Cancer Research

Melphalan, Antimelanoma Immunity, and Inflammation—Letter

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The recent study by Dudek-Perić and colleagues aimed at delineating immunogenic properties of melphalan, with focus on its use in isolated limb perfusion (Mel-ILP) in metastatic melanoma (1). The authors demonstrated that mice vaccinated with melphalan-treated melanoma cells were protected from challenge with viable melanoma cells *in vivo* in a $CD8^+$ T-cell–dependent manner (1). However, it remains to be clarified whether Mel-ILP triggers T-cell–dependent regression of melanoma also in humans. We asked whether the patients' T-cell phenotypes in blood prior to Mel-ILP might herald efficiency of response. Thus, the absolute counts of peripheral blood $CD8^+$ T cells and their expression of activation markers immediately prior to Mel-ILP were assessed by flow cytometry in 43 patients with in-transit melanoma metastases, as described in a previous pilot study (2). We observed that patients who achieved a complete response (CR) after Mel-ILP, i.e., a complete disappearance of macroscopic tumors, showed higher counts of $CD3^+CD8^+$ $CD45RA^+$ T cells and of activated $CD3^+HLADR^+$ T cells than those not achieving CR (Fig. 1A). The levels of $CD3^+CD8^+$ $CD45RA^+$ T cells remained significantly associated with CR also after correction for multiple analyses using the Bonferroni method. We also noted that patients achieving CR had significantly higher ratios of $CD8^+CD45RA^+/CD8^+CD45RO^+$ T cells in blood ($P = 0.004$, Mann–Whitney test; Fig. 1B). Fifteen of 19 patients achieving CR had a $CD8^+CD45RA^+/CD8^+CD45RO^+$ ratio above 1 versus 6 of 19 patients not achieving CR ($P = 0.008$, Fisher exact test). As CD45RA is expressed by naïve as well as by effector T cells, further studies are needed to define which subpopulation of T cells correlates to melphalan responsiveness. Our results, which should be validated in larger studies, provide indirect support to the concept of immunogenic cell death after Mel-ILP in human melanoma and point toward $CD8^+$ T cells as a relevant effector cell population.

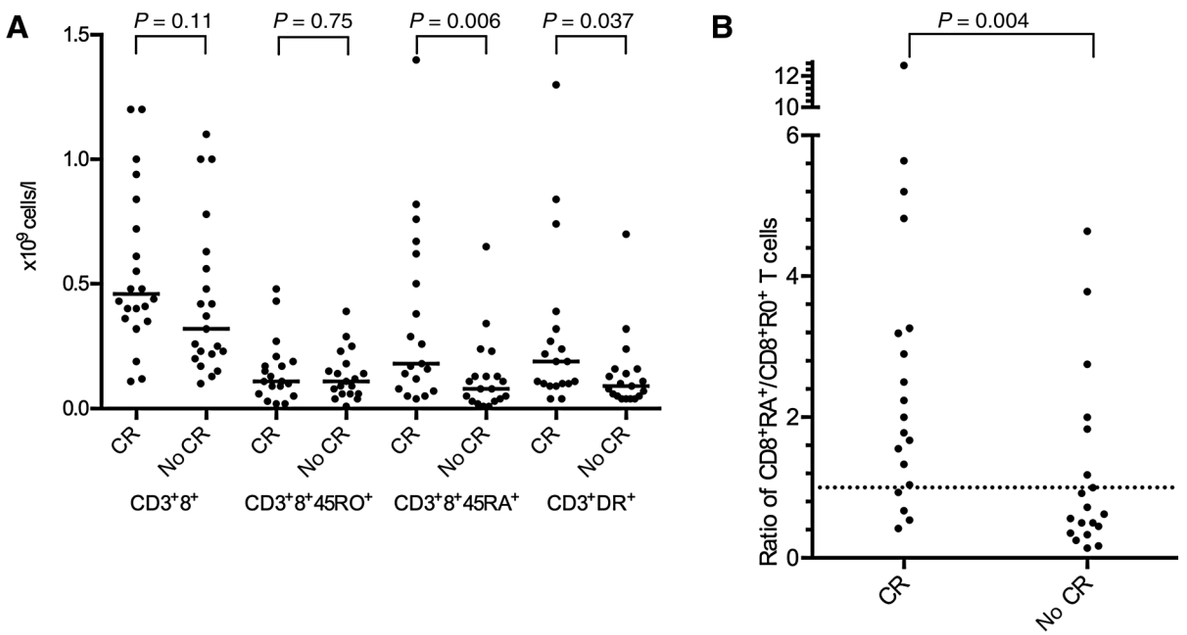

Figure 1.
The absolute counts of subpopulations of T cells (A) and the ratio of $CD3^+8^+RA^+/CD3^+8^+RO^+$ T cells (B) in peripheral blood before treatment with melphalan-based isolated limb perfusion were analyzed as predictive factors for the clinical response evaluated at 3 months after perfusion ($n = 43$ for $CD3^+8^+$ cells, $n = 38$ for the other subgroups and for the ratio of $CD3^+8^+RA^+/CD3^+8^+RO^+$ T cells). *P* values were calculated using the Mann–Whitney test. CR, complete response; No CR, no complete response.

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