THERAPEUTIC APPLICATLONS OF THE INTERLEUKINS

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Introduction

The use of cytokines (interleukins) in the clinic to augment host defenses has been problematic because of toxic side effects. The symptoms produced by cytokines that stimulate lymphocytes and monocytes are those usually associated with inflammation caused by infecttous microbes, including fever, rigor, fatigue, myalgia, malaise and vascular collapse.

Thus, the classic signs of inflammation, rubor, calor, tumor and dolor are now understood to result from the actions of cytokines produced during the host defense reaction, and not due to the direct effects of microbial products per se. Accorcfingly, the therapeutic chatlenge in attempting to stimulate or enhance host defenses is to establish a therapeutic index, i.e. a beneficial therapeutic: toxic ratio.

Interleukin 2 (IL-2), the first cytokine molecule to be identified and characterized is prototypic, in that when first used in the clinic very high doses were administered as intravenous bolus injections. Thus, 50 million IU (3.3 mg) were injected every 8 hours for a total dose of 15 million IU (10 mg) per day. This regimen results in severe toxicity (WHO Grade III-IV), and consists of the Systemic Inflammatory Response Syndrome (SIRS). Consequently, individuals treated in this manner can only tolerate such toxicity for a few days, and must be cared for in an intensive care unit. The basis for the toxicity of high dose IL-2 can be traced to the type and distribution of IL- receptors (IL-2R). There are 3 classes of IL-2Rs, which are distinguishabie by the affinity with which they bind IL-2. High affinity IL- 2Rs (Kd=10-11 M) are onty expressed by antigen-activated T cells and B cells, and 10% of Natural Killers (NK) cells. By comparison, intermediate affinity IL-2Rs (Kd=10-9 M) are expressed by the majority of NK cells. Because NK cells comprise 10% of circulating mononuclear cells, there are (approximately) 109 NK cells that are capable of responding to IL-2, when high doses are administered. NK cells produce secondary cytokines when activated by IL-2, in particular cytokines that target monocytes and macrophages, including IFN-gamma, TNF-alpha, and GM-CSF. These cytokines stimulate their target cells to release pro-inflammatory cytokines, such as IL-1, li-6, IL-12 and TNFalpha. The result is the SIRS.

It is possible to circumvent the activation of this cascade of cytokine release by lowering the IL-2 dose 400-fold, to 0.375 million IU (25 ug). At this dose injected subcutaneously, a peak plasma IL-2 concentration of only 25 pM is attained. Since 25 pM will occupy (approximately) 70% of high affinity IL-2Rs, but <2% of the intermediate affinity IL-2Rs expressed by most NK cells, the large amounts of cytokines produced by the NK cells can be avoided. In this manner, daily subcutaneous injections of IL-2 in ultralow doses can be given continuously without toxicity. Thus far, we have administered IL-2 for more than 2 years. This therapy boosts host defenses, as indicated by increased circulating NK cells, eosinophils, monocytes, and T cells. Moreover, delayed-type hypersensitivity is markedly augmented. Therefore, there are now many indications whereby IL-2 immunostimulatory therapy may be beneficial, including infectious diseases, immunodeficiencies and cancer.