Tapping the Immune Microenvironment in B-cell Lymphomas

The success of immunotherapy depends on the tumor microenvironment (TME) and the immune evasion mechanisms. Although cancer immunotherapy has increasingly been applied in solid tumors, we are far from understanding how to utilize these options to optimize clinical benefit in B-cell lymphomas.

TME is a highly heterogeneous milieu consisting of different cell types and abundant molecules produced and released by tumor cells, stromal cells, and immune cells. While traditional therapies such as chemotherapy and radiotherapy target the tumor directly, immunotherapies, generally target the microenvironment and specifically the immune system.

Checkpoint inhibitors have changed the cancer therapeutic landscape in solid tumors, while immunotherapeutic approaches such as CAR-T cell therapies have improved outcomes in hematological malignancies. Clinical benefits of checkpoint inhibitors are observed in only limited hematological tumors that are particularly characterized by a high infiltration of immune cells such as Hodgkin's lymphoma (HL). The TME of classical HL consists of rare (0.1–1%) malignant cells called Hodgkin Reed-Sternberg (HRS) cells and an abundant immune cell infiltrate which is markedly distinct from the TME observed in non-Hodgkin's lymphoma (NHL).

Recent studies have demonstrated that the characteristics of immune cells in the TME of lymphomas may be a druggable therapeutic target and biomarker for immunotherapy. The immune cell constitution in the TME varies between the B-cell lymphoma subtypes. Immune cells in the TME of diffuse large B-cell lymphoma (DLBCL) include natural killer (NK) cells (+/−20% of total cell content), dendritic cells (DCs) (+/−15%), M2-type macrophages (+/−15%), CD4+ T cells (+/−10%), and CD8+ T cells (<5%). Follicular lymphoma is rich in T-cells, constituting up to 50% of the total cell count. Among them, follicular helper T (Tfh) cells, a CD4+ T-cell subset of recently defined functional entities, plays a major role.[1,2]

Emerging data shows that targeting cancer cells by modulating the immune system has become an important new therapeutic option in B-cell lymphomas. Immune signaling pathways are being investigated and applied to various hematologic malignancies with the intent to open new treatment opportunities and guide treatment decisions in resistant population.[3,4]

Enhanced T-cell infiltration predicts the outcome in NHL patients *(CD27 acts as a co-stimulatory molecule, enhancing T- and B-cell responses)*

CD27 is an activation molecule expressed on the majority of both CD4+ and CD8+ resting T cells in the peripheral blood. Upon activation by antigen, expression of CD27 increases. Varlilumab, CD27 agonist in combination with rituximab induced >100-fold increased CD4 T-cell infiltration in PRs vs. PDs (p=0.027) whereas T-cell enriched signaling pathway was absent in rituximab monotherapy arm *(Gene expression analysis, Phase II RiVa study - **NCT03307746, n=27 iNHL: n=15 and aNHL: n=12, median 4 prior lines of therapy)**.*[5]

Exploring therapeutic potential of extracellular vesicle (EV) CD47 in DLBCL *(CD47 blockade mainly inhibits the CD47-SIRPα axis to prevent tumor immune escape)*

CD47/SIRPα axis plays a critical role in the innate immune system. It presents two druggable targets for therapeutic intervention—CD47 and/or SIRPα. SIRP-α is expressed at very high levels in macrophages or dendritic cells, while CD47 is expressed ubiquitously, including on cancer cells. Upon engagement of CD47, SIRPα sends signals that inhibit the prophagocytic action of macrophages. Blockade of the CD47/SIRP-α interaction can inhibit tumor growth by inhibiting the suppressive effects of SIRP-α and promoting macrophage activity.[2]

DLBCL cells that had higher levels of cellular CD47 protein packaged greater amounts of CD47 into EVs and these EVs displayed an increased binding to SIRPa of macrophages, thus inhibiting macrophage-mediated phagocytosis of DLBCL cells. In DLBCL xenograft models, injection of EVs derived from DLBCL cells promoted the growth of tumors, whereas pretreatment of the EVs with anti-CD47 antibodies (IBI188, letaplimab), inhibited the effect.[6]

Preliminary conclusions which need further validation include:

- Disrupting the interaction between the EV CD47 and macrophage SIRPa is a mechanism in the CD47–SIRPa blockade-based therapies.
- High levels of circulating EV CD47 correlate positively with the phagocytic activity of macrophages.

Next generation cereblon immunomodulators as differentiated immunostimulating agents in B-cell lymphoma

Cereblon is a substrate receptor protein for the CRL4A E3 ubiquitin ligase complex, and drugs like immunomodulators have been reported to be able to inhibit or alter the substrate specificity of the E3 ligase activity of CRL4A cereblon.

A new investigational cereblon E3 ligase modulator, **Iberdomide (BMS)** is currently being studied in clinical trials for B-NHL and multiple myeloma (MM). The agent has shown superior cereblon binding affinity as compared to lenalidomide and has demonstrated ability to function with lower levels of cereblon.

In DLBCL cell lines, comprising **activated B-cell** (ABC) and **germinal centre B-cell** (GCB) DLBCL models, iberdomide was active in both DLBCL subtypes (ABC and GCB), whereas revlimid is preferentially active in the aggressive ABC-DLBCL.[7]

Earlier studies have reported that iberdomide has **20 times higher cereblon-binding affinity than lenalidomide,** leading to significantly faster degradation of target substrates.[8] As monotherapy, it has demonstrated an overall response rate of 40% in heavily pretreated patients (including 3 FL, 1 FL grade IIIB, and 6 DLBCL).[9]

The in vitro and in vivo characterization of immune enhancement and antitumor effects of iberdomide vs. lenalidomide elicited:

- Increased leukocyte trafficking, with iberdomide demonstrating a greater increase than revlimid (46% vs. 21%, p<0.01).
- Iberdomide increased the proliferative capacity of CD8+ T and NK cells compared to Rev (10- and 3.6-fold vs. 4- and 2.8-fold, respectively).

The differentiated efficacy of next generation immunomodulators is likely associated with its differential effects on leukocyte trafficking and immune activation.

Identifying resistant subgroups by characterizing immune cell subsets may guide treatment decisions

Gene expression analysis of BTK inhibitor (BTKi) treated (n=42) mantle cell lymphoma (MCL) patient tissue samples revealed distinct TME-associated signatures which were identified as normal lymph node like, immune cell-enriched, mesenchymal, and immune depleted or deserted.

BTKi-resistant MCL primarily exhibited immune-depleted TME subtype. Somatic mutations TP53, NSD2, NOTCH1, KMT2D, and SMARCA4, which were previously reported in ibrutinib-resistant MCL and/or in refractory high-risk MCL patients, were predominant in the immune-depleted TME cluster.[10]

- The evidence supports defining BTKi sensitivity and resistance by immune-hot and immune-cold TME.
- The immune-depleted TME subtype was characterized by dominant proliferation gene signature, overexpressed PI3K pathway, BTKi resistance, and poor outcomes in MCL patients.

Although the role of TME has not been fully elucidated in B-cell lymphoma, the therapeutic strategies described above highlight the potential clinical value of targeting TME in B-cell lymphoma. Emerging research is expected to focus on not only eliminating the tumor cells but also influencing the TME. Extensive clinical validation will develop more robust insights about inter- and intracellular signaling, interaction of TME and immune cells, the impact of therapy on the TME, and its predictive implications.

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