

fate decisions. In agreement with this finding, the authors showed that PLAG1-S<sup>OE</sup> maintained low global translation rates in ex vivo cultivated HSPCs (see figure).

Mechanistically, PLAG1-S directly binds and activates the imprinted loci IGF2/H19 and DLK1/MEG3. IGF2 stimulates the PI3K-AKT-mTOR signaling pathway, whose activation in turn facilitates protein synthesis. Here, phosphorylated AKT activates mTOR to phosphorylate 4EBP. In the phosphorylated state, 4EBP cannot inhibit protein synthesis. However, intracellular flow cytometry revealed reduced phosphorylation of AKT and 4EBP, which suggests that PLAG1-S represses phosphorylation of 4EBP and thus contributes to reduced protein synthesis. Indeed, the pharmacological inhibition of AKT and mTOR decreased total cell count but increased the proportion of HSPCs. However, only mTOR inhibition, but not AKT inhibition, attenuated protein synthesis. The DLK1/MEG3 locus encodes four microRNAs (eg, miR-127)<sup>7</sup> that were upregulated in PLAG1-S<sup>OE</sup>. The targets of these miRNAs included genes involved in complex cap-dependent translation and RNA and peptide metabolic processing, which were downregulated in PLAG1-S<sup>OE</sup>. In the presence of an inhibitory miR-127-5p sponge, PLAG1-S<sup>OE</sup> reduced HSPC output and increased protein synthesis, whereas overexpression of miR-127 enhanced HSPC output and reduced protein synthesis (see figure).

Intriguingly, MYC expression, a major transcriptional activator of cytoplasmic translation and ribosome biogenesis,<sup>8</sup> was not reduced in PLAG1-S<sup>OE</sup>. PLAG1-S<sup>OE</sup> instead upregulates MYC-regulated nuclear ribosome assembly targets, suggesting that PLAG1-S acts independently of MYC repression. PLAG1-S<sup>OE</sup> in the presence of c-MYC<sup>OE</sup> was able to reduce protein synthesis and increase HSPC output, which was previously negatively impacted by c-MYC<sup>OE</sup>.

Keyvani Chahi et al identified PLAG1-S as a novel enforcer of human CB HSC dormancy and self-renewal via its dampening of protein synthesis upon ex vivo culture-induced stimulation. These results further highlight the physiological importance of low translation rates and suggest targeting proteostasis to manipulate ex vivo human CB HSCs for therapeutic benefits (eg, gene therapy). Furthermore, it has been demonstrated that translational inhibitors

can eliminate primitive leukemic cells while sparing healthy HSCs.<sup>9</sup> Targeting components of the PLAG1-S signaling pathway could provide novel therapies for patients with leukemia.

It is worth highlighting the great effort the scientific community is making to understand how human stem cells are regulated, which will pave the way for the discovery of new ways to maintain and genetically modify these rare and precious blood cells.

*Conflict-of-interest disclosure:* The authors declare no competing financial interests. ■

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## LYMPHOID NEOPLASIA

Comment on Brink et al, page 1009

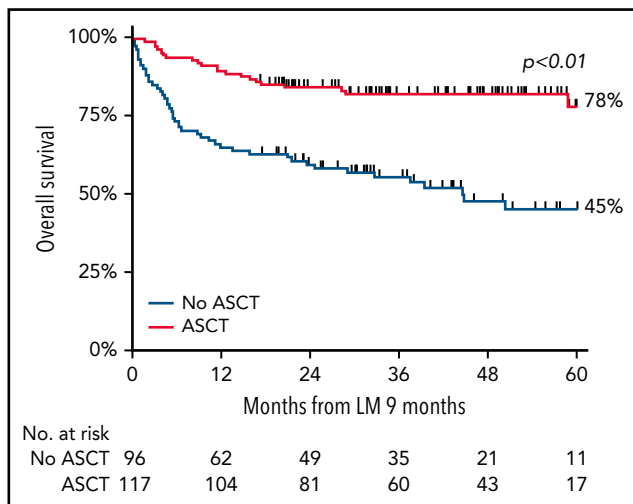
# To transplant or not to transplant: that is the question in PTCL

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**Peripheral T-cell non-Hodgkin lymphoma (PTCL) represents a heterogeneous group of lymphomas with historically poor prognosis for most subtypes, with the exception of ALK<sup>+</sup> anaplastic large-cell lymphoma (ALCL).<sup>1</sup> Although the chemotherapy used for B-cell lymphomas, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), has been the standard of care for many years, the long-term disease-free survival (DFS) and overall survival (OS) are poor.<sup>2</sup> One strategy used to improve these outcomes has been the addition of etoposide to CHOP (CHOEP), which has improved the DFS in some subtypes of PTCL in some smaller studies<sup>3</sup>; and another strategy includes the use of high-dose chemotherapy and autologous peripheral stem cell transplantation (ASCT) in the first complete remission (CR1).<sup>4</sup> A large randomized trial in a homogenous patient population to confirm these modifications has not been undertaken. In this issue of *Blood*, Brink et al<sup>5</sup> analyze data from a nationwide population-based Netherlands Cancer Registry to evaluate this point.**

In an extensive analysis, Brink et al evaluated patients 18 to 65 years of age with stage II to IV ALCL, angioimmunoblastic

T-cell lymphoma (AITL), or PTCL and grouped the patients into 5 broad categories: (1) chemotherapy followed by



Overall survival of patients <65 years of age with stage II to IV ALCL, AITL, or PTCL treated with or without consolidation with ASCT after first-line chemotherapy. See Figure 4A in the article by Brink et al that begins on page 1009.

consolidation with ASCT, (2) chemotherapy without transplantation, (3) a combination of chemotherapy and radiotherapy, and (4) no antineoplastic treatment. A total of 1427 patients were included in their extensive analysis divided into 2 study cohorts: those treated from 1989 through 2008 and those treated from 2009 through 2018.

Various analyses were performed in the patient subpopulations. The analysis of the impact of the addition of etoposide to CHOP (CHOEP) revealed an improvement in OS compared with that obtained with CHOP. However, when adjusted for age, PTCL subtype, International Prognostic Index Score, and no stem cell transplantation, the risk of mortality was similar. In a landmark analysis, the 5-year OS of patients who underwent consolidation with ASCT was 78% vs 45% without ASCT ( $P < .01$ ; see figure). A superior 5-year OS with ASCT consolidation was also observed for each subtype separately, with the exception of ALK<sup>+</sup>ALCL.

In the past few years, brentuximab vedotin (BV) when combined with CHP chemotherapy (BV+ cyclophosphamide, doxorubicin, and prednisone) has been the only treatment demonstrated to

improve the outcome of patients with newly diagnosed CD30<sup>+</sup> PTCL. However, in a retrospective analysis of patients with PTCL treated with BV-CHP, ASCT performed in CR1 still improved OS.<sup>6,7</sup> Unfortunately, for patients with PTCL who are not CD30<sup>+</sup>, no new therapies have been found that improve their survival.

Population-based cancer registry data are not a prospective randomized trial; however, this analysis contains data from a large number of patients, and the results are very convincing. Although the reasons for not taking patients to transplant in CR1 are not available in the registry, it does present real-world data that heavily favor ASCT in CR1 for eligible patients. The strong data continue to support the use of ASCT in CR1 for the common types of PTCL: PTCL-not otherwise specified, AITL, and ALK<sup>-</sup>ALCL subtypes. The use of ASCT in CR1 should also be considered in patients with PTCL who are >65 years of age, as some patients in this age group would also be transplant eligible and may benefit from this treatment. Unfortunately, many patients with PTCL do not achieve CR1 with any induction chemotherapy, and the benefit of ASCT for them is less than for

those in CR1, as demonstrated in this population-based study.

We can hope that someday science-driven analysis and well-designed clinical trials will find targeted agents to enhance the outcomes of patients with PTCL. In the meantime, based on the available data from this registry, ASCT in CR1 should be considered for all eligible patients with PTCL.

*Conflict-of-interest:* The author declares no competing financial interests. ■

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