publications, lymphocytic infiltrate was described as a positive occurrence. Numerous studies concluded that the greater lymphocyte infiltration the better the prognosis and treatment efficacy. However, in the course of cancer, the lymphocyte function and phenotype are changed to those promoting tumor progression, with an increasing number of cells inhibiting anticancer response. These are regulatory T lymphocytes, regulatory B lymphocytes, and lymphocytes with dominant expression of suppressive molecules. Predominance of regulatory T cells (T_{regs}) and expression of the transcription factor forkhead box P3 (FoxP3) were found to be markedly unfavorable prognostic factors.[7] Moreover, attenuation and modification of immune response was reported to be associated with an increased expression of inhibiting molecules on immune cells: programmed cell death protein 1 (PD-1), CTLA-4, and Fas.[8] Nevertheless, due to the development of specific individualized methods of immunotherapy, the markers of immune response may become useful predictive factors. Apart from PD-L1, numerous other parameters have been recently proposed as candidates for useful biomarkers, including suppressive molecules (FoxP3, CTLA-4, LAG-3, Tim-3), lymphocyte activation markers (CD25, CD69), and cytokines (interleukins: IL-6, IL-8, IL-12; intereferon γ; transforming growth factor β).[9-11]

The article by Rutkowski et al[12] published in the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*) discusses the effect

Correspondence to:
Prof. Joanna Domagala-Kulawik, MD, PhD, Klinika Chorób Wewnętrznych, Pneumonologii i Alergologii, Warszawski Uniwersytet Medyczny, ul. Banacha 1a, 02-097 Warszawa, Poland, e-mail: domagalakulawik@gmail.com
Received: April 27, 2017.
Accepted: April 27, 2017.
Published online: April 28, 2017.
Conflict of interest: none declared.
Pol Arch Intern Med. 2017; 127 (4): 233-234
doi:10.20452/pamw.4015

of stereotactic ablative radiotherapy (SABR) on the activation of immune anticancer response.[12] This study concerns the widely investigated aspects of cancer immunity and immunotherapy presented above. In a large group of well-selected patients treated by SABR (n = 89), the dynamics of the changes in the peripheral blood lymphocyte profile was assessed. The blood samples were collected at baseline, before SABR, and at 2 and 12 weeks after the therapy. Using flow cytometry, the authors analyzed the expression of $CD4^+$ and $CD8^+$ T cells, as well as the expression in T cells of the following transcription factors: T-box transcription factor (T-bet), transacting T–cell-specific transcription factor 3 (GATA-3), retinoic acid-related orphan receptor γt (ROR-γt), and FoxP3. The authors reported that T-bet, GATA-3, ROR-γt, and Foxp3 were related to Th1-, Th2-, Th17-, and T_{reg}-type immune responses, respectively. Thus, the cells with anticancer activity and those with regulatory function were detected. The main finding of this study was that at the end of the follow-up, that is, at 12 weeks after SABR, the profile of T cells changed from regulatory to activated. After SABR, an increased proportion of $CD8^+$ T cells and the proportion of $CD4^+$ T cells expressing GATA-3, T-bet, and ROR-γt were observed, while the proportion of $CD4^+/FoxP3^+$ cells was significantly lower than at baseline.

The immune markers selected by Rutkowski et al[12] for this study are untypical. The transcription factors are attractive but, to some extent, unspecific; they are very susceptible to numerous factors in health and disease states. These molecules are per se capable of modulating the immune response, so it seems that referring them to commonly known subpopulations of T lymphocytes was not so necessary.

Interestingly, SABR is a valuable lung cancer treatment option in patients with early NSCLC excluded from surgery for any reason. The main cause of the low resection rate in lung cancer is not only a small number of cases with locally advanced disease at recognition but also an increasing number of contraindications to surgery, such as chronic obstructive lung disease (COPD), impaired pulmonary function, and cardiovascular comorbidities.[13] The coexistence of COPD and lung cancer is estimated at 40%. In the study of Rutkowski et al,[12] it was 64%.[12] Thus, the growing incidence of COPD indicates that the use of SABR in lung cancer will be more and more widespread.

De Goeje et al[14] reported a similar activation of peripheral T cells after SABR for NSCLC. The authors observed a significant increase of the fraction of proliferating ($Ki67^+$) $CD4^+$ and $CD8^+$ cells and $PD\text{-}1^+$ T cells producing interferon γ during 6 weeks after SABR. This finding and the results presented by Rutkowski et al[12] theoretically support the additional effect of SABR in the field of reactivation of immune host defense in lung cancer. Galuzzi et al[15] reported the effectiveness of the combination of immunotherapy with conventional treatment: chemotherapy and radiotherapy. The effect of radiotherapy on the immune system is complex: irradiated cancer cells release a wide panel of biologically active mediators, reactive oxygen and nitrogen species, and various immunomodulatory cytokines. An immunogenic cell death causes stimulation of cytotoxic cell response. Increased antigenicity that activates antigen-presenting cells is observed.

The results of the presented studies are very promising, although nowadays we are still far from implementing them into clinical practice.

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