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WHO classification of myeloid neoplasms and leukemia

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Response

To force the expression of CCR4 and/or of CCR5 chemokine receptor in T cells for immunotherapy of Hodgkin lymphoma: that is the question

We have recently shown that forced expression of CCR4 by effector T cells enhances their migration to Hodgkin tumor, so that coexpression of both CCR4 and a chimeric antigen receptor directed to the Hodgkin lymphoma (HL)–associated antigen CD30 produces better tumor control when these cells are infused intravenously in mice engrafted with human CD30$^+$/thymus and activation-regulated chemokine–secreting HL.[1]

In their letter to the editor, Aldinucci and colleagues point out that Hodgkin Reed-Sternberg cells also produce CCL5/Rantes in addition to other, previously reported chemokines, such as thymus and activation-regulated chemokine and macrophage-derived chemokine.

Although we agree with the suggestion by Aldinucci et al that it is therefore appropriate to consider overexpressing CCR5 (the receptor for CCL5/Rantes) in T cells to maximize tumoral migration, we chose not to do this for two reasons. First, CCL5/Rantes is constitutively expressed in normal lung,[2,3] where it mediates T-cell transmigration from the pulmonary vasculature compartment into the interstitium.[4] Expression is increased during infection or inflammation. Hence, T cells overexpressing CCR5 could well be diverted to normal lung tissue. Because pulmonary vascular trapping of infused T lymphocytes undoubtedly occurs even with unmodified cells, we were anxious not to further increase this process.

Our second reason relates to receptor desensitization.[5] As previously described,[6] many activated T cells themselves secrete CCL5/Rantes and this secretion may block or down-regulate receptor expression and interfere with migration in response to paracrine production of CCL5/Rantes by tumor cells.

Hence, we agree that migration of T cells may, in principle, benefit from the expression of multiple chemokine receptors, but we suggest that addition of CCR5 may be problematic, and that for the present, CCR4 may be the most suitable single-receptor option for increasing T-cell migration to the HL microenvironment.

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To the editor:

WHO classification of myeloid neoplasms and leukemia

Vardiman et al have focused their paper[1] on major changes in the 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and leukemia compared with the 2001 edition and have provided the rationale for those changes. Many of these changes and new definitions follow biologic features and include important information for prognosis. They pave the way not only to a better understanding of acute myeloid leukemia (AML) but also will advance outcome for patients. However, we cannot agree with the rationale for maintaining the category of "acute myeloid leukemia with multilineage dysplasia" (MLD), first established in the third edition in 2001, that is now subgrouped in the group of "AML with myelodysplasia-related changes."

We have shown in 2 large AML studies[2,3] of 2 different study groups (Study Alliance Leukemia and German AML Cooperative Group) in 2380 patients that MLD has no independent prognostic relevance if compared for patients when cytogenetics are also available (a must in WHO classification). Even more, MLD per se has absolutely no prognostic significance in patients 60 years of age or younger with de novo AML and, additionally, in the important subgroup of patients with normal karyotype.

We could show that it is of prognostic relevance to include now "MDS [myelodysplastic syndrome]–related cytogenetic changes"[1p945] in the definition of this new WHO subgroup. However, to define only by morphology AML that "exhibit dysplasia in 50% or more of the cells in 2 or more myeloid lineages"[1p946] cannot be justified based on published data. Thus, MLD as a marker of an AML subgroup should be omitted because it is prognostically and clinically misleading.

Vardiman et al further stated that there is no data concerning the correlation of "morphologic dysplasia" and the molecular mutations *NPM1* and *FLT3*-ITD. As published in our paper in *Blood*,[2] we could show in more than 1200 patients with AML that *NPM1* was mutated in 30% of patients with AML and MLD, which was

exactly the same percentage as in patients without MLD. *FLT3-ITD* mutations were, interestingly, significantly more prevalent in MLD-negative versus -positive patients (34% vs 24%, $P < .001$), that is, appear to be associated with de novo disease. In a multivariate analysis including MLD, age, cytogenetics, history of AML, and different *NPM1*/*FLT3*-ITD combinations only the combination NPM^+/$FLT3\text{-}ITD^-$ has shown a significant prognostic relevance besides age and cytogenetics as the most powerful prognostic factors.[2]

We conclude that a more biologic understanding of AML, as requested by the WHO classification, should omit a group of patients classified only by the morphologic criteria of MLD in the future but further extend the cytogenetic, molecular, and other biologic criteria to define clinically significant disease entities.

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Response

Factors considered in the 2008 WHO classification of myeloid neoplasms and acute leukemias

We appreciate the positive comments of Drs Wandt, Haferlach, Thiede, and Ehninger regarding the 2008 World Health Organization (WHO) classification of acute leukemias and their concern regarding the clinical significance of the subgroup of acute myeloid leukemia (AML) with myelodysplasia-related changes (AML-MRC) defined only by morphologic dysplasia. The members of the WHO myeloid writing committee and of the Myeloid Clinical Advisory Committee (MCAC) were aware of the publications of these authors[1,2] that suggested that in multivariate analyses, myelodysplasia-related morphologic abnormalities had no independent prognostic significance compared with myelodysplasia-related cytogenetic abnormalities. Indeed, their data supported the addition of the subgroup of AML-MRC defined by specific myelodysplasia-related cytogenetic abnormalities in the revised 2008 WHO classification,[3] and it also prompted discussion at the MCAC meeting as to whether AML-MRC defined by morphologic criteria alone should remain in the classification. However, data presented at that meeting and some published subsequently[4] suggested such a subgroup may yet prove to have clinical relevance.

Many patients who meet only the WHO morphologic criteria for AML-MRC would be otherwise classified as "AML, not otherwise specified (NOS)." Intuitively, severe dysplasia in the majority of maturing leukemia cells seems to be as much of a unifying factor for classification and further investigation as dispersing such cases among the categories of AML, NOS that also lack clear prognostic significance. Weinberg and colleagues[4] used the 2008 WHO criteria to compare patients with AML-MRC (most defined solely by morphologic multilineage dysplasia) with patients classified as AML, NOS, and found patients with AML-MRC were significantly older and had decreased frequency of mutated *CEBPA* and significantly worse overall and progression-free survival than patients with AML, NOS. This prognostic difference remained when cases classified as AML-MRC solely on the basis of multilineage dysplasia were compared, which supports the notion that subclassification by morphology as AML-MRC is clinically more relevant than classification as AML, NOS. We can only speculate as to why multilineage dysplasia had clinical significance in the study by Weinberg et al, but not in the larger studies cited.[1,2] Of note is that neither of the latter studies used the WHO classification criteria. The study by Haferlach et al included only AML patients with 30% or more blasts, which would exclude a significant number of cases of AML-MRC were the WHO criterion for AML of 20% or more blasts applied. Wandt et al included cases of therapy-related AML, which is recognized as a separate category in the WHO classification. Furthermore, both studies used only blood and bone marrow aspirate smears whereas Weinberg et al also evaluated bone marrow biopsies. Megakaryocytic dysplasia may be difficult to identify on aspirated material alone but is usually readily observed in core biopsies. Also some cases with AML-MRC present with fibrosis, which may limit evaluation of aspirate material.

A second issue raised by some members of the MCAC in favor of retaining the morphologic diagnosis of AML-MRC was that some such cases might be patients evolving to AML from a previously unrecognized myelodysplastic syndrome who have a borderline blast count of barely 20% or more, and who might be better served initially by judging the pace of their disease rather than immediately categorizing them as AML, NOS.

The WHO writing committees were also aware of the data regarding the incidence and clinical significance of *FLT3* and *NPM1* mutations in the setting of AML with multilineage dysplasia.[2] However, what was not clearly defined is the impact of these mutations in patients who have AML-MRC. More data are needed to decide whether a patient defined morphologically to have AML-MRC with mutated *NPM1* would be best categorized as AML-MRC, as AML, NOS, or in the provisional category of AML with mutated *NPM1*.