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Letter to Editor

Metronomic Effect as A New Hypothesis in Maintenance Therapy of Acute Lymphoblastic Leukemia

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Dear Editor

Growing evidence indicates that the innate and adaptive immune system has an important role in both development and treatment of cancer. The concept of metronomics therapy and mechanism of chemotherapeutic agents during maintenance phase of acute lymphoblastic leukemia (ALL) is an obscure topic for oncologists compared with treatment of other phases of this malignancy.

Some new immunological mechanisms have been proposed for the treatment of ALL during the maintenance phase of chemotherapy in addition to traditional irradication mechanisms. Using regular continuous low-dose chemotherapeutic drugs during the maintenance phase is similar to metronomic strategy that may restore or mediate anticancer immune responses or antiangiogenic effects.[1] Anti-pyrimidines (6-mercaptopurine or 6-thioguanine), dexamethasone or prednisone, oral methotrexate and vincristine are standard approaches in maintenance therapy of ALL.

Malignant cells can escape from immune surveillance in different phases of tumor interaction with the host's immune system. Regulatory T cells (Treg) are $CD4^+$ $CD25^+$ lymphocytes, enriched in FoxP3, glucocorticoid-induced TNF receptor and cytotoxic T-lymphocyte-associated antigen-4 that can inhibit antigen-specific immune response both in a cytokine-dependent and cell contact-dependent method.[2] Treg cells can inhibit anti-tumor immune response by suppressing the activity of both tumor-specific effector cells ($CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T helper cells) and tumor-nonspecific effector cells (natural killer [NK] and NK T cells.[1] Also, Treg cells have been shown to be increased in a variety of human cancers. Increased frequency of Treg cells is associated with tumor progression and loss of treatment response.[3] Moreover, suppression of Treg cell activity by either specific blockade or depletion of them can enhance immune response against tumor-associated antigens.[1]

During the last decade novel mechanisms has been found for methotrexate in the treatment of rheumatoid arthritis. It restores defective Treg cell function through demethylation of the FOXP3 locus, leading to subsequent increase in FoxP3 and CTLA-4 expression.[4] Dexamethasone improves the function of regulatory T-cells and sets up a new balance of Th1/Th2 that markedly enhances FOXP3 expression and generates CD25(high) cells with phenotypic characteristics attributable to natural Treg cells.[5]

6-Thioguanine inhibits different steps of the angiogenesis process in vitro and uses a potent anti-angiogenic activity in vivo. Its anti-angiogenic ability together with its antimetabolite activity towards tumor cells may contribute to its action during maintenance therapy in acute myeloid leukemia (AML). These results

suggest a new rationale for the use of purine analogs in the management of AML.[6,7]

6-mercaptopurine (6-MP) specifically inhibits both the early and the late phases of the angiogenesis process in vitro and exerts a potent anti-angiogenic activity in vivo.[6] Vincristine also suppresses angiogenesis and the anti-angiogenic activity may be enhanced by combination with 6-TG.[8]

In summary we consider low dose continuous conventional chemotherapy as a metronomic mechanism of action with induction of antitumor immune response and antiangiogenic effects in ALL patients. This hypothesis needs to be more investigated specially in pediatric ALL.

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