blood advances

CHIP shot: aiming at therapy-induced clonal hematopoiesis

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In this issue of *Blood Advances*, Nead et al[1] provides critical insights into the relationship between cancer therapy and clonal hematopoiesis (CH). CH, also known as CHIP (CH of indeterminate potential) in the setting of clonal expansion driven by acquired somatic mutations, is associated with increased risk of myeloid malignancy, cardiovascular risks, and all-cause mortality.[2-5] Although increasing age is the strongest risk factor for CH, emerging evidence highlights the role of genotoxic cancer therapies such as cytotoxic chemotherapy and radiation therapy as other key risk factors.[6-8] Importantly, the initiation and progression of CH after therapy have been inadequately studied, primarily because of the challenges of obtaining serial blood samples before and after treatment, and the need for advanced sequencing technologies to detect small clone sizes.

Nead et al investigated the origin and growth of CH after cancer therapy and its impact on clinical outcomes. The team analyzed 87 blood samples from 29 patients with esophageal or lung cancer. Blood samples were collected at multiple time points: before the initiation of treatment, midway through chemoradiation therapy, at the conclusion of treatment, and at subsequent follow-up visits. The median time from the start of chemoradiation therapy to the first blood sample was 5 months and the last analyzed blood sample was 17 months (range, 7-37 months). The study used error-corrected duplex DNA sequencing to detect very small CH clone sizes with low variant allele fractions (VAFs) <2%, sometimes termed "micro-CH." This highly accurate sequencing method resulted in an average sequencing depth of >15 000× and a median VAF of 0.4%. The baseline CH mutations were consistent with prior studies, with *DNMT3A*, *TET2*, and *ASXL1* as the most mutated genes. A significant finding from the study was that *TP53* mutations doubled in number after chemoradiation therapy (46 before treatment vs 95 after treatment). These changes were unique to *TP53*, as other commonly mutated genes such as *DNMT3A*, *TET2*, and *ASXL1* did not show significant changes in incidence or VAF before and after chemoradiation therapy. Additionally, 38% of patients who carried *TP53* mutations had an increase in CH clone size. Most importantly, individuals who had more *TP53* mutations after therapy were correlated with shorter overall survival (hazard ratio, 7.07; $P = .014$).

The strength of the study is the prospective and longitudinal collection of blood samples from patients at multiple stages of cancer treatment. Previous studies on CH in patients with solid tumors have been hampered by a lack of serial blood samples obtained before and after cancer therapy. An interesting and reassuring finding from the longitudinal aspect of the study is that few CH emerged after chemoradiation therapy, at least within the time frame that was evaluated. The overall number of CH mutations was stable in 27 of the 29 genes assayed. There was no major trend in CH VAF before and after therapy, and no patient developed therapy-related myeloid malignancy. These findings are corroborated by a longitudinal study of CH in 380 patients with breast cancer that found a few CH mutations that emerged after chemotherapy treatment.[9] The relatively low risk of de novo CH mutations suggests that cancer therapy, compared with age, may not be a strong modifier of CH risk in the short-to-intermediate term (6-18 months) after cancer therapy. We do not know how soon after cancer therapy CH mutations develop. To fully assess the risk of therapy-induced CH, we will need to examine blood samples over a longer follow-up period.

This study reaffirmed the role of chemoradiation in selecting mutations in the DNA damage response (DDR) pathway genes. In addition to TP53, the authors found that *RAD21* showed an increase in incidence after chemoradiation therapy. The predilection for CH mutations involved in the DDR pathway is a hallmark of cancer therapy–associated CH. Coombs et al reported a higher prevalence of *PPM1D* and *TP53* mutations after chemotherapy and their association with shorter patient survival.[7] Bolton et al

found that prior cancer therapy significantly increased the likelihood of carrying CH mutations in DDR genes such as *TP53*, *PPM1D*, and *CHEK2*.[6] The effect is most pronounced after radiation therapy, platinum chemotherapy, and topoisomerase II inhibitors. *PPM1D* and *CHEK2* were not assessed in the limited CH panel used by Nead et al, a limitation that should be carefully considered in future studies.

The findings of the study have significant clinical implications. At present, TP53 CH mutations are frequently detected as an incidental finding in routine clinical care through liquid biopsies or tumor/normal sequencing. The association between increased *TP53* mutations and shorter overall survival highlights the potential role of incorporating CH monitoring into risk stratification for patients with cancer undergoing therapy. Monitoring CH mutations could provide early indicators of adverse prognosis and tailor treatment strategies.

The study also needs to be interpreted with caution and replicated in other settings, including larger prospective clinical trials. Notably, the study did not have genomic data from primary tumors; therefore, we cannot exclude the possibility that *TP53* mutations were derived from circulating tumor DNA. In addition, the exact cause of death in patients was not examined; therefore, the etiology by which acquired *TP53* mutations contribute to worse survival needs to be further investigated.

In conclusion, the study by Nead et al provides compelling evidence of the impact of cancer therapy on CH mutations, particularly *TP53*, and their association with adverse clinical outcomes. The findings underscore the importance of monitoring CH mutations in patients with cancer undergoing therapy and highlight the potential of *TP53* as a critical biomarker for predicting prognosis and guiding treatment strategies.

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