Immunological Disorders and Immunotherapy

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Commentary

The Efficacy of Immunotherapy in Elderly Patients with Cell Cancer

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DESCRIPTION

Aging means remodeling of the immune system. It is the result of physiological aging of cells and tissues combined with environmental factors and chronic antigen exposure. The aging immune system contains more differentiated cells with an accumulation of highly differentiated CD4 and CD8 T cells. The naive T cell pool decreases with age-related exponential thymic regression. Differentiated T cells have similar, if not more, functions, but few studies address the effects of senescence on specific her T cells. When stimulated, other immune cells (monocytes, dendritic cells, and NK) change function with age. Older people's immune systems, which are fundamentally more efficient, seem to be less efficient after stimulation than younger people, probably because they have a lower reserve.

In terms of clinical significance, the elderly are more susceptible to certain pathogens and their clinical presentation differs from that of young people. Severe influenza and its reactivation of VZV are more commonly associated with altered cellular responses to vaccination. Unvaccinated people may have adverse effects on those who meet criteria for frailty. The vulnerability of older people is exacerbated by comorbidities and diseases such as cancer. Therefore, chemotherapy is used with caution in elderly patients. Therefore, the use of anti-PD-1/PD-L1 immunotherapy is attractive due to fewer side effects and better response compared to chemotherapy. Current research and clinical studies do not include older participants. Several subgroup or pooled analyzes have found improved response without increased toxicity in older patients, but their inclusion criteria differ from reality. The increasing prevalence and general aging of the population require specific studies focused on this population. Aging is associated with a mildly proinflammatory environment. We report that aging may increase immune-mediated toxicity in cancer immunotherapy, as treatments that are well tolerated in young mice can be lethal in older mice.

Most cancer immunotherapies have been tested in mice between 2 and 4 months of age. Although this is consistent with treating adolescents and young adults, cancer very commonly affects middle-aged and older people. Antiviral antibodies and interleukin-2 (IL-2) therapy were tested and previously shown to be safe and effective in young mice. Strikingly, the aged mouse, whether tumor-bearing or healthy, died within two days of starting treatment as a result of severe multi-organ lesions. Immunotherapy-induced mortality was also observed in 9-month-old but not 6-month-old mice and was independent of mouse strain.

Treatment with CD40-specific antibodies and IL-2 showed that older mice, before treatment, had even higher levels of circulating pro-inflammatory cytokines than younger mice, and tumor necrosis factor (TNF), IL-6, and interferon. It was shown to significantly increase serum levels of gamma. Notably, depletion of T cells or natural killer cells failed to prevent immunotherapy-induced cytokine storms in aged mice. In contrast, macrophage depletion protected aged mice from immunotherapy-related lethality and liver pathology and prevented increased cytokine production. Consistent with these findings, levels of macrophage-produced TNF and IL-6 in healthy subjects after stimulation correlated with donor age, suggesting that aging promotes macrophage proinflammatory activity. This may be detrimental to older people receiving immunotherapy.

But could blocking proinflammatory cytokines prevent the lethal consequences of immunotherapy in aged mice? Administration in combination with a CD40-specific antibody and IL-2 to aged mice reduced liver pathology and IL-6 levels and improved survival. Importantly, aged lung cancer mice treated with CD40-specific antibody and IL-2 together with etanercept showed prolonged survival and increased $CD8^+$ T cell lytic activity.

Therefore, the age-related proinflammatory environment may predispose patients undergoing immunotherapy to immune-mediated toxicity. The authors propose to investigate whether immune-mediated toxicity of chemotherapy and radiotherapy in elderly and middle-aged patients can also be circumvented by TNF blockade.

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