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R-CHOP in NLPHL: who should receive it?

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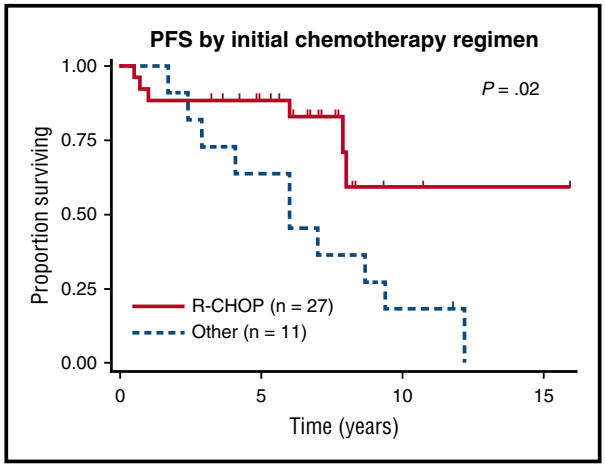
In this issue of *Blood*, Fanale and colleagues report promising treatment results for patients with newly diagnosed nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) receiving R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (see figure).[1]

The rare histologic subtype of NLPHL accounts for ~5% of all Hodgkin lymphoma (HL) cases. Unlike the disease-defining Hodgkin and Reed-Sternberg cells in classical HL, the malignant lymphocyte predominant cells in NLPHL stain consistently positive for CD20 but are negative for CD30. Clinically, NLPHL is characterized by a rather indolent course. However, there is a tendency toward late relapses and histologic transformation into aggressive B-cell non-Hodgkin lymphoma (B-NHL).[2-4]

Fanale and colleagues report a retrospective analysis including a total of 27 NLPHL patients (stage I/II: 11 patients; stage III/IV: 16 patients; concurrent aggressive B-NHL: 4 patients) who had R-CHOP as first-line treatment. A median of 6 (range: 4-8) cycles were given. Seven patients had consolidating radiotherapy (RT). All patients responded to treatment; the complete remission rate was 89%. After a median follow-up of 6.6 years, the 5-year PFS estimates were 88.5% for all patients, 91.3% for patients without concurrent diagnosis of aggressive B-NHL, and 85.3% for patients with stage III/IV disease. There were no cases of histologic transformation into aggressive B-NHL.

Patients with early-stage NLPHL, who represent the majority of cases, have an excellent long-term prognosis after RT alone (stage IA without risk factors) or combined-modality treatment consisting of a brief chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) followed by RT (early stages other than stage IA without risk factors).[5,6] In contrast, the optimal approach for advanced NLPHL is undefined. Treatment with ABVD was shown to be associated with an unacceptably high 10-year rate for disease recurrence or histologic transformation into aggressive B-NHL of ~40%.[7] Therefore, alternative options are required for this patient group.

Because of an overall response rate of 100% after single-agent anti-CD20 antibody treatment with rituximab and the clinical similarity to indolent B-NHL, R-CHOP was considered to be a promising alternative to ABVD.[8,9]



Comparison of progression-free survival (PFS) after R-CHOP and alternative chemotherapy protocols. See Figure 1A in the article by Fanale et al that begins on page 472.

The present analysis by Fanale and colleagues included a larger series of NLPHL patients receiving first-line treatment with R-CHOP. The reported 5-year PFS rates with this protocol were excellent. No patient developed histologic transformation into aggressive B-NHL. However, PFS and transformation rates have to be interpreted with caution because the median follow-up of 6.6 years is not sufficient for definitive conclusions. According to an analysis by the German Hodgkin Study Group evaluating characteristics and outcome of relapsed NLPHL, the median time from initial diagnosis to disease recurrence was 6.2 years.[10] Similarly, a Canadian report on histologic transformation in NLPHL patients revealed a median time to transformation of 8.1 years.[3]

Nonetheless, the use of R-CHOP optionally followed by RT in newly diagnosed advanced NLPHL is supported by the results from the present study despite all limitations associated with retrospective analyses and indirect comparisons. The R-CHOP protocol appears to be more effective than ABVD and less toxic than BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and thus has a more favorable risk-benefit ratio than these regimens.[4,7] In contrast, patients with early-stage NLPHL are usually not candidates for R-CHOP treatment because they have an excellent outcome after RT alone (stage IA without risk factors) or a brief ABVD-based chemotherapy followed by RT (early stages other than stage IA without risk factors).[5,6]

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Comment on Rodrigues et al, page 478

A novel role for p53 in self-tolerance

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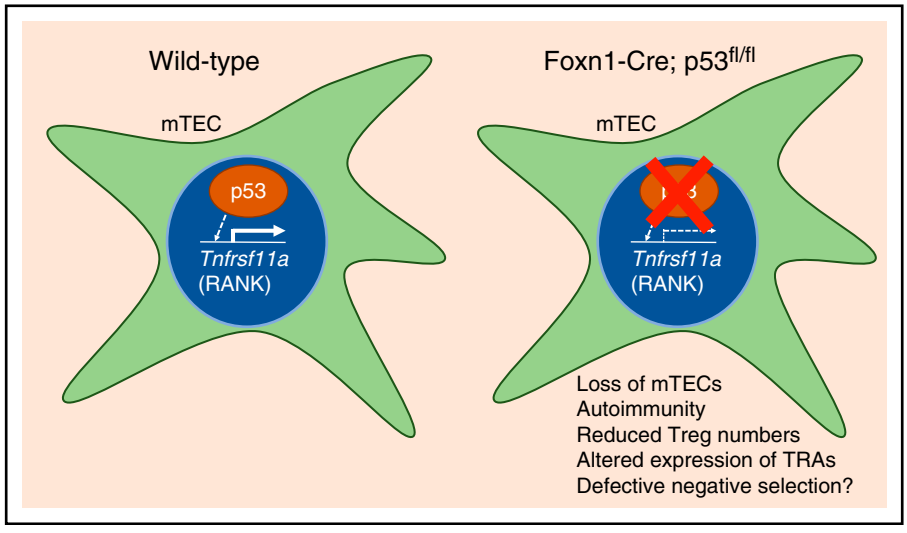
In this issue of *Blood*, Rodrigues et al use a conditional knockout mouse model to describe a novel role for p53 in the differentiation and maintenance of medullary thymic epithelial cells (mTECs), tissue-restricted antigen (TRA) expression, and self-tolerance.[1]

The thymus is essential for the generation of mature, self-tolerant T cells. Within the thymus, maturing T cells interact with 2 distinct epithelial cell types. Cortical thymic epithelial cells (cTECs) mediate positive selection, and mTECs establish self-tolerance. For this reason, mTECs promiscuously transcribe TRAs whose expression is otherwise restricted to differentiated organs. The presentation of such self-antigens to maturing T cells results in the deletion of autoreactive T cells and also guides the development of regulatory T cells (Tregs). The transcription factors controlling the expression of TRAs in mTECs therefore play an essential role in generating the self-tolerant T-cell repertoire, but our knowledge of these factors is incomplete. Aire and Fezf2 are 2 transcriptional controllers known to be required for the expression of many TRAs in mTECs, but not all TRA expression is controlled by these 2 factors, suggesting the existence of additional, currently unidentified factors necessary for the expression of TRAs.[2,3]



p53 is expressed in mTECS and promotes the expression of Tnfrsf11a (RANK). Conditional knockout of p53 in TECs results in reduced expression of RANK, a reduction in the overall number of mTECs, tissue-specific autoimmunity, and altered expression of TRAs. p53 is a critical modulator of mTEC homeostasis and the generation of a self-tolerant T-cell repertoire.

Rodrigues et al investigated p53 function in TECs by crossing p53 conditional knockout (p53cKO) mice with *Foxn1*-Cre mice to disrupt p53 function in both cTEC and mTEC populations (see figure).[1] Most healthy cells contain low levels of p53 protein, which is continuously degraded by the proteasome. p53 is stabilized in response to many different cellular stresses, including genomic damage, oncogene activation, ribosomal stress, and loss of cell-matrix adhesion.[4] When stabilized, p53 induces transcription of many genes to regulate processes such as cell cycle arrest, DNA repair, apoptosis, and control of mitochondrial respiration.[4] The authors found that postnatal p53cKO mice showed a significant reduction in the number of mTECs, but the cTEC compartment was only minimally affected.

Interestingly, the authors observed reduced expression of *Tnfrsf11a* (receptor activator of nuclear factor κB [RANK]) in p53cKO mTECs. RANK binds RANK ligand (RANKL), which is produced by T cells, and RANKL/RANK signaling is essential for the growth and maturation of Aire-expressing mTECs.[5] The authors identified p53 response elements upstream of the *Tnfrsf11a* promoter and demonstrated that p53 is capable of inducing expression from those sites by induction of luciferase in p53-deficient mouse embryonic fibroblasts (MEFs).[6] Taken together, these results suggest that one function of p53 is to guide the maturation of Aire-expressing mTECs via expression of RANK.

The authors investigated additional functions of p53 by transcriptionally profiling cTECs and mTECs from wild-type and p53cKO animals. Surprisingly, they identified thousands of differentially expressed genes in p53-deficient mTECs, many of which were TRAs. Levels of *Aire* and *Fezf2* were unchanged in adult p53cKO mTECs, although expression of *Aire* was developmentally delayed. Many TRAs with differential expression in p53cKO mTECs are known to be