To the editor:

Toxic effects of sorafenib when given early after allogeneic hematopoietic stem cell transplantation

We read with interest the article by Metzelder et al showing sorafenib had antileukemic activity and could be given safely to patients with FLT-3 mutated AML relapsing after allogeneic stem cell transplantation (ASCT).1 Because sorafenib delays progression of renal cell carcinoma, we administered this drug to patients who had progression of metastatic kidney cancer after an ASCT. Besides the classic sorafenib hand-foot syndrome, we observed new-onset, biopsy-confirmed chronic graft-versus-host disease (cGVHD) of the skin (including one case of sclerodermoid cGVHD) and exacerbations of preexisting chronic skin GVHD in 4 of 7 patients treated with 400 mg of sorafenib given orally twice daily. Metzelder et al also noted cGVHD occurred in 2 of 4 patients receiving sorafenib after ASCT, although the temporal association of this drug with cGVHD is unclear from their study. Although the authors speculate sorafenib might be effective when given prophylactically after an ASCT to reduce FLT-3 mutated AML leukemia burden, it is important to note that the initiation of sorafenib in the 4 patients in their study was delayed months after the transplantation (87-322 days). In vitro and murine findings from our laboratory raise the concern that sorafenib may result in substantial toxicity and increase the risk of GVHD when this drug is administered early after a T cell–replete ASCT.

Using a major histocompatibility complex (MHC)–matched murine model of ASCT, we explored whether sorafenib would slow tumor progression potentially facilitating GVT effects in mice with established RENCA tumors. Balb/C mice conditioned with 950 cGy total body irradiation received either a T cell–depleted (bone marrow alone) or T cell–replete (bone marrow plus splenocytes) ASCT from MHC-matched, minor antigen–mismatched B10.d2 donors. Nontransplanted tumor-bearing Balb/C control mice that received sorafenib by oral gavage (60 mg/kg/day) had no evidence of drug toxicity and had slower tumor growth which improved survival compared with mice not receiving sorafenib (median survival 49 vs 34 days, respectively; P = .04). In recipients of a T cell–depleted ASCT, sorafenib by oral gavage was not associated with overt toxicities and also delayed tumor progression and

References

To the editor:

Connecting the dots: monocyte/DC and NK subsets in human peripheral blood

A recent paper in Blood reported that lineage (CD3/14/19)–negative CD56+ mononuclear cells in human peripheral blood contain 2 populations: bona fide CD7+ natural killer (NK) cells and CD7− monocyte/dendritic cells (DCs).1 Whereas this study delivers a valuable improvement in the definition of peripheral blood NK cells, it leaves unresolved the question of which monocyte/dendritic cells were found to express CD56.

Approaching this problem from the other direction, we characterized the CD56 expression of monocytes and DC subsets from healthy volunteers. Figure 1 revisits the analysis of Milush et al with additional intermediate plots to show the location of monocytes and DCs.

Figure 1A shows the distribution of CD56 among lineage (CD3/14/19/20)–negative cells, as previously illustrated by Milush and colleagues, in comparison with isotype control. Anti-CD56 clone MY31 (IgG1) from Becton Dickinson was used.

Figure 1B then maps on top of these dot plots (now shown in gray as background) the major populations of CD14+ monocytes, CD16+ monocytes/DC, CD123+ plasmacytoid DCs (PDCs), and CD11c myeloid DCs,2 to reveal where CD56 expression appears above isotype.

Figure 1C shows the key results as histograms. A defined population, 12.8% to 15.4% (range; n = 3), of CD11c myeloid DCs express CD56. A small population of CD14+ monocytes also express CD56 as previously described.3,4 CD16+ monocytes and CD123+ PDCs do not express significant CD56. Because Milush and colleagues used CD14+ in their lineage cocktail, CD14+ monocytes are excluded. We therefore identify the CD56+ cells described in their article as a subset of CD11c+ myeloid DCs.

A further contribution of these authors was to show that, although certain DCs fall into lymphoid side scatter gates and express CD56, these cells do not express CD7. CD7 antibodies are therefore a potentially useful addition to the lineage cocktail for DC biologists eager to exclude NK cells from their analysis. The utility of this strategy critically requires that no other DCs express CD7. We confirmed that CD11c+ myeloid DCs are negative for CD7 but found a population, 15.2% to 22.8% (range; n = 3), of CD123+ PDCs expressing CD7 (Figure 1C). Within the lineage-negative DR− gate, approximately 10% of CD34+ peripheral blood stem cells also expressed CD7, although these are not typically included as a subset of DCs.

Finally, we compared the addition of CD7 and CD56 singly or in combination to a lineage cocktail of CD3/14/19/20 (Figure 1D) in a plot of HLA-DR versus lineage. It is evident that the addition of both antibodies improves the separation of NK cells (depicted in black) from the DR− lineage− region containing monocytes and DCs (background, gray). This is particularly useful for excluding activated NK cells that express HLA-DR. However, as we have now shown, the caveat is that CD7 and CD56 each removes a population of CD123+ PDCs or CD11c+ myeloid DCs, respectively. Whether these subpopulations of DCs have distinct functional properties remains to be determined.

Reference

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