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CLINICAL TRIALS AND OBSERVATIONS

Comment on Ghesquières et al, page 983

Aging Kairos: treating older Hodgkin patients

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In this issue of *Blood*, Ghesquières et al[1] conclude that the prednisone, vinblastine, doxorubicin, and bendamustine (PVAB) regimen, which lacks any novel drugs, could be a valuable nonbleomycin regimen for older patients with classical Hodgkin lymphoma (cHL). They also note that the outcome of older patients with chemotherapy-treated cHL remains dismal, regardless of the chemotherapy regimen used, and needs improvement.

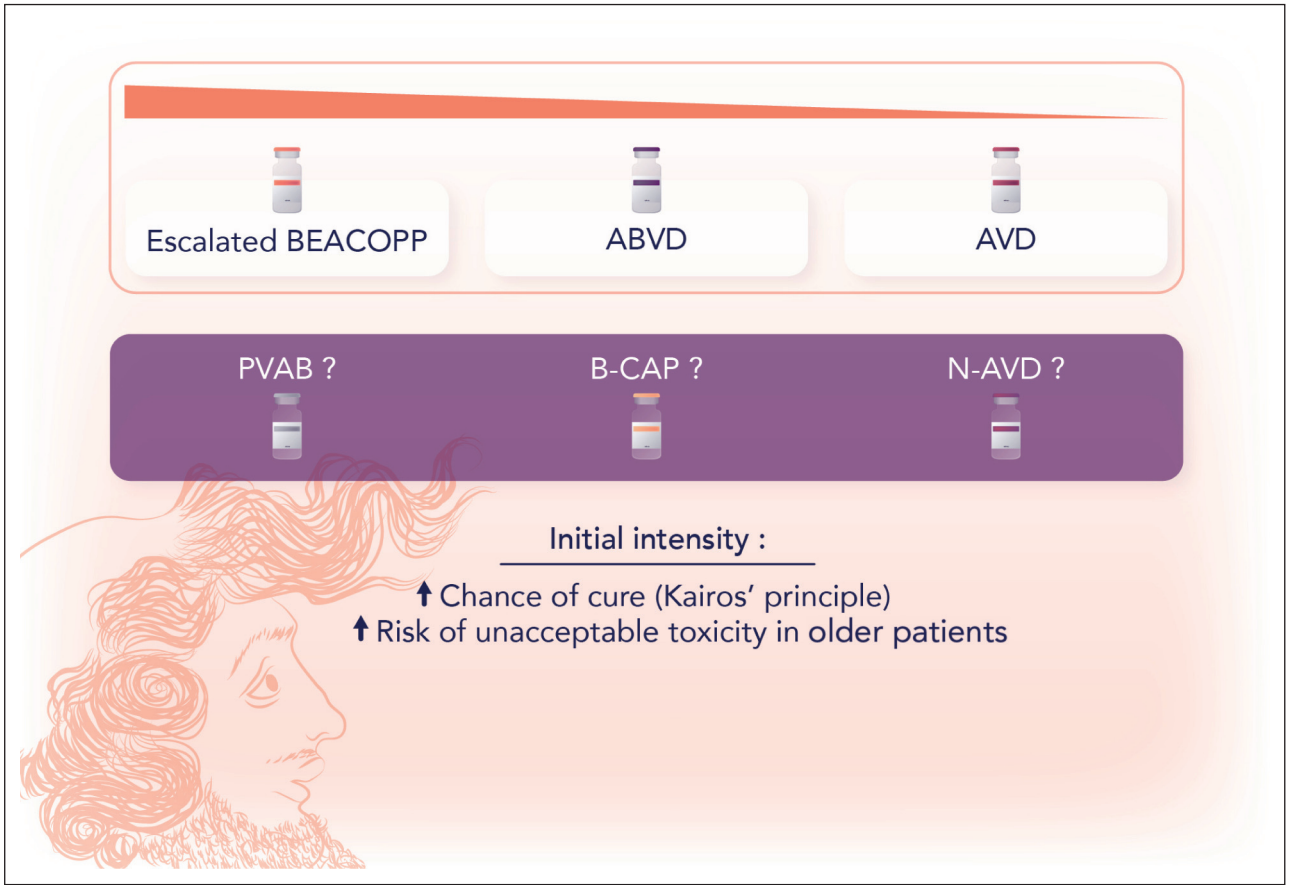
Older patients with cHL do not share the favorable prognosis of their younger counterparts. They often suffer from more comorbidities and have a lower tolerance to toxic chemotherapy. There is no chemotherapy gold standard demonstrated by large randomized trials to guide the treatment decisions in this group. The Kairos principle (coined by Volker Diehl; Kairos had hair in the front but was bald at the back of his head), to hit hard early to grab the chance of cure, seems valid for young patients, given the evidence for dose-dense therapies like escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). Unfortunately, older patients do not tolerate that approach. Hence, less intensive regimens, like the regimen studied here, PVAB, are used (see figure).

The inferior prognosis for older patients with cHL is partly explained by comorbidities and frailness.[2] The biological characteristics of the disease are also different in older compared with younger patients. Older patients more commonly have mixed cellularity histology, advanced disease stage, and more frequent Epstein-Barr virus positivity. Anthracycline-based therapy remains important in curative treatment, but more intensive regimens like BEACOPP often result in intolerable toxicity and even death.[3] Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is commonly used in clinical practice, but bleomycin-induced lung toxicity is a major problem for older patients.[4-6] Also, granulocyte colony-stimulating factor is not recommended after ABVD, due to the risk of bleomycin toxicity. Omission of bleomycin (AVD) has been tried and seems to be a feasible strategy, but cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) seems inferior.[7] PD-1 inhibitors and the antibody drug conjugate brentuximab vedotin are promising additions to standard therapy but both the optimal timing and combination of agents are still being explored.[8,9] The latest contribution is combining brentuximab vedotin with dacarbazine or nivolumab for the slightly different group of patients not eligible for chemotherapy.[10]

The patients in the Ghesquières study were all aged >60 years and diagnosed with advanced stage disease. The 89 included patients had a median age of 68 years. They received treatment with 6 cycles of the chemotherapy combination PVAB. Complete metabolic remission after treatment was 77.5%. Four-year progression-free survival (PFS) and overall survival (OS) were 50% and 69%, respectively. Patients aged >69 years were evaluated according to the geriatric cumulative illness rating scale (CIRS-G) and, interestingly, a mini nutritional assessment. Unfortunately, the relatively small sample size limits the power of the study. However, compared with other prospective studies of this age group, 89 patients is a respectable number. Performing a study of older patients with cHL is, in itself, quite an achievement. Despite this limitation, as older patients with cHL have worse PFS and OS than young patients, the statistics in the study are convincing.

The PVAB regimen contains no novel agents such as PD-1 inhibitors or antibody drug conjugates. Combining the standard anthracycline doxorubicin, with the proven (yet not too toxic) agent vinblastine and bendamustine, which has known efficacy both as a single agent and in combination in the relapse setting, seems reasonable. The absence of bleomycin is positive considering the risk of lung toxicity, and all patients received granulocyte colony-stimulating factor.

This study, like other cHL studies in this age group, is a nonrandomized phase 2 study. Ideally, a randomized trial should



According to the Kairos principle, coined by Volker Diehl, the chance of cure increases with initial intensity of chemotherapy, but intensive combinations, like BEACOPP, may result in unacceptable toxicity in older patients with cHL. Professional illustration by Somersault18:24.

be performed in the older age group but that seems all but impossible, even for very large international groups. The results of the study, in terms of PFS and OS, seem to be relatively in line with other combinations. Unfortunately, the lack of randomization, different inclusion criteria, and different time points for evaluation make it impossible to draw any firm conclusions.

In conclusion, the PVAB regimen seems tolerable, resulting in PFS and OS in line with other combinations. If possible, a large, randomized study would be performed, which would require a vast international collaboration. The introduction of a tolerable and relatively effective new combination is valuable and moves the field forward. Standard PVAB will probably fall short compared with PD-1 inhibitor and brentuximab vedotin combinations but might still prove very helpful since the optimal chemotherapy backbone for combinations with novel drugs is not yet established. Very good results have been seen using pretreatment with brentuximab vedotin or PD-1 inhibitors, a kind of Kairos principle where the opportunity is taken but in a more careful way, not to tear the gray hair away from the aging Kairos' head.[11]

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MYELOID NEOPLASIA

Comment on Greiner et al, page 1006

Systemic mastocytosis: dying or survivin

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In this issue of *Blood*, Greiner et al[1] demonstrate that aberrant mast cells in systemic mastocytosis with the *KIT* D816V mutation release tumor necrosis factor (TNF), which gives the cells a growth advantage, compared with nonmutated myeloid cells, and worsens the clinical outcome for the patients (see figure).

Systemic mastocytosis is a heterogeneous mast cell disease, where most of the patients have a D816V mutation in KIT, the receptor for stem cell factor, causing receptor autoactivation. The majority of the patients have an indolent form of the disease, suffering from mast cell mediator symptoms from various organs, whereas advanced forms of systemic mastocytosis have a much worse prognosis.[2] The *KIT* D816V mutation affects many important functions in mast cells; besides growth advantages and improved survival, the mutant cells also exhibit increased migration and enhanced cytokine production and release. At least some of the cytokines that are elevated in systemic mastocytosis are driven by the *KIT* D816V mutation. An example is interleukin-6 (IL-6),[3] and the serum level of IL-6 is associated with risk of disease progression.[4] However, the insights into how the altered cytokine production affects disease have remained limited. A deregulated cytokine production could potentially affect the mast cells themselves, disturb hematopoiesis, and/or have systemic effects on other cell types and organs, leading to some of the symptoms related to systemic mastocytosis. Thus, deciphering the contribution of different cytokines to the pathophysiology of systemic mastocytosis can shed light on the disease mechanisms and has potential to identify new drug targets. Here, we discuss the results from Greiner et al and highlight how the neoplastic mast cells transform their microenvironment to promote their own dominance.

Greiner et al identified that patients with systemic mastocytosis display elevated serum levels of TNF. By comparing mast cells with and without the *KIT* D816V mutation, the study shows that the presence of the *KIT* D816V mutation results in dramatically increased TNF production. These results demonstrate that *KIT* D816V mutant mast cells constitute a possible source of the elevated TNF levels observed in the patients. More importantly, they showed that TNF can suppress myelopoiesis and the proliferation of mast cells without the *KIT* D816V mutation. By contrast, TNF has no effects on the proliferation of *KIT* D816V mutant mast cells. Thus, the neoplastic clone has the potential to promote its dominance over nonmutated mast cells through TNF production—an advantage beyond the cell-intrinsic effects of bypassing stem cell factor binding to stimulate cell proliferation and survival. Translated into the clinical setting, *KIT* D816V mutant mast cells are likely promoting a TNF-rich microenvironment in which only the neoplastic clone thrives and the growth of normal mast cells is suppressed. Over time, this would result in the complete takeover of mutant mast cells in the patients.

That elevated TNF levels promote a neoplastic clone has been reported in myeloproliferative neoplasms[5] and juvenile myelomonocytic leukemia.[6] In myeloproliferative neoplasms, the *JAK2* V617F mutation promotes TNF production while conferring resistance to the myelopoiesis-suppressing effects of TNF. In juvenile myelomonocytic leukemia, not only is the neoplastic monocyte clone resistant to the high TNF levels, but TNF also stimulates the neoplastic monocytes' growth. In Greiner et al, the tryptase levels (as proxy of mast cell burden) in systemic mastocytosis correlated weakly with the systemic TNF levels, which indicates that cells other than mature mast cells contribute to the TNF-rich microenvironment that promotes the neoplastic mast cell dominance. One possibility is that the acquisition of the *KIT* D816V mutation results in gained TNF-producing capacity also in a non–mast cell population and that these cells contribute to the TNF production in disease. The hematopoietic progenitor cell population expresses *KIT* and harbors the *KIT* D816V mutation in various patients with systemic mastocytosis[7] and could potentially contribute to the increased TNF levels and worse outcome. However, the lack of correlation between *KIT* D816V mutation burden and TNF levels is difficult to interpret in this context. An alternative scenario is that nonmutated monocytes gain potential to produce excessive amounts of TNF in the atypical disease setting,[8] thereby contributing to the mutated mast cell expansion and worse disease outcome.

The molecular mechanisms behind the *KIT* D816V mutant mast cells' resistance to TNF is possibly attributed to the *BIRC5* gene, coding for the antiapoptotic protein survivin. Mast cells that harbor the *KIT* D816V mutation upregulate survivin following TNF treatment, and the knockdown of *BIRC5* in the cells results in impaired cell proliferation. Together, the results hint that the *KIT* D816V mutation confers resistance to TNF via survivin. However, it is important to point out that