УДК 61:615.1(043.2)
ББК 5:52.82
ISBN 978-985-21-0251-3

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ANTI-CANCER THERAPY BASED ON INHIBITION OF NEGATIVE IMMUNE REGULATION

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In recent years, there has been a significant increase in the development and implementation of anti-cancer immunotherapies. The approval of anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1) antibodies for human use has already resulted in significant improvements in disease outcomes for various cancers such as bladder cancer, head and neck cancer, Hodgkin's lymphoma, kidney cancer, lung cancer (non-small cell), especially melanoma. Unlike radio- and chemotherapy, which aim to directly interfere with tumor cell growth and survival, immunotherapies target the tumor indirectly by boosting the anti-tumor immune responses that spontaneously arise in many patients.

Crucial leap was made when Allison and Honjo characterized two very important and potent pathways – called "immune checkpoints" – that can shut down the immune response. These pathways inhibit T cells – white blood cells that destroy virus-infected cells and tumor cells – and prevent them from recognizing and attacking the tumor.

The roles of CTLA-4 and PD-1 in inhibiting immune responses, including antitumor responses, are largely distinct. CTLA-4 is thought to regulate T-cell proliferation early in an immune response, primarily in lymph nodes, whereas PD-1 suppresses T cells later in an immune response, primarily in peripheral tissues. The clinical profiles of immuno-oncology agents inhibiting these 2 checkpoints may vary based on their functional differences.

Although PD-1 and CTLA-4 targeting therapies have been able to increase average life expectancy for cancer patients, mortality remains high among advanced-stage patients, emphasizing the need for further innovation in the field. Both anti-PD-1 and anti-CTLA-4 therapies appear to be more effective in patients with pre-existing anti-tumor immunity, suggesting that, in patients without such immunity, these drugs are unable to mediate anti-tumor immune responses.

As our understanding of the mechanisms of these drugs improves, perspectives are being opened to improve their use not only by specifically targeting those patients who are most likely to respond through appropriate biomarker screening procedures, but also by combining currently used immune checkpoint inhibitors with other complimentary drugs to help those patients unable to respond to the current regimens.