PRINCIPLES OF THERAPY

Risk–Benefit Factors

Immunosuppression is a serious, life-threatening condition that may result from disease processes or drug therapy. At the same time, immunosuppressant drugs are used to treat serious illnesses, and their use may be required. Rational use of these drugs requires thorough assessment of a client's health or illness status, clear-cut indications for use, a lack of more effective and safer alternative treatments, analysis of potential risks versus potential benefits, cautious administration, and vigilant monitoring of the client's response. If a decision is then made that immunosuppressant drug therapy is indicated and benefits outweigh risks, the therapeutic plan must be discussed with the client (ie, reasons, expected benefits, consequences for the client's health, behavior, and lifestyle).

In addition to the specific risks or adverse effects of individual immunosuppressant drugs, general risks of immunosuppression include infection and cancer. Infection is a major cause of morbidity and mortality, especially in clients who are neutropenic (neutrophil count <1000/mm^3) from cytotoxic immunosuppressant drugs or who have had bone marrow or solid organ transplantation. For the latter group, who must continue lifelong immunosuppression to avoid graft rejection, serious infection is a constant hazard. Extensive efforts are made to prevent infections; if these efforts are unsuccessful and infections occur, they may be fatal unless recognized promptly and treated vigorously. Common infections are bacterial (gram-positive, such as *Staphylococcus aureus* or *S. epidermidis*, and gram-negative, such as *Escherichia coli*, *Klebsiella*, and *Pseudomonas* species), fungal (candidiasis, aspergillosis), or viral (cytomegalovirus, herpes simplex, or herpes zoster).

Cancer, most commonly lymphoma or skin cancer, may result from immunosuppression. The normal immune system is thought to recognize and destroy malignant cells as they develop, as long as they can be differentiated from normal cells. With immunosuppression, the malignant cells are no longer destroyed and thus are allowed to proliferate.

The consequences of immunosuppression may be lessened by newer drugs that target specific components of the immune response rather than causing general suppression of multiple components. However, there is apparently still some risk of infection and malignancy.

Use in Transplantation

The use of immunosuppressant drugs in transplantation continues to evolve as new drugs, combinations of drugs, and other aspects are developed and tested. Specific protocols vary among transplantation centers and types of transplants. As a general rule, immunosuppressant drugs used in transplantation are often used in highly technical, complex circumstances to manage life-threatening illness. Consequently, except for corticosteroids, the drugs should be used only by specialist physicians who are adept in their management. In addition, all health care providers need to review research studies and other current literature regularly for ways to maximize safety and effectiveness and minimize adverse effects of immunosuppression.

Combinations of Immunosuppressant Drugs

Most immunosuppressants are used to prevent rejection of transplanted tissues. The rejection reaction involves T and B lymphocytes, multiple cytokines, and inflammatory mediators. Thus, drug combinations are rational because they act on different components of the immune response and often have overlapping and synergistic effects. They may also allow lower doses of individual drugs, which usually cause fewer or less severe adverse effects. For example, most organ transplantation centers use a combination regimen (eg, azathioprine, a corticosteroid, and either cyclosporine, sirolimus, or tacrolimus) for prevention and treatment of rejection reactions. Once the transplanted tissue is functioning and rejection has been successfully prevented or treated, it often is possible to maintain the graft with fewer drugs or lower drug dosages. Some recommendations to increase safety or effectiveness of drug combinations include the following:

- *Lymphocyte immune globulin, antithymocyte globulin* is usually given with azathioprine and a corticosteroid.
- *Azathioprine* is usually given with cyclosporine and prednisone.
- *Basiliximab* and *daclizumab* are given with cyclosporine and a corticosteroid.
- *Corticosteroids* may be given alone or included in multidrug regimens with cyclosporine and muromonab-CD3. A corticosteroid should always accompany cyclosporine administration to enhance immunosuppression. In prophylaxis of organ transplant rejection, the combination seems more effective than azathioprine alone or azathioprine and a corticosteroid. A corticosteroid may not be required, at least long-term, with tacrolimus.
- *Cyclosporine* should be used cautiously with immunosuppressants other than corticosteroids to decrease risks of excessive immunosuppression and its complications.
- *Methotrexate* may be used alone or with cyclosporine for prophylaxis of GVHD after bone marrow transplantation.
- *Muromonab-CD3* may be given cautiously with reduced numbers or dosages of other immunosuppressants. When co-administered with prednisone and azathioprine, the maximum daily dose of prednisone is 0.5 mg/kg, and the maximum for azathioprine is 25 mg. When muromonab-CD3 is co-administered with cyclosporine, cyclosporine dosage should be reduced or the drug temporarily discontinued. If discontinued, cyclosporine is restarted 3 days before completing the course of muromonab-CD3 therapy, to resume a maintenance level of immunosuppression.