Monitoring of immunotherapy with cytokines or monoclonal antibodies

C. Erik Hack
Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Laboratory for Experimental and Clinical Immunology, University of Amsterdam, and Department of Internal Medicine, Free University Hospital, Amsterdam, The Netherlands

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Abstract
Recombinant cytokines and monoclonal antibodies (mAbs) are increasingly used in the treatment of a number of human diseases. Monitoring of the clinical efficacy of these agents requires specific clinical and laboratory measurements. A number of these novel therapies share common side effects, ranging from fever, headache and general malaise to hypotension, the development of edema leading to the vascular leak syndrome, the occurrence of thromboembolic processes and, in severe cases, organ dysfunction. As an example of the pathogenesis of these side effects, recent data are presented which were obtained in patients receiving immunotherapy with high doses of the cytokine interleukin-2 as an anti-cancer treatment.

Introduction
Two so-called biological response modifiers are increasingly used in the treatment of human disease:

1. Monoclonal antibodies

Since its introduction in 1975 by Köhler and Milstein, the hybridoma technology has become a standard tool in immunology. Large quantities of mAb can be obtained by large-scale cell culture techniques. MAbs have considerable potential for clinical applications. However, the administration of mouse mAbs to humans may cause adverse effects, due to an immune response against the mouse antibodies. Therefore, methods to prepare human mAbs have been studied, but these appeared to be less successful.

A promising approach is the use of large combinatorial repertoires of antibody fragments displayed by on filamentous bacteriophage and the selection with antigen. Thus, mAbs either mouse, humanized or human, will be increasingly available for clinical application. At present, there are a few examples of successful treatment of human diseases by passive immunization with mAbs: various mAbs have been used for the treatment of several forms of cancer; the mouse mAb OKT3, directed against the CD3-complex of T-lymphocytes, is used to suppress rejection of renal transplants in humans; mAbs that neutralize endotoxin or endogenous tumor necrosis factor-α have been evaluated as a therapy for septic shock; and a mAb against the fibrinogen receptor on platelets (gpIIb/IIIa) have been used in patients with coronary artery disease.

2. Cytokines

It is now well-established that immune cells communicate with each other by means of small hormone-like peptides, initially called interleukins or lymphokines and later renamed “cytokines”, although a number of them are still designated as interleukins. Large quantities of cytokines can be obtained by cloning and expressing their genes, facilitating studies of their role in (patho)physiology.

Cytokines resemble hormones in that they exert their effects at picomolar-femtomolar concentrations and affect the function of target cells by binding to
specific membrane receptors. In contrast to classical hormones, however, cytokines can be produced by many cells in the body, in particular blood mononuclear, phagocytic and endothelial cells, and they also have multiple target-cells. Consequently, their biologic effects are pleiotropic. Unlike most hormones, cytokines do not seem to play a major role in normal homeostasis. Binding of cytokines to their specific receptors on target cells is often followed by the transduction of signals into the cell interior, which may induce a change of the functional state of the target cell. For further information of this topic the reader is referred to recent reviews (Larrick and Wright, 1990; Taga, 1992; Kishimoto et al., 1992; Dinarello, 1991).

Cytokines may be grouped according to their main biological effects (see Table 1). The division of cytokines into various classes is, however, somewhat artificial since some cytokines have features of more than one class. For example, IL-4 has antiinflammatory properties, whereas interferon-γ also can be considered as an pro-inflammatory cytokine since it may enhance the biological effects of TNFα.

At present, cytokines and their inhibitors are therapeutically used in an increasing number of diseases. For example, CSFs, in particular granulocyte(G)-CSF, are used to stimulate hematopoiesis in patients with depressed function of the bone marrow; various interferons as well as IL-2 and TNFα are used for the treatment of cancer; interferon-α for chronic hepatitis, interferon-β for multiple sclerosis.

### Table 1. Properties of some cytokines

| Cytokines with pro-inflammatory properties: | TNFα; IL-1α/β; IL-6; IL-8 family; MCP family; LIF (?) |
| Cytokines with anti-inflammatory properties: | IL-10; IL-13; IL-1ra |
| Cytokines with effects on immune cells: | IL-2; IL-4; IL-5; IL-7; IL-12; IFNγ |
| Cytokines involved in hematopoiesis: | G/GM-CSF; IL-3; erythropoietin; thrombopoietin |
| Cytokines involved in tissue repair: | TGFs; PDGF |

The administration of cytokines or mAbs to patients with a given disease may induce side effects that are unique for the agent used and/or for the disease treated. Such specific side-effects will not be discussed here. However, a number of cytokines or mAbs share a common pattern of toxicity (see Table 2), varying from mild symptoms such as fever, headache, general malaise to more severe symptoms such as edema formation due to vascular leakage, hypotension, and even multiple organ failure. Many of these side-effects are mediated by a strong stimulation of endogenous host defense systems, resulting in the release and activation of endogenous inflammatory mediators. It is conceivable that such responses may also be induced by extracorporeal circulation circuits, major surgery, burns, multiple trauma, ischemia, etc. Furthermore, extensive stimulation of these systems occur during sepsis. Here we will discuss some aspects of these endogenous host defense systems by reviewing our studies in patients receiving immunotherapy with the cytokine IL-2.

### The endogenous host defense systems

A large body of evidence indicates that sepsis and septic shock result from an an extensive triggering of host defense systems by the invading microorganisms and their products (Morrison and Ulevitch, 1978; McCabe et al., 1983). It is therefore not surprising...