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Novel targeted therapy combined with immune checkpoint inhibition in AML

Acute myeloid leukemia (AML) is an aggressive and very lethal blood tumor with different subtypes, each with different treatment sensitivities and prognoses. It represents around 90% of leukemia cases in adults and accounts for ~60% of leukemia deaths. AML affects people of all ages; its incidence, however, increases in older adults. The development and research of targeted therapies alternative to the detriment of conventional chemotherapy provide a new spark of hope for these patients.

The immune system has a significant role in tumor cell elimination. A common problem in AML is tumor cell immune escape due to both intrinsic and extrinsic mechanisms, leading to progression and relapse. One promising method of immunotherapy is the activation of the immune response through monoclonal antibodies targeting immune checkpoints on T cells. Inhibition of immune checkpoints such as cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) enhances T-cell activation and tumor-associated antigens recognition enabling lysis of tumor cells and cancer regression. This immunotherapy option is already in use in solid tumors and in some hematological malignancies. Even though it is not widely used in AML, it emerges as worthy for patients that suffer from relapsed or high-risk disease or for patients ineligible for standard therapy. In solid tumors, it is emerging that the genetic landscape of the tumor has a direct effect on the tumoricidal immune responses and response to immunotherapeutic treatment. However, there is little information as to whether genetic abnormalities affect anti-leukemic immune responses. The curative potential of allogenic hematopoietic stem cell transplantation in AML coupled with the preservation of the T-cell population in the bone marrow of AML patients, and increased expression of targetable immune receptors are the main reasons behind the growing interest in using T-cell-harnessing therapies in this disease entity. Given the complex heterogeneity of AML, the natural diversity of blasts and the complex crosstalk within the blasts-hematopoietic niche-cells of the immune system, it is reasonable to speculate that the best strategy to beat AML lies in the rational combination of immunotherapeutic strategies with chemotherapy or targeted therapies.

In our proposal, we seek to improve the clinical outcome of immunotherapy in different AML subtypes. The outcomes will have an important positive translational impact to define the best management of patients that suffer from a deadly disease.