Different molecular and genetic biomarkers in Hodgkin lymphoma and its treatment.

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Introduction

Pediatric HL prognostic biomarkers have been studied; however, none have provided information that is useful enough for clinical practise. Therefore, the need for molecular markers that can recognise high-risk individuals and forecast the likelihood of therapy failure exists. Furthermore, the availability of predictive biomarkers may facilitate the identification of potential therapeutic targets that would assist balance the effectiveness of treatment and its long-term side effects.

Bcl-2

By orchestrating LMP-1-driven immortalization and enabling cells to avoid programmed cell death, B-cell leukemia/lymphoma 2 (Bcl-2) bestows a protective advantage. About 50% of juvenile HL patients express Bcl-2, and multivariate analysis shows that this Bcl-2 positivity is related with lower EFS in low-risk patients and worse EFS in individuals at higher risk. The predictive usefulness of Bcl-2 expression in HL is uncertain, while some investigations claimed that it had little impact on outcomes [1].

Ki-67

Numerous studies have shown that elevated levels of the cell proliferation marker Ki-67 are typical of HL and can have a detrimental effect on results. High Ki-67 expression in HRS cells as well as lymphocytic and histiocytic cells, however, was not associated with either advanced clinical stage or poor clinical outcome, according to an immunohistochemical study of 224 paediatric patients enrolled in the German Society for Pediatric Oncology and Hematology (GPOH) HD-90 and HD-95 trials. Repp86 expression was low, indicating that HRS or lymphocytic and histiocytic cells are stalled in the G1 phase of the cell cycle. Repp86 expression is typically detected near the G1-S boundary.

IL-10 and IL-12

About 30–50% of HL cases express the Th2 cytokine IL-10. IL-12 is expressed in primary cHL malignancies and is implicated in Th1 differentiation. Cancer patients frequently experience alterations in Th1/Th2 cytokine ratios toward Th2 predominance due to the antagonistic activities of IL-10 and IL-12. In juvenile patients, elevated IL-10 and IL-12 levels were found to have prognostic relevance and to be associated with recurrence, a poor response to therapy, a shorter EFS, and a shorter overall survival. Additionally, symptomatic patients' IL-10/IL-12 ratios were considerably greater ($p = 0.044$) than those of asymptomatic patients, pointing to a potential function for these cytokines in HL [2].

CD30

The activation of the transcription factors NF-B and activator protein-1 (AP-1) by constitutive signalling caused by overexpression of CD30 is essential for the survival of HRS cells. The specific expression of CD30 on HRS cells, which is unusual for most human tissues under normal physiologic settings, makes it an ideal target for directed therapy. It is possible that CD30 expression in paediatric HL has prognostic relevance given the correlation between high CD30+ RS cell counts and poor survival.

Intercellular adhesion molecule-1 (ICAM-1, CD54)

ICAM-1, which is overexpressed by HRS cells, is implicated in the emergence and progression of the malignant phenotype. Pediatric HL patients have been shown to have serum ICAM-1 levels that are 2–7 times higher than normal, and levels either fall or return to normal with complete remission (CR). Additionally linked to advanced stages, B symptoms, greater ESR, relapses, and poor outcomes are high blood ICAM-1 levels. Additionally, elevated ICAM-1 levels in patients with late disease stages may signify a heightened host immune response to tumour cells or merely reflect a greater tumour burden [3].

CD44

A hyaluronic acid receptor called CD44 is implicated in the growth of tumours. Pediatric HL patients with elevated blood sCD44 levels have worse survival, B-symptoms, and advanced stages. Additionally, greater serum sCD44 levels are linked with higher CD44 expression levels in tumour tissues, indicating that at least some of the sCD44 detected in HL patients came from tumour cells.

Alpha-1-antitrypsin (AAT)

Neutrophil elastase is inhibited systemically by AAT (NE). Tumor initiation, invasion, and metastasis can result from tissue damage brought on by an imbalance between AAT and NE. Using surface enhanced laser desorption/ionization (SELDI-TOF), alpha-1-antitrypsin was found to be a biomarker of tumour stage severity in 22 paediatric HL patients.

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Natural Killer (NK) cells

NK cells have been investigated as prognostic markers in several cancers because of their cytotoxic efficacy against tumours in vivo. Patients with low CD57+ cell counts (NK cells) compared to those with high CD 57+ cell counts saw a substantial decline in EFS, according to an immunohistochemistry examination of NK cells in 38 juvenile HL patients. A different paediatric HL study (n = 17) discovered no connection between NK cell activity and prognosis, in contrast. These results differed, which might be explained by the various NK cell identification techniques that were employed [4].

Nuclear Factor-κB (NF-κB)

A family of inducible transcription factors known as the NF-B family contains the proteins p65 (RelA), RelB, c-Rel, NF-B1 (p105/p50), and NF-B2 (p100/p52). These transcriptional regulators control the expression of genes involved in inflammation, the immune system, cell growth, tumour metastasis, and viral replication. Different homodimers and heterodimers of NF-B proteins are formed, and they are kept in an inactive state by cytoplasmic interaction with the IB-inhibitory protein.

Heparanase

Heparanase is an endoglycosidase that breaks down heparan sulphate proteoglycans (HSPG) to change the extracellular matrix's (ECM) structure. It also plays a significant part in the spread of tumours. Heparanase levels were 6-fold higher in juvenile HL patients upon diagnosis and decreased in association with complete remission (CR) or a favourable partial response, demonstrating the prognostic relevance of heparanase in these patients.

Vascular growth endothelial factor (VEGF)

Cancer cells produce VEGF, and when it is activated, it encourages endothelial cell migration and proliferation, which results in the growth of new blood vessels. It is generally known that having high levels of circulating VEGF indicates a poor prognosis.

Treatment

In the 1970s, high therapeutic success rates were achieved using the standard chemotherapy regimen of MOPP, which included vincristine, procarbazine, prednisolone, and nitrogen mustard (mechlorethamine). However, because this regimen included an alkylating drug (mechlorethamine), negative side effects, such as risks of secondary cancer, gonadal damage, and female infertility, only became apparent 20 years later. Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine, or ABVD, finally took the place of MOPP as the standard of therapy in the United States because it was more successful than MOPP and had a reduced incidence of later leukaemia and infertility. ABVD therapy does, however, come with a unique set of risks, such as cardiac toxicity brought on by the cumulative dose of doxorubicin and bleomycin and the addition of RT [5].

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