Use of Cytotoxic Agents and Cyclosporine in the Treatment of Autoimmune Disease

Part 2: Inflammatory Bowel Disease, Systemic Vasculitis, and Therapeutic Toxicity

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When cytotoxic agents were introduced, their ability to disrupt nucleic acid and protein synthesis led to their effective use for the treatment of neoplastic disease. During the course of this use, however, it became apparent that these agents also suppress the immune system. This usually unwelcome effect was subsequently studied and beneficially directed toward the treatment of non-neoplastic diseases in which autoimmune mechanisms were considered important to pathogenesis. As a result of these investigations, cytotoxic agents and, more recently, cyclosporine have emerged to become an important part of the therapeutic regimen for many autoimmune diseases. Nonetheless, these medications may still cause treatment-induced illness or even death. It is therefore particularly important to weigh the benefits and risks of cytotoxic therapy when treating a non-neoplastic disease.

This two-part Clinical Staff Conference reviews data on the efficacy and toxicity of cytotoxic drugs and cyclosporine in selected autoimmune diseases. In part 2, we focus on the role of these agents in treating inflammatory bowel disease and systemic vasculitis and review the toxic effects of these agents.


Dr. Carol A. Langford (National Institute of Allergy and Infectious Diseases [NIAID], National Institutes of Health [NIH], Bethesda, Maryland): Cytotoxic agents and cyclosporine have emerged to play an important role in the treatment of many autoimmune diseases. Despite their potential efficacy, these drugs can have significant toxicity; thus, it is important to weigh the risks and benefits of treatment on the basis of available data. In part 2 of this Clinical Staff Conference, we examine the use of these agents in inflammatory bowel disease and systemic vasculitis and review the toxic effects of these drugs, emphasizing the strategies that can be used to monitor for and minimize drug-related side effects. (Part 1 of this Conference, published in the 15 June 1998 issue, covered the role of cytotoxic agents and cyclosporine in the treatment of rheumatologic and renal diseases).

Inflammatory Bowel Disease

Dr. Stephen P. James (Division of Gastroenterology, University of Maryland School of Medicine, Baltimore, Maryland): The current approaches to therapy for Crohn disease and ulcerative colitis overlap considerably. Although the treatments for these diseases are similar, the many differences in specific therapies and nuances of optimal management are beyond the scope of this summary. In this section, we summarize the evidence for the utility of azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine in the treatment of Crohn disease and ulcerative colitis.

The evidence for the current approach to the use of immunosuppressive drugs in inflammatory bowel disease is based on many observational studies and randomized, controlled trials. Clinical trials of inflammatory bowel disease are difficult to conduct for several reasons. Among the numerous variables to consider are the type, location, extent, and severity of disease; duration of relapse; type and duration of concurrent therapies; presence of protean symptoms; potential complications and previous surgery; and different disease indices that are used to assess activity. These factors also complicate the comparison of trials in patients with inflammatory bowel disease. Despite these problems, a reasonable consensus has emerged on the current state of knowledge about immunosuppressive drugs.

Azathioprine and 6-mercaptopurine, which will be considered as equivalents here, have been the most extensively evaluated for inflammatory bowel disease. Pearson and colleagues (1) performed a thorough meta-analysis of randomized, placebo-
controlled trials of these agents in patients with Crohn disease. Although the individual results of the included trials vary widely, the analysis of seven of these trials (a total of 177 patients with Crohn disease) showed a highly significant overall odds ratio of 3.09 (95% CI, 2.45 to 3.91) for the response of active Crohn disease to azathioprine/6-mercaptopurine compared with placebo. The overall response rate was 56%; this observation corresponds not only to the results of clinical trials but also to the extensive clinical observation that many patients with Crohn disease do not respond to azathioprine/6-mercaptopurine. In addition, the overall placebo response rate was a remarkable 32%. High placebo response rates frequently occur in inflammatory bowel disease trials; this emphasizes the importance of controlled trials to evaluate inflammatory bowel disease.

In the same meta-analysis, trials were evaluated for the utility of azathioprine/6-mercaptopurine to maintain remission of Crohn disease. The overall odds ratio was 2.27 (CI, 1.76 to 2.93) for the active drug, and the overall response rate was 67%. Given the slow onset of action of low-dose azathioprine, it was not unexpected that the duration of therapy had an important correlation with efficacy; substantial efficacy was not seen for therapy lasting less than 17 weeks. One approach to the problem of the slow onset of action of azathioprine for Crohn disease is the use of high intravenous loading doses of azathioprine. Sandborn and colleagues (2) showed the efficacy of this approach in a small pilot study. However, this potentially risky approach requires further study before it can be recommended.

As indicated above, azathioprine/6-mercaptopurine can be used to maintain remission of Crohn disease. An important remaining question, however, is the duration of this therapy in patients who remain in remission. Bouhnik and colleagues (3) retrospectively analyzed 157 patients who had achieved remission while receiving azathioprine/6-mercaptopurine. The 5-year relapse rate was 32% for patients who continued to receive therapy and 75% for patients who discontinued therapy. These figures suggest that it is better to continue receiving treatment; however, the investigators stratified patients according to how long they had been in remission. Three cases of non-Hodgkin lymphoma in patients with inflammatory bowel disease have suggested that the risk for non-Hodgkin lymphoma in inflammatory bowel disease is associated with a significant increase in the risk for anorectal and colon cancer. Furthermore, several case reports have described non-Hodgkin lymphomas in patients with inflammatory bowel disease who have been treated with azathioprine/6-mercaptopurine. The risk for non-Hodgkin lymphoma in inflammatory bowel disease is unknown, but an uncontrolled study suggested that the incidence of lymphoma may be increased in patients with inflammatory bowel disease who have not received these drugs (8). A long-term retrospective study found no cases of non-Hodgkin lymphoma in 755 treated patients (9).

Uncontrolled observations of methotrexate in inflammatory bowel disease have suggested that the drug’s efficacy may be similar to that of azathioprine/6-mercaptopurine, but few randomized, controlled trials have been completed. Feagan and colleagues (10) conducted a randomized, double-blind, placebo-controlled trial of methotrexate in 141 patients with active Crohn disease. Patients received 25 mg of methotrexate intramuscularly once weekly for 16 weeks. Methotrexate was significantly better than placebo in inducing remission, which occurred in 39% of methotrexate-treated patients (relative risk, 1.95 [CI, 1.09 to 3.48]). In addition, glucocorticoid use was significantly lower in methotrexate recipients. However, 17% of patients withdrew from therapy because of side effects (10). It was not clear from this study whether patients received supplemental folate. Although open pilot studies have suggested that methotrexate may be useful for ulcerative colitis, only one randomized, controlled trial has been published. In this double-blind trial (11), 67 patients with active ulcerative colitis who had
received glucocorticoids or immunosuppressive drugs for 4 months within the previous 12 months were treated with 12.5 mg of oral methotrexate once weekly for 9 months (11). Methotrexate was not found to differ from placebo for induction or maintenance of remission. However, this study has been criticized for using a methotrexate dose that was too low to disprove the potential efficacy of methotrexate in ulcerative colitis.

The use of cyclosporine to treat inflammatory bowel disease initially held considerable promise. In a randomized, double-blind, placebo-controlled trial (12), 71 patients with active Crohn disease were treated with cyclosporine, 5 to 7.5 mg/kg of body weight per day for 3 months; 59% of patients in the treatment group improved compared with 32% of patients in the placebo group. However, relapse promptly occurred after discontinuation of treatment. Uncontrolled observations have also suggested that high-dose cyclosporine may have efficacy for fistulizing Crohn disease (13), but three more recently completed trials of lower doses of cyclosporine did not show efficacy. In the Canadian Crohn's Relapse Prevention Trial, 305 patients with mild or inactive Crohn disease received cyclosporine, 5 mg/kg per day for 18 months; the treated patients had worse results than patients receiving placebo (14). In another study of 146 patients with active Crohn disease requiring glucocorticoids or azathioprine who were treated with cyclosporine for 3 months, no significant differences were reported between cyclosporine recipients and placebo recipients (15). A similar study of 182 glucocorticoid-treated patients with Crohn disease found no benefit of cyclosporine treatment (16).

The results of these studies clearly indicate that low-dose cyclosporine plays no role in the treatment of chronic active Crohn disease or maintenance of remission. High-dose intravenous cyclosporine was reported to have efficacy in a small controlled trial of patients with severe ulcerative colitis who might otherwise have undergone immediate colectomy (17). An uncontrolled study of cyclosporine for severe ulcerative colitis reported high efficacy but also severe toxicities, including one death from Pneumocystis carinii pneumonia (18).

In summary, high-dose cyclosporine therapy may be indicated for severely ill patients as a bridge to other forms of therapy, but the optimal use of cyclosporine for this purpose is still unknown. Furthermore, the substantial toxicity of the drug must be weighed against the ability to cure ulcerative colitis with surgery.

Table 1 summarizes the potential uses of azathioprine/6-mercaptopurine, methotrexate, and cyclosporine for treatment of inflammatory bowel disease, based on published reports of controlled trials.

These drugs are frequently used in combination with other agents, and their use requires careful monitoring. The optimal use of various drug combinations requires not only a knowledge of appropriate indications and dosage but also a thorough assessment of patient expectations and quality of life, careful weighing of the various risks of medical and surgical therapies, judicious use of other supportive measures, and extensive patient education. Although treatment of inflammatory bowel disease has many limitations, current approaches improve the quality of life in most patients.

### Systemic Vasculitis

Dr. Michael C. Sneller (NIAID, NIH, Bethesda, Maryland): Vasculitis is a clinicopathologic process characterized by inflammation and necrosis of blood vessels that leads to vessel occlusion and tissue ischemia. Vasculitis may occur as a primary process or as a component of another underlying disease. The primary vasculitis syndromes are generally thought to be mediated by immunopathogenetic mechanisms (19), and current therapy for these syndromes often involves nonspecific immunosuppressive agents, such as glucocorticoids and cytotoxic drugs (Table 2). The spectrum of disease severity among the various systemic vasculitides is broad. At one end of the spectrum are such diseases as Henoch–Schönlein purpura, in which the manifestations of vasculitis are relatively mild and rarely lead to irreversible major organ dysfunction. These syndromes are usually self-limited, and therapy with immunosuppressive agents has not been shown to alter the natural history. At the other end of the spectrum are such diseases as generalized Wegener granulomatosis, in which the manifestations of vasculitis are frequently severe and lead to irreversible major organ system dysfunction or death if they are not aggressively treated.

The systemic vasculitides are uncommon and have diverse manifestations that can be acutely life-threatening. These factors make it difficult to con-
duct large randomized trials of therapy. Thus, recommendations for treatment are based largely on the results of uncontrolled prospective studies. In many instances, definitive conclusions on the efficacy of cytotoxic therapy cannot be made because the only clinical data available are limited by small sample sizes, retrospective designs, or the absence of clear definitions of disease and disease activity.

**Wegener Granulomatosis**

Generalized (classic) Wegener granulomatosis is one systemic vasculitis syndrome for which cytotoxic drug therapy is clearly beneficial. This syndrome is characterized by a necrotizing, granulomatous vasculitis of the upper and lower respiratory tract together with necrotizing glomerulonephritis. Disseminated vasculitis involving the small arteries and veins often occurs as the disease progresses. Untreated generalized Wegener granulomatosis usually progresses rapidly and leads to death. In one series of untreated patients (20), the mean survival time was 5 months; more than 90% of patients died within 2 years of diagnosis. Glucocorticoids are somewhat effective at suppressing the inflammatory symptoms of Wegener granulomatosis. In one study, glucocorticoids increased the median survival time to 12.5 months (21). However, glucocorticoids alone cannot control clinically significant pulmonary or renal disease, and most glucocorticoid-treated patients die of uncontrolled disease or infectious complications (21).

In the late 1960s, Fauci and Wolff at the NIH began to use low-dose, daily cyclophosphamide therapy combined with prednisone to treat patients with generalized Wegener granulomatosis. In 1973, they reported on the induction of sustained disease remission in 12 of 14 patients with generalized Wegener granulomatosis who received daily cyclophosphamide and prednisone therapy (22). These encouraging initial results led to a prospective trial of cyclophosphamide in generalized Wegener granulomatosis that lasted 24 years (23, 24). In this trial, therapy consisted of prednisone, 1 mg/kg per day, and oral cyclophosphamide, 2 mg/kg per day. It is important to note that the goal of cyclophosphamide therapy was not to produce leukopenia. Rather, the dose was decreased from 2 mg/kg per day as needed to keep the leukocyte count above $3.0 \times 10^6$ cells/L. In a few patients with fulminating and rapidly progressive disease, the cyclophosphamide dosage began at 3 to 4 mg/kg per day and was subsequently decreased as needed to prevent leukopenia. The prednisone dose was tapered and therapy with the drug was eventually discontinued as the disease came under control; cyclophosphamide therapy was continued for at least 1 year after the patient achieved complete remission. Of the 133 patients with Wegener granulomatosis treated with this regimen at the NIH, major organ system disease markedly improved in 121 (91%) and complete remission occurred in 100 (75%) (24). Remission analysis focused on the 98 patients with at least 5 years of follow-up found that complete remission occurred at least once in 94 (96%) of these 98 patients. However, at least one relapse occurred in 49% of patients who achieved remission. Eleven percent of patients died of active Wegener granulomatosis, chronic sequelae of previously active disease, complications of treatment, or a combination of these factors (24). These results firmly establish the efficacy of cyclophosphamide therapy in generalized Wegener granulomatosis.

Despite the clear efficacy of this therapy for active Wegener granulomatosis, extended treatment with cyclophosphamide for many years to prevent disease relapse is not feasible because of cumulative drug toxicity. Furthermore, it has become increasingly clear that the repeated courses of cyclophosphamide used to treat disease relapses are associated with considerable cyclophosphamide-related morbidity.

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**Table 2. Use of Cytotoxic Drugs in the Treatment of Systemic Vasculitis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener granulomatosis with major organ system involvement</td>
<td>Daily cyclophosphamide plus glucocorticoid Methotrexate plus glucocorticoid</td>
<td>Consider methotrexate plus glucocorticoid in patients without immediately life-threatening disease or in patients with significant cyclophosphamide-related toxicity</td>
</tr>
<tr>
<td>Polyarteritis nodosa Microscopic polyangitis</td>
<td>Glucocorticoid alone Daily cyclophosphamide plus glucocorticoid</td>
<td>Limited data support the use of cyclophosphamide in patients with severe renal, gastrointestinal, pulmonary, cardiac, or central nervous system vasculitis</td>
</tr>
<tr>
<td>Churg-Strauss syndrome Takayasu arteritis Giant-cell arteritis Other vasculitides</td>
<td>Glucocorticoid alone</td>
<td>Available data are insufficient to support specific recommendations; decision to use cytotoxic therapy must be individualized and based on disease severity, response to glucocorticoid therapy, and potential drug toxicity</td>
</tr>
</tbody>
</table>
As described above, treatment with high-dose monthly pulses of cyclophosphamide is effective for severe manifestations of systemic lupus erythematosus and is associated with less toxicity than daily low-dose therapy. Unfortunately, the results of prospective trials using high-dose monthly pulses of cyclophosphamide to treat generalized Wegener granulomatosis have been discouraging. Hoffman and colleagues (25) treated 14 patients with monthly pulses of cyclophosphamide combined with daily prednisone therapy. Although 13 patients initially improved, only 3 patients (21%) achieved sustained improvement or remission. In a larger trial, Reinhold-Keller and coworkers (26) used high-dose monthly pulse cyclophosphamide to treat 43 patients with Wegener granulomatosis. Only 42% of these patients showed complete or partial remission of disease with pulse cyclophosphamide therapy. In a third randomized trial, Guillemin and associates (27) randomly assigned 50 patients to receive intravenous monthly pulses of cyclophosphamide (27 patients) or daily oral cyclophosphamide (23 patients). Although the rate of initial response to therapy was similar in the two groups, disease relapsed in 52% of patients in the pulse therapy group compared with 17.6% of those in the daily cyclophosphamide therapy group ($P < 0.05$). The unusually high mortality rate among patients in both study groups (33.3% in the pulse therapy group and 43.5% in the daily therapy group) may be related to specific aspects of the cyclophosphamide and glucocorticoid regimens used (28). Taken together, the results of these three trials suggest that treatment with monthly pulses of cyclophosphamide is less effective at producing a sustained disease remission than low daily doses (2 mg/kg per day) and should not be used as first-line therapy in patients with severe generalized Wegener granulomatosis.

In 1990, we began a prospective study to investigate the efficacy of low-dose weekly methotrexate treatment of selected patients with Wegener granulomatosis. Oral methotrexate was given at a dosage of 17.5 to 20 mg/wk, and the prednisone regimen was the same as that used in the standard cyclophosphamide protocol. Although we excluded patients with rapidly progressing renal or pulmonary failure, 60% (25 of 42) of patients in our study had active disease involving three or more organ systems and 50% (21 of 42) had active glomerulonephritis (29). Complete remission occurred in 33 of 42 patients (79%). Only 3 patients had progressive disease that required institution of cyclophosphamide therapy, and no patient died of uncontrolled Wegener granulomatosis. Disease relapsed in 19 (38%) of the 33 patients who achieved remission, with a median time to relapse of 29 months (29, 30). In 15 of these 19 patients (79%), relapses occurred either after methotrexate therapy was discontinued or after the dose had been decreased to 15 mg/wk or less (30). These results suggest that low-dose weekly methotrexate therapy is acceptable initial treatment in patients with Wegener granulomatosis who do not have immediately life-threatening disease. Weekly methotrexate therapy may also prove useful as maintenance therapy for patients in whom remission has been induced with cyclophosphamide (31).

Although combined therapy with glucocorticoids and a cytotoxic agent is required for successful treatment of major organ system disease, not all clinical manifestations of Wegener granulomatosis require such therapy. For example, cytotoxic drugs should not be used to treat isolated sinus disease or subglottic stenosis (32, 33).

### Polyarteritis Nodosa

Although cytotoxic therapy is clearly beneficial in the treatment of generalized Wegener granulomatosis, the situation with regard to polyarteritis nodosa is less clear. Treatment with glucocorticoids alone increases the 5-year survival rate from 13% for untreated cases (34) to 60% to 80% (35, 36). Although some studies have reported improved survival when a cytotoxic agent is combined with glucocorticoids (37), others have not (35, 38). Studies of therapy for polyarteritis nodosa have many methodologic flaws that limit the interpretation of their results. Many studies were retrospective and used historical controls that were not treated according to a single protocol and were not well matched for duration or severity of disease. In the few randomized trials, the small number of patients in each study group severely limited the power of these studies to detect a significant difference in outcome (36, 38, 39). Disease severity has also varied considerably between studies. The presence of abdominal, renal, or central nervous system vasculitis is associated with a poor prognosis (40, 41), and it is often difficult to compare the results of individual studies because they vary in the proportion of patients with these manifestations. Finally, most series have contained a variable number of patients in whom small-vessel vasculitis and diffuse necrotizing glomerulonephritis are prominent features. These patients seem to have a distinct syndrome, often called microscopic polyangiitis, that differs from the "classic" form of polyarteritis nodosa; the latter is characterized by vasculitis that predominantly involves the medium-sized vessels and leads to organ infarction (42, 43). The distinction between classic polyarteritis nodosa and microscopic polyangiitis is important.
because the prognosis and response to treatment may be different for these two syndromes (42, 44). Although it has not been established that treatment with a cytotoxic agent is necessary or beneficial in all patients with polyarteritis nodosa, there are subgroups of patients in whom the addition of cyclophosphamide or other cytotoxic agent is likely to improve outcome. Current information supports the initial use of cyclophosphamide in patients with immediately life-threatening disease manifestations, such as vasculitis affecting the heart, central nervous system, or gastrointestinal tract (39). Patients who have recurrent or progressive manifestations of vasculitis involving major visceral organs despite adequate glucocorticoid therapy may also benefit from the addition of cyclophosphamide (or other cytotoxic agents) (45, 46).

Other Systemic Vasculitides

Cytotoxic agents have been used with variable success to treat small numbers of patients with severe or refractory manifestations of hypersensitivity vasculitis, Henoch-Schönlein purpura, the Churg-Strauss syndrome, Takayasu arteritis, giant-cell arteritis, and essential mixed cryoglobulinemia (45, 47). The available clinical data are not sufficient to support specific recommendations; therefore, the decision to use a cytotoxic drug in the treatment of one of these vasculitis syndromes must be individualized and consider the severity of disease, clinical response to glucocorticoid therapy, and potential for drug-related morbidity.

Toxicity

Dr. Langford: In using cytotoxic agents, the risks must always be carefully considered because each of these medications may cause drug-induced illness and death (Table 3) (48-50). The underlying disease can influence side effects in many ways: for example, through damage to an underlying organ (which may predispose the patient to toxicity) or through clinical features (whose appearance may be similar to that of a medication toxicity). In several studies that rigorously examined toxicity, it has not always been easy to establish whether an adverse event resulted from disease, treatment, or a combination of both (24). Despite this, it is apparent from the experience in both neoplastic and non-neoplastic diseases that each of these agents possesses a specific toxicity profile. This section focuses on the more serious medication-related toxicities and the strategies that can be used to monitor for and prevent them.

Infection is a universal concern in patients receiving immunosuppressive medications. Although concomitant glucocorticoid therapy increases the rate of infection, alternate-day administration lessens this risk and should be pursued when possible (51). Because of the broad effects of these drugs on the immune response, the host may be susceptible to a wide spectrum of bacterial and opportunistic organisms (52). Pneumocystis carinii pneumonia is one of the most common opportunistic infections seen in patients with autoimmune disease who are receiving cytotoxic therapy (52). Prophylaxis with low-dose trimethoprim-sulfamethoxazole has been shown to be effective in preventing P. carinii infections in patients with leukemia and HIV infection (53, 54) and should be considered in any non-sulfa-allergic patient receiving a cytotoxic agent and high-dose daily glucocorticoid therapy (29, 52, 55).

Although information in humans is limited, animal data suggest that all of these agents should be

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Table 3. Therapeutic Toxic Effects*

<table>
<thead>
<tr>
<th>Toxic Effect</th>
<th>Cyclophosphamide</th>
<th>Chlorambucil</th>
<th>Methotrexate</th>
<th>Azathioprine</th>
<th>Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher risk for infection</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>50% to 100%; D, F</td>
<td>5% to 30%; D</td>
<td>5% to 30%; D, F</td>
<td>5% to 30%; D</td>
<td>0</td>
</tr>
<tr>
<td>Leukemia or lymphoma</td>
<td>1% to 2%</td>
<td>1% to 2%</td>
<td>1% to 2%</td>
<td>Indeterminate</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5% to 50%; D</td>
<td>1% to 10%</td>
<td>1% to 20%; D</td>
<td>Indeterminate</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>5% to 100%; D</td>
<td>2% to 20%; D</td>
<td>2% to 50%; D, R</td>
<td>5% to 20%</td>
<td>5% to 20%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1%</td>
<td>&lt;1%</td>
<td>1% to 30%</td>
<td>Indeterminate</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>Elevated aminotransferase levels</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>10% to 70%</td>
<td>1% to 30%</td>
<td>1% to 20%</td>
</tr>
<tr>
<td>Hepatic fibrosis</td>
<td>0</td>
<td>0</td>
<td>1% to 25%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>1% to 10%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Indeterminate</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>Permanent renal toxicity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urothelial mucosal injury</td>
<td>1% to 50%; F</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Transitional-cell carcinoma</td>
<td>1% to 6%; F</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gonadal dysfunction</td>
<td>10% to 100%; D</td>
<td>Yes</td>
<td>Indeterminate</td>
<td>Indeterminate</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>1% to 5%</td>
<td>1% to 5%</td>
<td>1% to 20%</td>
<td>1% to 20%</td>
<td>5% to 20%</td>
</tr>
</tbody>
</table>

* Frequencies represent a compilation of data from reports of use in autoimmune diseases. D = not observed or case reports; D = risk differs on the basis of administered or cumulative dose; F = risk differs on the basis of frequency of administration; R = risk differs on the basis of route of administration.
viewed as potentially teratogenic (56). Contraception is therefore recommended for all patients while they receive therapy and for at least 3 months after discontinuation of therapy.

Cyclophosphamide

The toxic effects of cyclophosphamide sometimes differ according to the frequency of administration. Because bone marrow suppression occurs in all cyclophosphamide-treated patients, monitoring the complete blood count is critical. In the setting of intermittent therapy, complete blood counts obtained 7, 10, 14, and 21 days after administration can be used to follow the leukocyte nadir, which usually occurs between days 7 and 14. For many protocols, dose adjustments are based on achieving a leukocyte nadir of no lower than $2.0 \times 10^6$ cells/L. With daily therapy, complete blood counts are usually obtained every 1 to 2 weeks; the goal is avoidance of leukopenia, with the leukocyte count maintained above $3.0 \times 10^6$ cells/L (22, 23). The blood counts should be expected to decline both as the glucocorticoid dose is tapered and over time because of a cumulative effect on the bone marrow.

Urothelial toxicity occurs much more frequently in patients receiving daily cyclophosphamide therapy. This is believed to be due to a greater degree of mucosal exposure to the toxic metabolite acrolein. Cyclophosphamide-induced cystitis has been estimated to occur in 50% of patients receiving daily therapy (57). Because life-threatening hemorrhage can occur, cyclophosphamide should be withheld and cystoscopy promptly performed in any patient who develops gross hematuria.

Strategies that minimize bladder acrolein exposure are important in decreasing urotoxicity. The daily cyclophosphamide dose should be taken all at once in the morning with a large amount of fluid. In patients receiving intermittent cyclophosphamide therapy, the bladder can be protected by intravenous hydration or even direct lavage by way of a triple-lumen urethral catheter. A further option with intermittent therapy is sodium 2-mercaptoethanesulfonate (mesna), which binds and inactivates acrolein (50).

Transitional-cell carcinoma of the bladder has developed in 6% of the patients with Wegener granulomatosis followed at the NIH who received daily cyclophosphamide therapy (57). According to Kaplan-Meier analysis, the estimated incidence of bladder cancer in this population was found to be as high as 16% 15 years after the first exposure to cyclophosphamide. Because transitional-cell carcinoma has been diagnosed up to 17 years after discontinuation of therapy (58), the risk for bladder cancer and the need for monitoring should be considered life-long. Urine cytology is useful if the results are abnormal, but the test has poor sensitivity for detecting low-grade cancers. Nonglomerular hematuria has been found to be the most useful marker in identifying patients at risk for bladder cancer. Thus, urinalysis with microscopic examination should be performed every 3 to 6 months, even after cyclophosphamide therapy has been discontinued (57). In patients with a known history of nonglomerular hematuria, cystoscopy every 1 to 2 years should be considered. In addition to bladder cancer, cyclophosphamide has also been associated with the long-term development of leukemia, lymphoma, and skin cancer (58).

Permanent infertility has been reported in 10% to 100% of both men and women and seems to increase with age and cumulative dose (56, 59). In men, cyclophosphamide damages the germinal epithelium; in women, sterility seems to be due to primary ovarian failure from premature follicle depletion (59, 60). According to these patterns of injury, hormonal manipulation would be hypothesized to be beneficial (60), but this has not yet been shown in large series. Banking of ova or sperm before initiation of therapy may be considered, but the accompanying delay in treatment is usually not an option in life-threatening diseases.

Chlorambucil

Bone marrow suppression is the main dose-limiting toxicity of chlorambucil, and irreversible marrow failure has been reported (61). Development of neoplasia and, in particular, acute myeloblastic leukemia, is one of the most serious therapeutic complications. In one study (62), leukemia developed in 11% of 431 patients with polycythemia vera who were treated with chlorambucil; this represents a risk that is 13 times greater than that in patients treated with phlebotomy. Although few long-term studies have examined this risk in autoimmune disease, small series suggest an increase in the incidence of leukemia and other tumors (63, 64). The use of chlorambucil in children should be considered with particular caution because their risk for cancer seems greater.

Methotrexate

Bone marrow suppression has been observed in up to 30% of patients receiving methotrexate for non-neoplastic diseases. Marrow toxicity is further enhanced with renal insufficiency, folic acid deficiency, viral illness, and the concurrent use of certain medications.

Methotrexate pneumonitis has been reported in 1% to 7% of patients (29, 65). Cough, dyspnea, headache, and fever are the main presenting symptoms. Clinical findings include hypoxia, decreased diffusion capacity, and bilateral radiographic interstitial infiltrates. Although pneumonitis is usually
reversible with discontinuation of therapy, deaths have been reported. Glucocorticoid treatment has been used in most reported cases and is considered beneficial.

Hepatic enzyme levels increase in up to 70% of methotrexate-treated patients, and these increases are usually reversible with dose reduction. Of greater concern is the risk for permanent hepatic fibrosis and cirrhosis. The risk for cirrhosis remains unclear and may be influenced by the underlying disease state and associated factors, such as alcohol consumption. Cirrhosis has been reported to occur in 0% to 25% of methotrexate-treated patients with psoriasis; in contrast, investigators of a rheumatoid arthritis series reported cirrhosis in less than 1% of combined biopsy specimens (66). Although liver biopsy is the gold standard for monitoring hepatic fibrosis, it has potential risks. Recent guidelines for performing this procedure have diverged between different diseases. In the case of psoriasis, the American Academy of Dermatology recommends that liver biopsy be performed after each cumulative 1500-mg dose (67). In contrast, for methotrexate use in rheumatoid arthritis, the American College of Rheumatology recommends that liver biopsy be performed only when monitoring laboratory studies have abnormal results (68). Further studies are needed to fully clarify the risk for liver fibrosis and the effectiveness of established guidelines.

Because some of the toxic effects associated with methotrexate may be related to folate depletion, the role of replacement therapy with folic acid or leucovorin has been examined (69). Studies in rheumatoid arthritis suggest that such replacement may lessen gastrointestinal symptoms, mucositis, and bone marrow suppression but does not affect hepatotoxicity or pneumonitis. Because leucovorin is a reduced folate that can bypass the metabolic block created by methotrexate, there have been concerns that it may negate drug effectiveness. A biologically active leucovorin dose of up to half of the methotrexate dose has been administered without an apparent change in efficacy, although rheumatoid arthritis has been exacerbated when the folate-to-methotrexate ratio exceeded this level.

As has been seen in transplant recipients, Epstein-Barr virus has been demonstrated in lymphoproliferative lesions that have developed in methotrexate-treated patients (70). In the setting of immunosuppressive treatment, pharmacologic suppression of the host immune response to Epstein-Barr virus may result in the outgrowth of Epstein-Barr virus–transformed B-cell clones. Through this mechanism, the immunosuppressive properties of methotrexate, as well as other immunosuppressive agents, may contribute to the development of lymphoproliferative disorders in certain cases (70).

Azathioprine and 6-Mercaptopurine

In vivo, azathioprine is metabolized to 6-mercaptopurine; thus, these agents have similar adverse effects. Bone marrow suppression occurs in up to 50% of patients and is the main dose-limiting toxicity (71). Elevated hepatic enzyme levels have been seen in 10% to 30% of patients and usually improve with dose reduction. Although an increased incidence of lymphoproliferative disorders has been observed in transplant recipients, this has not been clearly established in autoimmune diseases. Azathioprine hypersensitivity is a rare and potentially fatal adverse effect characterized by fever, hypotension, and oliguria (72). Treatment consists of discontinuation of drug therapy and supportive measures.

Cyclosporine

Hypertension may develop in 20% to 50% of cyclosporine recipients and must be controlled by pharmacologic management, dose reduction, or discontinuation of therapy (73). Cyclosporine has also been associated with irreversible renal injury that is histologically characterized by tubular atrophy, interstitial fibrosis, or arteriolar alterations. Higher doses and maximum increase in serum creatinine levels seem to play a critical role in the development of renal toxicity (74). Although end-stage renal disease has been observed in up to 10% of cardiac transplant recipients, the risk for nephrotoxicity seems greatly lessened in patients with autoimmune disease who receive lower cyclosporine doses. Accordingly, strategies have been put forth to minimize the risk for cyclosporine nephropathy in autoimmune disease (75). These include using the minimum effective dose, with the maximum dose not to exceed 5 mg/kg per day; close monitoring of the serum creatinine level throughout treatment, with the dose being decreased for elevations in creatinine level greater than 30% above the precyclosporine level; and monitoring and managing hypertension. Drugs known to be nephrotoxic or to interfere with the bioavailability of cyclosporine should be avoided while patients are receiving this agent.

Conclusion

Dr. Langford: During the past 25 years, cytotoxic agents and, more recently, cyclosporine have emerged to become an important part of the therapeutic approach to many non-neoplastic autoimmune diseases. Although they have given us options that we did not previously have, they are probably not the ultimate therapeutic answer because they do not prevent the relapse of disease in many instances and have some side effects. Infection remains an important cause of
illness and death that is largely related to the nonspecific actions of these agents on the immune response. A growing area of study is the investigation of therapeutic agents directed toward the disruption of more specific pathways of the immune response, including antigen processing, cell trafficking, and local inflammation. With such approaches, the pathologic mechanisms of disease may be more specifically targeted and the toxicities lessened. However, this work is in its early stages, and substantial investigation is needed to study the efficacy and side effects of such therapies. Until other alternatives become available, cytotoxic agents and cyclosporine will remain some of our most useful and beneficial options in the treatment of autoimmune disease.

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