Treatment of childhood ALL with IKZF1 deletion (Malaysia-Singapore ALL 2010 Study)

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Mullighan et al found that deletion of *IKZF1* gene (*IKZF1*^{del}), which encodes for the lymphoid transcription protein IKAROS, confers a significantly worse outcome for ALL. *IKZF1*^{del} is seen in 2 out of 3 cases of *BCR-ABL1*-positive and ~15% of *BCR-ABL1*-negative childhood ALL. The availability of the multiplex ligation-dependent probe amplification (MLPA) assay allows for a rapid, affordable method to determine *IKZF1*^{del} status, enabling its incorporation into contemporary ALL trials.

Although*IKZF1*^{del} confers a higher risk of relapse in childhood B-lymphoblastic leukemia (B-ALL), it is uncertain whether treatment intensification will reverse this risk and improve outcome. Clappier*et al* in the retrospective analysis of BFM-based EORTC protocol 58951 study, reported that vincristine-dexamethasone/prednisolone pulses during maintenance therapy reduced the cumulative risk of relapse in *IKZF1*^{del} patients in average risk *BCR-ABL1*-negative patients. However, Hinze*et al* reported that similar vincristine/dexamethasone pulses in ALL BFM-95 study actually worsen the outcome. [25]Specifically, patients with *IKZF1*^{del} had 5-yr EFS 57% with pulses compared to 74% without pulse due to increased relapse and non-relapse mortality.

Malaysia-Singapore ALL 2010 (MS2010) study prospectively upgraded the risk assignment of patients with *IKZF1*^{del} to the next higher level and added imatinib to all patients with *BCR-ABL1* fusion. A total of 823 B-ALL patients treated on MS2003 (n=507) and MS2010 (n=316) were screened for *IKZF1*^{del} using multiplex ligation-dependent probe amplification (MLPA) assay.

In MS2003 where *IKZF1*^{del} was not used in risk assignment, *IKZF1*^{del} conferred a significantly higher 5-yr CIR (30.4% vs. 8.1%, $p=8.7\times10^{-7}$), particularly in intermediate risk (IR) group who lacked high-risk features (25.0% vs. 7.5%, p=.01). For *BCR-ABL1*-negative patients, *IKZF1*^{del} conferred a higher 5-yr CIR (20.5% vs 8.0%, p=.01). In MS2010 the 5-yr CIR of patients with *IKZF1*^{del} significantly dropped to 13.5% (p=.05) and no longer showed a significant difference in *BCR-ABL1*-negative patients (11.4% vs. 4.4%, p=.09). The 5-yr overall survival (OS) for patients with *IKZF1*^{del} improved from 69.6% in MS2003 to 91.6% in MS2010 (p=.007).

The Ma-Spore ALL 2010 study showed that intensifying therapy for childhood B-ALL with *IKZF1*^{del} significantly reduced the risk of relapse and improved overall survival. Incorporating *IKZF1* deletion screening significantly improved treatment outcome in contemporary ALL therapy.