Immunological Landscape of CML

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Antitumor immune competence is a critical determinant of therapeutic efficacy and immune-related toxicity in chronic myeloid leukemia (CML). We performed multidimensional immunophenotypic and functional analyses in CML patients who achieved an early molecular response (EMR; BCR-ABL1 <10% IS) but required dose reduction to dasatinib 80 mg once daily after 3 months of therapy. Circulating immune subsets, including natural killer (NK) cells, $CD4^+$ and $CD8^+$ T cells, B cells, and regulatory T cells (Tregs), were evaluated for frequency, phenotype, and cytotoxic function.

Patients with treatment failure at 12 months exhibited a sustained reduction in NK cell frequencies compared with responders, whereas B cell proportions were increased at 6 months. Among patients with rising BCR-ABL qRT-PCR (% IS) levels between 6 and 12 months, NK cell frequencies declined significantly at 12 months, revealing an inverse relationship between leukemic burden and NK cell maintenance.

Phenotypic profiling of antitumor effector cells demonstrated elevated expression of the immunosuppressive checkpoint ligand PD-L1 on NK cells at baseline and on $CD8^+$ T cells at baseline and 6 months in the treatment failure group. In contrast, responders displayed enhanced cytotoxic programming, characterized by increased granzyme B expression in $CD8^+$ T cells at 6 months. These findings indicate that early acquisition of immunosuppressive phenotypes in cytotoxic immune cells is associated with impaired long-term molecular control.

Analysis of immune correlates of myalgia revealed that affected patients exhibited reduced NK cell frequencies alongside sustained differentiation into central memory, effector memory, and terminally differentiated effector memory T-cell subsets, suggesting persistent T-cell activation in the context of diminished innate immunity. Longitudinal functional assessment further showed that NK cells from CML patients have intrinsically impaired antitumor activity compared with healthy controls. Collectively, these results identify NK cell dysfunction as a key immunological determinant of therapeutic response and adverse events in CML and support the development of NK cell–targeted immunotherapeutic strategies.