Clinical and genetic studies of high-risk myelodysplastic syndromes and acute myeloid leukemia with chromosome 5q deletion

av

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Abstract

Patients with high-risk myelodysplastic syndromes (MDS) with a chromosome 5q deletion (del(5q)) have a poor prognosis and are often associated with a complex karyotype and *TP53* mutations, factors worsening the prognosis. The hypomethylating agent azacitidine (AZA) is the first-line treatment. Lenalidomide (LEN) is an effective therapy for lower-risk MDS with del(5q).

The aim of this thesis were clinical and genetic studies in patients with high-risk MDS and acute myeloid leukemia (AML) with 20-30% marrow blasts with a karyotype including del(5q). In a prospective, multicenter, open-label, randomized phase II study, we studied if AZA + LEN was superior to AZA alone in high-risk MDS and AML with 20-30% marrow blasts with del(5q). Seventy-two patients were included between 2012 and 2017. The overall response rate (ORR) in the treated cohort was 39% for AZA and 44% for AZA + LEN (P=0.63). The addition of LEN to AZA did not improve outcome. In paper II we studied the influence of cytogenetics on treatment response in the study and if specific cytogenetic findings could predict outcome. Patients with del(5q) and complex karyotype or an unbalanced translocation of 5q had a shorter median overall survival (OS) (P=0.004). The aim in paper III was to optimize diagnostic procedures and follow-up assessment with cytomorphology, bone marrow trephine biopsy and immunohistochemistry (IHC) in patients with higher-risk MDS and AML with 20-30% blasts with a karyotype including del(5q). In 18 patients (25%) a higher bone marrow blast percentage was detected by IHC compared to cytomorphology, shifting the diagnosis to either a higher-risk MDS subgroup or AML and is useful for correct subclassification in del(5q) high-risk myeloid disease and for response assessment.

In conclusion, the findings in this thesis show that high-risk MDS with del(5q) is a myeloid disorder with a dismal prognosis. There seems to be a window of molecular response to AZA after 3 months of treatment. Future studies should focus on the therapeutic window as a possibility for allogeneic stem cell transplantation.

Keywords: *Myelodysplastic syndromes, Acute myeloid leukemia, Chromosome 5q deletion, Complex karyotype, TP53 mutation, Clinical trial, azacitidine, lenalidomide, bone marrow trephine biopsy, IHC p53*