UKE Paper of the Month January 2025

Clearance of Driver Mutations after Transplantation for Myelofibrosis

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The New England Journal of Medicine

ABSTRACT:

Background: Allogeneic hematopoietic stem-cell transplantation is the only curative treatment for myelofibrosis. Driver mutations are the pathophysiological hallmark of the disease, but the role of mutation clearance after transplantation is unclear.

Methods: We used highly sensitive polymerase-chain-reaction technology to analyze the dynamics of driver mutations in peripheral-blood samples from 324 patients with myelofibrosis (73% with *JAK2* mutations, 23% with *CALR* mutations, and 4% with *MPL* mutations) who were undergoing transplantation after reduced-intensity conditioning. Mutations were detected before transplantation and at 30, 100, and 180 days after transplantation to measure clearance and its effect on relapse and cure. The two primary end points were relapse and disease-free survival.

Results: At day 30 after transplantation, mutation clearance was found in 42% of the patients who had *JAK2* mutations, 73% of those who had *CALR* mutations, and 54% of those who had *MPL* mutations; the corresponding percentages at day 100 were 63%, 82%, and 100%. The cumulative incidence of relapse at 1 year was 6% (95% confidence interval [CI], 2 to 10) among patients with mutation clearance at day 30 after transplantation and 21% (95% CI, 15 to 27) among those without mutation clearance at day 30. Disease-free and overall survival at 6 years were 61% and 74%, respectively, among patients with mutation clearance at day 30 after transplantation and 41% and 60%, respectively, among those without mutation clearance at day 30. Mutation clearance at day 30 appeared to outperform traditional donor chimerism as a measure of response; it was independently associated with a reduced risk of relapse or progression (hazard ratio, 0.36; 95% CI, 0.21 to 0.61) and appeared to overcome differences in prognosis based on the type of driver mutation (*JAK2* vs. *MPL* or *CALR*).

Conclusions: In patients with myelofibrosis, clearance of driver mutations at day 30 after transplantation appeared to influence relapse and survival, irrespective of the underlying driver mutation.

STATEMENT:

We consider our paper as "Paper of the Month" because it provides, for the first time, groundbreaking, solely academic, and independent insights into the prognostic significance of early driver mutation clearance after allogeneic stem-cell transplantation in myelofibrosis. Published in the prestigious New England Journal of Medicine and conducted entirely at the Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf (UKE) over a period of 20 years, this study highlights that mutation clearance at day 30 is the strongest predictor of relapse and survival, outperforming traditional measures like donor chimerism. Importantly, the highly sensitive PCR assays used for monitoring were developed at UKE, underlining the department's innovation and commitment to advancing the field. These findings establish mutation clearance as a transformative measure to guide clinical decision-making and relapse prevention strategies.

BACKGROUND:

Dr. Gagelmann is a physician in training at the Department for Stem Cell Transplantation at the UKE. Marie Quarder is a medical student at the UKE, Anita Badbaran is a Master of Science and has developed together with Prof Fehse and Prof Kröger the PCR technology. The Department of Stem Cell Transplantation under the leadership of Prof Kröger is the largest german center and has developed several practice changing transplantation strategies and is worldwide leading in transplantation for myelofibrosis. The members of the department are highly committed to improve patient outcome by innovative translational and clinical research with cellular therapies.