Clinical Trials

Major finding: The VEGFR inhibitor cediranib has antitumor activity in unresectable alveolar soft part sarcoma.

Concept: Vasculogenesis and angiogenesis genes are downregulated in tumors in response to cediranib.

Impact: Anti-VEGFR therapy may be an effective systemic treatment for patients with alveolar soft part sarcoma.

CEDIRANIB IS EFFECTIVE IN ALVEOLAR SOFT PART SARCOMA

Alveolar soft part sarcoma (ASPS) is a rare soft-tissue sarcoma that can be cured by radical surgery, but there is no effective systemic treatment for unresectable disease. Although it is a relatively indolent cancer, ASPS frequently metastasizes, and the 5-year survival rate is only 20% for patients with unresectable metastatic ASPS. Because ASPS is highly vascular, is it possible that antiangiogenic therapies may be effective in this cancer. Kummar and colleagues therefore evaluated the objective response rate of cediranib, an orally bioavailable pan-VEGFR inhibitor, in patients with unresectable metastatic ASPS in a phase II trial. Biopsies were also obtained from a subset of patients after a week of cediranib treatment to determine if gene expression changes consistent with on-target VEGFR inhibition occurred. Of 43 evaluable patients, 15 (35%) had a partial response, including 1 patient who subsequently underwent resection and is disease-free after 16 months, and another 26 patients (60%) experienced disease stabilization. The disease control rate (partial response plus stable disease) for patients who had completed at least 6 cycles of therapy was 84%. Although dose reduction was necessary in 17 patients (40%), cediranib was generally well tolerated, with few serious adverse events. Consistent with on-target inhibition of VEGFR, the most significantly downregulated genes after cediranib treatment included genes with known roles in vasculogenesis and angiogenesis, such as angiopoietin 2, cadherin 13, and endothelial cell-specific molecule 1. These findings indicate that cediranib has single-agent activity in ASPS and support further clinical development of anti-VEGFR therapies for this cancer type. A randomized phase II study to compare the activity of cediranib with sunitinib, another VEGFR inhibitor, in advanced ASPS is ongoing. ■

Kummar S, Allen D, Monks A, Polley EC, Hose CD, Ivy P, et al. Cediranib for metastatic alveolar soft part sarcoma. J Clin Oncol 2013 Apr 29 [Epub ahead of print].

Immunology

Major finding: $CD11c^{+}CD11b^{+}Ly6C^{hi}$ antigen-presenting cells mediate anthracycline antitumor immune responses.

Mechanism: ATP from dying tumor cells induces inflammatory DC-like cell recruitment and differentiation.

Impact: This subset of TILs is essential for the anticancer activity of anthracycline chemotherapy.

TUMOR-INFILTRATING LEUKOCYTES ARE REQUIRED FOR ANTHRACYCLINE EFFICACY

Chemotherapeutic agents such as anthracyclines stimulate immunogenic cell death, in which dying cancer cells activate antitumor immune responses that further enhance the clinical efficacy of these drugs. ATP release from dying tumor cells and dendritic cell (DC) activity have been implicated in this process, but it is unclear how tumor cell antigens are presented to T cells in response to anthracycline chemotherapy. Ma and colleagues found that treatment of tumor-bearing mice with anthracyclines induced the recruitment of inflammatory $CD11b^{+}$ myeloid cells, including DCs, into the tumor bed. This accumulation of tumor-infiltrating lymphocytes (TIL) was dependent on the presence of ATP specifically within the local tumor microenvironment and on expression of purinergic ATP receptors. In particular, chemotherapy increased the frequency of the $CD11b^{+}Ly6C^{hi}Ly6G^{-}$ subset of TILs, which expressed DC markers and contained a population of granulocyte-monocyte progenitor (GMP) cells. Anthracycline treatment induced the expression of monocytic lineage transcription factors and shifted GMP cell differentiation from the default granulocyte pathway toward a $CD11c^{+}$ inflammatory DC-like phenotype; this effect was also dependent on chemotherapy-driven local ATP release from tumor cells and the activity of purinergic receptors. $CD11c^{+}CD11b^{+}Ly6C^{hi}$ cells efficiently captured and presented tumor cell antigens to T cells and protected naïve mice against tumor growth following adoptive transfer, suggesting that the antigen-presenting function of these cells is essential for anthracycline-induced antitumor immune responses. In support of this idea, inhibition of $CD11c^{+}CD11b^{+}Ly6C^{hi}$ cell accumulation within tumors abrogated the anticancer effect of anthracyclines in 4 distinct murine tumor models, whereas depletion of other DC subsets, macrophages, or neutrophils did not impair the chemotherapy response. These findings identify ATP-dependent inflammatory DC-like TILs as critical mediators of the therapeutic efficacy of anthracycline chemotherapy. ■

Ma Y, Adjemian S, Mattarollo SR, Yamazaki T, Aymeric L, Yang H, et al. Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. Immunity 2013;38:729–41.