Active Tumor-Specific Immunization of the Bone Marrow (Progenitor Stem Cell) Donor

It has now been well documented in both animal models (1) and in patients (2) that active "tumor-specific" immunization of the bone marrow donor may result in the transfer of immunity thus generated to the recipient. This is an extraordinary achievement (3) that is expected to improve the results of bone marrow and stem cell transplantation since it will not only regenerate the hematopoietic system, but it also will build solid immunity toward the oncoproteins targeted in the recipient.

With this note I plead that early bearers of similar ideas be not forgotten. Mathé et al. (4) and our team at the M. D. Anderson Hospital (5) in the early 1960s showed that mice could be immunized against viral leukemias, and leukemic mice (in small but still sizeable numbers: up to 25%) could be cured by whole-body irradiation followed by transplantation of hematopoietic and lymphopoietic cells of leukemia virus-immune donors (6,7).

In 1989, when Sullivan et al. (8,9) reported reduced relapse rates of human leukemias after chemoradiotherapy and bone marrow transplantation in recipients also sustaining graft-versus-host disease (and within it a graft-versus-leukemia reaction), I wrote a letter to the editor of another journal suggesting active immunization of bone marrow donors when leukemia-associated antigens become available; however, the letter was not accepted for publication. Fortunately, in 1994, Dr. Karel A. Dicke gave me an opportunity to elaborate on this theme (10).

We proposed active immunization of the donor with purified fusion oncoprotein p210ABL-BCR before bone marrow harvesting and transplantation for the treatment of chronic myelogenous leukemia. I referred to the procedure as the "ideal graft-versus-leukemia reaction" (10). This fusion oncoprotein is not tolerogenic: it elicits weak but detectable immune reactions in the host of origin, and donors are usually siblings willing to be immunized.

From the transfer of myeloma idio- type-specific immunity from an actively immunized donor (2), this procedure could now be developed toward the transfer of immunity to immunogenic gene product proteins of point-mutated HER-2 [also known as erbB2 or neu] → p185HER-2 or fused (abl-bcr → p210ABL-BCR) oncogenes combined with interleukin 2 or other lymphokines, thus re-enforcing the therapeutic value of the "graft-versus-leukemia (lymphoma; cancer)" reaction.

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References


Does Paclitaxel Penetrate Into Brain Tumor Tissue?

Glantz et al. (1) reported very low paclitaxel (Taxol) concentrations in the cerebrospinal fluid (CSF) of patients who received infusions of paclitaxel at doses between 90 and 200 mg/m2; these CSF concentrations were between 0.5% and 8.3% [Table 2 in (1)] of those in concomitantly taken plasma samples. In the same report, Glantz et al. (1) reported that paclitaxel could not be detected in rat brain and in rat C6 glioma tissue, although the plasma concentrations of the drug ranged from 0.62 to 153 μM [Table 3 in (1)]. The authors questioned whether the use of paclitaxel in the treatment of central nervous system (CNS) malignancies—also in combination with radiation therapy—must thus be reconsidered in light of this limited access to the CNS.

The limited transfer of paclitaxel into CNS tissue may be caused by the high protein-binding level and the high molecular weight (MW; 853.9). However, the lipophilic properties of the drug [logP (octanol/water) = 3.5], leading to a large distribution volume of the agent, make it likely that paclitaxel is able to cross the blood-brain barrier. Because of these theoretical considerations and the possible role of paclitaxel in the treatment of CNS tumors, we have measured paclitaxel concentrations (by high-performance liquid chromatography [HPLC] with a detection limit of 6 ng/mL in plasma and 25 ng/g in brain tissue) in the brain tumor tissue of three patients who were operated on for a recurrent glioma (2). These patients received a dose of 175 mg/m2 in a 3-hour infusion prior to surgery. We measured paclitaxel concentrations in plasma, CSF, cyst fluid, and brain and tumor tissue. Samples were taken at the