



**FIGURE 331-4** Management of patients at high risk for the tumor lysis syndrome.

\*See text.

during laboratory monitoring of the patient with TLS. Samples must be cooled immediately to deactivate the urate oxidase. Despite aggressive prophylaxis, TLS and/or oliguric or anuric renal failure may occur. Care should be taken to prevent worsening of symptomatic hypocalcemia by induction of alkalosis during bicarbonate infusion. Administration of sodium bicarbonate may also lead to urinary precipitation of calcium phosphate, which is less soluble at alkaline pH. Dialysis is often necessary and should be considered early in the course. Hemodialysis is preferred. Hemofiltration offers a gradual, continuous method of removing cellular by-products and fluid. The prognosis is excellent, and renal function recovers after the uric acid level is lowered to  $\leq 10$  mg/dL.

#### HUMAN ANTIBODY INFUSION REACTIONS

The initial infusion of human or humanized antibodies (e.g., rituximab, gemtuzumab, trastuzumab, alemtuzumab, panitumumab, brentuximab vedotin) is associated with fever, chills, nausea, asthenia, and headache in up to half of treated patients. Bronchospasm and hypotension occur in 1% of patients. Severe manifestations including pulmonary infiltrates, acute respiratory distress syndrome, and cardiogenic shock occur rarely. Laboratory manifestations include elevated hepatic aminotransferase levels, thrombocytopenia, and prolongation of prothrombin time. The pathogenesis is thought to be activation of immune effector processes (cells and complement) and release of inflammatory cytokines, such as tumor necrosis factor  $\alpha$ , interferon gamma, interleukin 6, and interleukin 10 (cytokine release syndrome [CRS]). Although its origins are not completely understood, CRS is believed to be due to activation of a variety of cell types including

monocytes/macrophages and T and B lymphocytes. Severe reactions from rituximab have occurred with high numbers ( $>50 \times 10^9$  lymphocytes) of circulating cells bearing the target antigen (CD20) and have been associated with a rapid fall in circulating tumor cells, mild electrolyte evidence of TLS, and very rarely, death. In addition, increased liver enzymes, D-dimer, and LDH and prolongation of the prothrombin time may occur. Diphenhydramine, hydrocortisone, and acetaminophen can often prevent or suppress the infusion-related symptoms. If they occur, the infusion is stopped and restarted at half the initial infusion rate after the symptoms have abated. Severe CRS may require intensive support for acute respiratory distress syndrome (ARDS) and resistant hypotension.

#### HEMOLYTIC-UREMIC SYNDROME

Hemolytic-uremic syndrome (HUS) and, less commonly, thrombotic thrombocytopenic purpura (TTP) (Chap. 341) may rarely occur after treatment with antineoplastic drugs, including mitomycin, gemcitabine, cisplatin, and bleomycin, and with VEGF inhibitors. It occurs most often in patients with gastric, lung, colorectal, pancreatic, and breast carcinoma. In one series, 35% of patients were without evident cancer at the time this syndrome appeared. Secondary HUS/TTP has also been reported as a rare but sometimes fatal complication of bone marrow transplantation.

HUS usually has its onset 4–8 weeks after the last dose of chemotherapy, but it is not rare to detect it several months later. HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Dyspnea, weakness, fatigue, oliguria, and purpura are also common initial symptoms and findings. Systemic hypertension and pulmonary edema frequently occur. Severe hypertension, pulmonary edema, and rapid worsening of hemolysis and renal function may occur after a blood or blood product transfusion. Cardiac findings include atrial arrhythmias, pericardial friction rub, and pericardial effusion. Raynaud's phenomenon is part of the syndrome in patients treated with bleomycin.

Laboratory findings include severe to moderate anemia associated with red blood cell fragmentation and numerous schistocytes on peripheral smear. Reticulocytosis, decreased plasma haptoglobin, and an LDH level document hemolysis. The serum bilirubin level is usually normal or slightly elevated. The Coombs' test is negative. The white cell count is usually normal, and thrombocytopenia ( $<100,000/\mu\text{L}$ ) is almost always present. Most patients have a normal coagulation profile, although some have mild elevations in thrombin time and in levels of fibrin degradation products. The serum creatinine level is elevated at presentation and shows a pattern of subacute worsening within weeks of the initial azotemia. The urinalysis reveals hematuria, proteinuria, and granular or hyaline casts; and circulating immune complexes may be present.

The basic pathologic lesion appears to be deposition of fibrin in the walls of capillaries and arterioles, and these deposits are similar to those seen in HUS due to other causes. These microvascular abnormalities involve mainly the kidneys and rarely occur in other organs. The pathogenesis of cancer treatment-related HUS is not completely understood, but probably the most important factor is endothelial damage. Primary forms of HUS/TTP are related to a decrease in processing of von Willebrand factor by a protease called ADAMTS13.

The case fatality rate is high; most patients die within a few months. There is no consensus on the optimal treatment for chemotherapy-induced HUS. Treatment modalities for HUS/TTP including immunocomplex removal (plasmapheresis, immunoadsorption, or exchange transfusion), antiplatelet/anticoagulant therapies, immunosuppressive