Therapeutic Apheresis for Patients With Cancer
Laura S. Connelly-Smith, MBBCh, DM, and Michael L. Linenberger, MD

Background: Disease complications associated with certain malignancies may be mediated by cells or soluble molecules that traffic in the bloodstream. Because of this, therapeutic apheresis (TA) methodologies have been used to selectively remove or manipulate specific molecules, antibodies, or cellular elements to treat the underlying pathological process. For some disorders, TA is utilized as a rapid-acting and short-term adjunct to conventional chemotherapy or immunotherapy. For others, a series of scheduled treatments is recommended for optimal management. In all cases, the risks, benefits, and costs must be strongly considered.

Methods: The current literature and published guidelines were reviewed to summarize the use of TA in the management of certain complications of cancer.

Results: Although TA is relatively safe and useful as a first-line or salvage modality for some disorders, few prospective, randomized clinical trials exist and the majority of evidence is derived from observational studies. Expert-based, clinical practice guidelines have been developed to inform hematology/oncology professionals and apheresis physicians about the efficacy and limitations of TA for malignancy-related indications.

Conclusions: Certain oncological conditions respond to TA and consensus guidelines are available to support clinical decision-making. However, well-designed, prospective intervention trials are needed to better define the role of TA for a variety of disorders.

Introduction
Therapeutic apheresis (TA) is used to treat certain disease complications in patients with cancer with the intention of removing or manipulating a specific molecule, antibody, or cellular element thought to be contributing to the underlying pathological process.

In general, TA is a relatively safe procedure; however, insufficient clinical evidence to support the economic cost of TA can be a limitation to its use for some conditions. Evidence-based clinical practice guidelines have been developed and periodically updated by the American Society for Apheresis (ASFA) to help support the decision making of health care professionals regarding the use of TA.1

In this article, we provide a brief overview of TA and discuss considerations for its use as a treatment option. The apheresis modalities most commonly used to treat patients with cancer include the therapeutic plasma exchange (TPE), leukocytapheresis, extracorporeal photopheresis (ECP), thrombocytapheresis, and erythrocytapheresis. Herein, we review the known oncological diseases or associations for which specific TA modalities have been successfully
employed. Table 1 summarizes these modalities, clinical conditions, and the most recent ASFA guideline recommendations. However, well-designed, prospective intervention trials are still required to fully define the role of TA for many of these disorders.

TA plays an important role in the management of various oncological diseases. It is a procedure in which blood is separated from a patient, a portion of which is then removed or otherwise manipulated and the remainder is then returned to the patient. TA procedures include TPE (in which plasma is replaced with a colloid or crystalloid solution) and modalities that selectively remove and dispose of plasma solutes (plasmapheresis), white blood cells (WBCs; leukocytapheresis), or platelets (thrombocytapheresis). ECP is a type of leukocytapheresis procedure whereby the removed white cells are manipulated prior to being reinfused into the patient.

Apheresis procedures can utilize centrifugation to separate blood components into layers within a rapidly rotating separation chamber based on their relative density — with red blood cells (RBCs; leukocytapheresis), or platelets (thrombocytapheresis). ECP is a type of leukocytapheresis procedure whereby the removed white cells are manipulated prior to being reinfused into the patient.

Apheresis procedures can utilize centrifugation to separate blood components into layers within a rapidly rotating separation chamber based on their relative density — with red blood cells (RBCs; leukocytapheresis), or platelets (thrombocytapheresis). ECP is a type of leukocytapheresis procedure whereby the removed white cells are manipulated prior to being reinfused into the patient.

Clinical Adverse Events
TA can be associated with minimal to potentially fatal adverse events, although the overall incidence is relatively low (5%–12%). Hypersensitivity reactions due to plasma or blood product replacement fluid can range from urticarial to anaphylactoid-type reactions. Hypocalcemia secondary to citrate anticoagulant can manifest as paresthesia, nausea, vomiting, lightheadedness, and twitching. Hypovolemia due to fluid shifts or vasovagal reaction may manifest as hypotension, muscle cramps, and headache. Rare, serious adverse events requiring the procedure to be interrupted or abandoned (0.8% incidence) or resulting in fatality (≤ 0.5%) due to cardiovascular events can include arrhythmia or ischemia, pulmonary edema, pulmonary embolism, and respiratory arrest; neurological

<table>
<thead>
<tr>
<th>Therapeutic Apheresis Modality</th>
<th>Indication</th>
<th>Disease Condition</th>
<th>Category</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic plasma exchange (TPE)</td>
<td>Hyperviscosity in monoclonal gammopathies</td>
<td>Symptomatic</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>Myeloma kidney/myeloma cast nephropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic neurological syndromes (see also Table 4)</td>
<td>Lambert Eaton myasthenic syndrome</td>
<td>II</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other paraneoplastic neurological syndromes</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td>Hematopoietic stem cell transplantation-associated thrombotic microangiopathy</td>
<td>Refractory</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Therapeutic leukocytapheresis</td>
<td>Hyperleukocytosis</td>
<td>With leukostasis clinical signs and symptoms</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prophylaxis (asymptomatic)</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Extracorporeal photopheresis</td>
<td>Cutaneous T-cell lymphoma, mycosis fungoides, Sézary syndrome</td>
<td>Erythrodermic</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonerythrodermic</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td>GVHD</td>
<td>Skin chronic GVHD</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin acute GVHD</td>
<td>II</td>
<td>1C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-skin acute and chronic GVHD</td>
<td>III</td>
<td>2B</td>
</tr>
<tr>
<td>Thrombocytapheresis</td>
<td>Thrombocytosis with myeloproliferative neoplasm</td>
<td>Symptomatic</td>
<td>II</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prophylactic</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Erythrocytapheresis</td>
<td>Polycythemia vera/primary erythrocytosis</td>
<td></td>
<td>I</td>
<td>1B</td>
</tr>
</tbody>
</table>

*Denotes American Society for Apheresis category.

*Denotes American Society for Apheresis grade.

For more information, refer to Tables 2 and 3.

GVHD = graft-vs-host disease.

Data from reference 1.
complications can also occur and may include tetany, seizures, and cerebrovascular accident. Hemorrhage, thrombosis, and infection are uncommon. The causes of death have included respiratory arrest, anaphylaxis, and catheter-associated sepsis. Vascular Access

The majority of apheresis procedures are centrifugation based; therefore, they require withdrawal blood flow rates of 50 to 150 mL/minute. Peripheral antecubital veins that can be cannulated using 16- to 18-gauge polytetrafluoroethylene- or silicone-coated, dialysis-type steel needles will accommodate blood flow rates of 80 mL/minute and is adequate for centrifugation techniques. By contrast, filtration therapies require a blood flow rate of at least 150 to 200 mL/minute, which is unsuitable for antecubital veins. Other considerations specific to TA include whether the treatment relies on discontinuous, sequential blood exchange cycles (1 lumen is sufficient) or continuous processing (2 lumens are needed). When a central venous catheter (CVC) is necessary for a limited (< 2 weeks) course of TA, a nontunneled, semi-rigid polyethylene catheter should be considered. For a longer duration (> 2 weeks) of TA, a tunneled CVC is preferred over a nontunneled CVC due to less risk of infection. Typically, tunneled catheters designed for long-term use (weeks to months) are made of silicone and are more biocompatible, flexible, and have the least thrombogenicity. The preferred venous site of CVC insertion is the internal jugular vein, and both ultrasonographic guidance and fluoroscopy have been shown to be associated with a lower rate of complications during insertion.

Central venous access is not always required. The Canadian Apheresis Study Group found that 67% of 5,234 TPE procedures could be completed with peripheral venous access alone. The frequency of complications due to CVC placement exceeds the frequency of complications directly related to the procedure. Central venous access has been identified as a major risk factor for complications of TPE in other studies. CVCs are associated with a higher total complication rate. These include infection (2%–28%), thrombosis (0.2%–11%), hemorrhage (2%–14%), and venous stenosis (10%–26%) with internal jugular catheters and up to 42% with subclavian vein catheters.

In most series, the incidence of total adverse events associated with all vascular access is low at 1% to 2%. Data from the International Apheresis Registry 2007 report that peripheral veins are commonly used in Europe and Australia (66%–70% of apheresis treatments), whereas CVCs are the most common vascular access type used for TA procedures in North America, South America, and Asia (84%–98%). This regional difference in the use of peripheral veins compared with CVCs has not been explained by differences in patient age, sex, the median number of treatments per patient, or the type of apheresis procedure. Nevertheless, peripheral venous access is underutilized in TA procedures and is the access of choice because it is associated with a lower risk of infection relative to CVCs and placement can be done immediately with a low risk of other serious complications. Complications of peripheral cannulation include risk of infection, venous infiltration, patient discomfort, thrombosis and sclerosis of veins, and the loss of future venous access. Peripheral vein access for TA is not a viable option in children due to their small venous caliber.

Peripherally inserted central catheters are too small in caliber (4–5 Fr) to accommodate the negative pressure and blood flow rates required for TA procedures. Arteriovenous fistulas and grafts are viable options for long-term access when the treatment duration is expected to be over a period of several months or years. Evidence and Decision Making

Hematologists and oncologists who may have incomplete knowledge of the indications, limitations, risks, and relative efficacy of the procedure might request TA. Because many procedures are for uncommon and infrequent indications, few randomized clinical trials or other high-level evidence studies are available to guide clinical decision-making. Therefore, the ASFA has undertaken a critical evaluation of published studies and observations, publishing periodic, evidence-based systematic reviews of TA applications since 2007. The ASFA clinical practice guidelines use the GRADE system, adopted from Guyatt et al., whereby each disease, including specific clinical presentations, is categorized for the role of TA and graded for the strength of recommendation and quality based on the published evidence (Tables 2 and 3).

Table 2. — American Society for Apheresis Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disorders for which apheresis is accepted as a first-line therapy, either primary stand-alone treatment or in conjunction with another mode of treatment.</td>
</tr>
<tr>
<td>II</td>
<td>Disorders for which apheresis is accepted as a second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>III</td>
<td>Optimum role of therapeutic apheresis is not established. Decision making should be individualized.</td>
</tr>
<tr>
<td>IV</td>
<td>Disorders for which published evidence demonstrates or suggests apheresis to be ineffective or harmful. Institutional Review Board approval is desired if apheresis treatment is undertaken in these circumstances.</td>
</tr>
</tbody>
</table>

ASFA category I and II indications are those for which TA is considered first-line or second-line therapy, respectively. Category III indications acknowledge the lack of high-level evidence to recommend the TA procedure as primary or second line; however, the treatment may be beneficial and, thus, individualized decision-making should be used to guide inclusion of TA in the treatment plan. Category IV reflects ineffectiveness or harm by TA with the risks outweighing benefits.21

The 6th edition published in 2013 is a compilation of 78 diseases or medical conditions assigned ASFA categories I to IV.1 All TA procedures discussed within this review are referenced according to the category and recommended grade per the ASFA 2013 guidelines with further updates as indicated.1

### Therapeutic Plasma Exchange

TPE involves the removal of a large volume of plasma and replacement with plasma, albumin, or both. The major mechanism of action of TPE is the removal of a pathological solute, such as autoantibodies, immune complexes, cryoglobulins, myeloma light chains, or cytokines. Of note, TPE may also have an immunomodulatory effect, including the modulation of the Th1/Th2 T-cell balance toward Th2,22 the suppression of interleukin 2 and interferon γ production,25,24 and an increase in suppressor T-cell function.

A standard TPE procedure exchanges 1 to 1.5 plasma volumes resulting in the removal of 60% to 70% of intravascular large molecular weight solutes.25 Some large molecules (eg, immunoglobulin [Ig] G) distribute in both the intravascular and the extravascular spaces; during TPE, the extravascular molecules can move into the intravascular space. Therefore, TPE may remove more total solute than might be predicted based on the pretreatment concentration because of re-equilibration occurring from the extravascular to the intravascular compartment.

Because TPE removes normal plasma coagulation factors, the activities of factors V, VII, VIII, IX, and X, as well as von Willebrand factor (vWF), may significantly decline.26,27 Activities of factor VIII, factor IX, and vWF return to normal within 4 hours after TPE, whereas the remaining coagulation factors achieve pre-TPE activity levels within 24 hours.26 The exception to this is fibrinogen, which reaches 66% of preapheresis levels within 72 hours.28 TPE may also remove medications, especially those highly protein bound. The clinical impact of this effect is understood for relatively few drugs.29,30

Albumin is the most commonly used replacement fluid for TPE procedures. Normal plasma has the same oncotic pressure as 5% albumin.31,32 Thus, replacing plasma with 4% to 5% human serum albumin will maintain plasma volume and avoid hypotension. However, because albumin is expensive,33 some health care professionals may prefer to use albumin and saline, with the majority of the albumin being given at the end of the procedure. The combination of albumin and saline is hypo-oncotic and has been associated with a greater frequency of hypovolemic reactions and edema compared with using albumin alone.16 Another disadvantage is that albumin does

---

**Table 3. — American Society for Apheresis Grading Recommendations**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
<th>Quality of Evidence</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade IA</td>
<td>Strong recommendation; high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation; can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Grade IB</td>
<td>Strong recommendation; moderate quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation; can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Grade IC</td>
<td>Strong recommendation; low-quality or very-low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Strong recommendation; may change when higher-quality evidence becomes available</td>
</tr>
<tr>
<td>Grade 2A</td>
<td>Weak recommendation; high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation; best action may differ depending on circumstances or patient or societal values</td>
</tr>
<tr>
<td>Grade 2B</td>
<td>Weak recommendation; moderate-quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation; best action may differ depending on circumstances or patient or societal values</td>
</tr>
<tr>
<td>Grade 2C</td>
<td>Weak recommendation; low-quality or very-low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial.

not replace coagulation factors, which may lead to significant post-treatment coagulopathy.

Plasma is used as replacement fluid with TPE in a limited number of disorders. It avoids postprocedure coagulopathy and immunoglobulin depletion. Its disadvantages include transfusion reactions, citrate toxicity, and the potential for viral transmission. Plasma is indicated as replacement fluid to reduce ADAMTS13 when treating thrombotic thrombocytopenic purpura (TTP) or when coagulopathy must be corrected.44

Neither cryosupernatant plasma nor solvent/detergent–treated plasma has been shown to offer any advantage over standard plasma for any indication.45 A meta-analysis of 3 trials comparing fresh frozen plasma and cryosupernatant plasma for the initial treatment of TTP did not reveal any benefit for patients receiving cryosupernatant plasma.46 Similarly, controlled studies failed to establish superiority of solvent/detergent–treated plasma over fresh frozen plasma.45 The only cohort of patients with TTP who may benefit from the use of solvent/detergent–treated plasma are those with severe allergies to standard plasma.46

**Hyperviscosity in Monoclonal Gammopathies**

Hyperviscosity syndrome (HVS) refers to the clinical sequelae caused by the altered physiology related to plasma hyperviscous states, most typically seen in Waldenström macroglobulinemia (WM; also known as lymphoplasmacytic lymphoma) associated with monoclonal IgM or, less frequently, with multiple myeloma associated with monoclonal IgA or IgG3. Specific signs and symptoms include mucosal bleeding, visual impairment with retinal hemorrhage or retinal detachment, headache, dizziness, vertigo, nystagmus, hearing loss, somnolence, coma, and seizure. Other manifestations include congestive heart failure (related to plasma volume overexpansion), respiratory compromise, coagulation abnormalities, anemia, fatigue, peripheral polyneuropathy (depending on the specific Ig properties), and anorexia.

WM represents approximately 2% of all cases of non-Hodgkin lymphoma.47 When the IgM protein associated with WM exceeds a concentration of 4 g/dL, the relative plasma viscosity can exceed 4 centipoise (cp; relative to water: normal range, 1.4–1.8 cp) and HVS can occur.48 Unlike the situation with IgG, IgM is predominantly intravascular (> 80%) and increased viscosity with IgM can become exponential above a concentration of 3 g/dL. In turn, a small reduction in IgM concentration can have a significant effect on lowering serum viscosity.

TPE is an effective, short-term treatment for complications of HVS.49-51 Because bleeding is the most common sign of HVS and retinal examination findings correlate with the symptomatic threshold for HVS in patients with WM, urgent TPE should be carried out to reduce the likelihood of blindness from retinal hemorrhages or retinal detachment.52,53 TPE is a safe and well-tolerated procedure in this setting.44 It is not typically necessary to reduce the plasma viscosity to normal levels to relieve symptoms. However, some evidence suggests that patients with monoclonal IgM antibodies that produce neuropathy or other target organ dysfunction may benefit from a more aggressive effort to maintain serum viscosity near normal levels.45,46

Hyperviscosity with WM is an ASFA category I indication for TPE (grade 1B recommendation).3 Generally, 1 to 1.5 plasma volumes are exchanged per session, and fluid replacement usually consists of albumin and saline in various proportions. Plasma exchange reduces plasma viscosity by approximately 20% to 30% per session.47 Thus, 1 or 2 procedures can return the plasma viscosity to near normal levels and reduce the IgM concentration for several weeks. Concurrent chemotherapy is required to treat underlying disease and prevent rebound HVS.

For asymptomatic patients with a serum viscosity level above 3 to 3.5 cp, an IgM concentration greater than 3 to 4 g/dL, or both, some experts suggest that TPE can be prophylactically used prior to starting rituximab therapy because significant transient increases in IgM levels can occur following single-agent rituximab therapy (considered a “flare”) in 50% to 70% of patients.58-60 Based on this concern, the ASFA guidelines have recommended TPE as prophylaxis treatment prior to rituximab to lower IgM concentrations of less than 5 g/dL (grade 1C recommendation).1 The flare phenomenon may be less with regimens that use chemotherapy prior to rituximab or regimens that omit rituximab for the first 1 or 2 cycles.

Patients with myeloma and IgG3 subclass monoclonal paraproteinemia are more likely to develop HVS than other patients with myeloma.50,51 This usually occurs at higher than 4 g/dL of monoclonal IgG3 in the plasma. In cases of IgG-associated HVS, the increase in serum viscosity is approximately proportional to the concentration of the paraprotein.52 HVS may also occasionally occur in IgA and light-chain myeloma because of the formation of polymers; in the majority of these cases, it occurs when the concentration of monoclonal IgG exceeds 6 to 7 g/dL.

**Myeloma Cast Nephropathy**

Nearly 50% of patients with multiple myeloma develop renal disease.53 Myeloma cast nephropathy, also known as “myeloma kidney,” is the most common type and accounts for 30% to 80% of cases.55,56 The development of acute kidney injury is associated with worse 1-year survival rates and reduces the overall therapeutic options available to patients.53,54 Cast nephropathy is due to the interaction
and aggregation of filtered free light chains (FLCs) and Tamm–Horsfall protein, thus causing intratubular obstruction and damage. When the light chain production overcomes the capacity of the tubular cells to endocytose and catabolize the FLCs, the increased light chains in the tubular fluid of the distal tubule and thick ascending loop of Henle form tubular casts with the Tamm–Horsfall protein. As tubular obstruction progresses, the decline in renal function becomes irreversible. Other factors, such as dehydration, diuretics, hypercalcemia, hyperuricemia, and intravenous contrast media, may all potentiate cast formation and acute kidney injury.

The key to treating cast nephropathy is the rapid lowering of FLCs. In addition to hydration and aggressive supportive care, antmyeloma chemotherapy is necessary, whether it be with an alkylating agent and prednisone therapy or one of the recent immune modulators (thalidomide, lenalidomide) and proteasome inhibitors (bortezomib). These latter agents have emerged as effective therapy and have been referred to as “renoprotective.” Supportive care with hemodialysis or peritoneal dialysis may also be needed.

TPE has been used in hopes of reducing the delivery of plasma FLCs to the renal glomerulus for filtration. Two studies suggested that TPE was beneficial. In addition, a small prospective comparison of forced diuresis, melphalan, and prednisone (10 patients) vs forced diuresis, melphalan, prednisone, and TPE (11 patients) found a trend in favor of TPE, and a subgroup analysis of patients dependent on dialysis revealed that renal function recovered in 43% of the TPE group compared with 0% in the control group. These studies led to an endorsement of TPE for myeloma kidney by the Scientific Advisors of the International Myeloma Foundation. Subsequently, a large randomized trial of bortezomib-containing chemotherapy and supportive care, with or without TPE, failed to demonstrate a benefit for 5 to 7 TPE procedures over 10 days. However, this study has been criticized for the lack of FLC measurements, the lack of histological evidence of cast nephropathy, and the failure to consider early end points more specific to the recovery of renal function. In a report from the Mayo Clinic, plasma exchange in combination with bortezomib-based chemotherapy in 7 patients was associated with 6 patients (86%) having at least a partial response.

Collectively, these observations suggest that a subgroup of patients with cast nephropathy might benefit from TPE, particularly those in nonoliguric renal failure who do not require dialysis. The severity of myeloma cast formation, including the need for dialysis, has been identified as the major factor associated with nonreversible renal failure, even in patients undergoing TPE. Moreover, biopsy findings that indicate potential reversibility (eg, absence of fibrosis of all affected glomeruli) may be important predictors of success.

The ASFA evidence-based guidelines lists TPE as a category II indication for myeloma kidney due to light-chain cast nephropathy. After initial management, especially in the case of nonoliguric patients, focus should be on fluid resuscitation (2.5–4 L/day), alkalinization of the urine, and chemotherapy. If serum creatinine remains elevated after several days, then renal biopsy should be considered to assess for cast nephropathy. If cast nephropathy is highly suspected or confirmed, then TPE can be initiated by processing 1 to 1.5 total plasma volumes every 1 to 2 days and using 5% albumin in saline as replacement fluid. Some studies support a course of 10 to 12 TPE procedures over 2 to 3 weeks and repeating this depending on patient response and clinical course. For patients who are oliguric, excrete at least 10 g of light chains per 24 hours, or whose serum creatinine level is at least 6 mg/dL, TPE may be included as adjunct therapy to initial chemotherapy and hemodialysis. If TPE and hemodialysis are to be performed on the same day, then the procedures can be performed in tandem without compromising the efficiency of the hemodialysis.

Paraneoplastic Neurological Syndromes
Paraneoplastic neurological syndromes (PNS) are symptoms or signs resulting from damage to the central or peripheral nervous system, including the neuromuscular junction and muscle, removed from the site of the malignancy or its metastases, and not due to remote effects caused by infection, ischemia, or metabolic disruptions. Many antibodies are associated with paraneoplastic syndromes (Table 4). Their role in neuronal dysfunction is unclear and they can occur in fewer than 50% of patients with cancer but may occur more frequently in those with non-Hodgkin lymphoma, small-cell lung cancer, and thymomas. In the majority of patients, PNS develop prior to the cancer diagnosis.

The pathogenesis of PNS is thought to be immune-mediated as a result of a cross-reaction against antigens shared by the tumor and nervous system cells. Many antibodies are associated with paraneoplastic syndromes (Table 4). Their role in neuronal dysfunction is unclear and they can occur in fewer than 50% of patients with PNS. No studies have proven that these antibodies are pathogenic; however, these antibodies have become useful diagnostic markers, particularly in monitoring for relapse. The severity of the majority of PNS cases is due to the early and nonreversible destruction of neural structures by the inflammatory process; in many cases, the patient is severely debilitated within weeks to months. Prompt initiation of therapy following the diagnosis of PNS may stabilize symptoms and prevent PNS spreading to further areas in syndromes with
onconeural antibodies.\textsuperscript{78} For patients with an identified tumor, antitumor therapy should be rapidly instituted for stabilization or symptom improvement. The use of immunomodulatory therapy does not substantially modify the neurological outcome of patients whose tumors are successfully treated.\textsuperscript{76,79} For many paraneoplastic syndromes, removal of the tumor is the only effective treatment.\textsuperscript{80,81} The role and timing of immunotherapy for PNS is not well defined; however, many reports indicate its apparent benefit.\textsuperscript{82,83} No systematic studies exist concerning the type of immunosuppressive therapy, and no RCTs or quasi-RCTs exist on which to base treatment or practice.\textsuperscript{84} In patients without detectable tumor but with a prior history of malignancy and clinicopathological findings consistent with progressive PNS, it is appropriate to empirically start immunosuppressive therapy with or without antitumor treatment.

Initial therapies often include corticosteroids, TPE, intravenous immunoglobulin (IVIG), immune adsorption, and/or rituximab. More aggressive second-line immunosuppression with cyclophosphamide, tacrolimus, mycophenolate, or cyclosporine may be used when no response to initial treatments is seen and the patient continues to lose neurological functions. More severe neurological deficits associated with antibodies against Yo, Hu, and CRMP5 are also the most refractory to immunosuppressive treatment. Survival from time of diagnosis is significantly worse in patients with anti-Yo (median, 13 months) or anti-Hu (median, 7 months) than in patients with anti-Tr (median, > 113 months) or anti-Ri (median, > 69 months).\textsuperscript{85} However, patients who receive antitumor treatment, with or without immunotherapy, live significantly longer than those who do not.\textsuperscript{76,84}

The rationale for TPE with PNS is that plasma

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Frequency of Paraneoplastic Origin (%)</th>
<th>Major Symptoms</th>
<th>Associated Tumor Types</th>
<th>Frequently Associated Paraneoplastic Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lambert–Eaton myasthenic syndrome</td>
<td>60</td>
<td>Muscle weakness, autonomic dysfunction</td>
<td>SCLC</td>
<td>VGCC antibodiesa</td>
</tr>
<tr>
<td>Paraneoplastic cerebellar degeneration</td>
<td>50</td>
<td>Truncal, limb ataxia, dysarthria, saccadic gaze pursuit, nystagmus</td>
<td>Ovary Breast SCLC Hodgkin lymphoma</td>
<td>Anti-Yo Anti-Hu Anti-VGCC Anti-CV2/CRMP5</td>
</tr>
<tr>
<td>Paraneoplastic opsoclonus/myoclonus</td>
<td>20</td>
<td>Saccades, ataxia, other cerebellar signs, generalized myoclonus, altered mental state, stupor, coma</td>
<td>Neuroblastoma Breast SCLC</td>
<td>Anti-Ri (ANNA-2)</td>
</tr>
<tr>
<td>Sensory neuronopathy</td>
<td>20</td>
<td>Pain, paresthesias (arms &gt; legs), numbness, ataxia</td>
<td>SCLC</td>
<td>Anti-Hu Anti-CV2/CRMP5 Anti-amphiphysin</td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>20</td>
<td>Seizures, short-term memory deficits, behavioral and psychiatric disturbances</td>
<td>SCLC Testicular</td>
<td>Anti-Hu ANNA-1</td>
</tr>
<tr>
<td>Paraneoplastic encephalomyelitis</td>
<td>10</td>
<td>Seizures, subacute dementia, personality changes (limbic encephalitis), subacute cerebellar signs, autonomic nervous system dysfunction</td>
<td>SCLC</td>
<td>ANNA-1 Anti-Hu</td>
</tr>
<tr>
<td>Cancer-associated retinopathy</td>
<td></td>
<td>Subacute visual loss, photosensitivity, night blindness, impaired color vision</td>
<td>SCLC Cervical Melanoma</td>
<td>Recoverin antibodies</td>
</tr>
<tr>
<td>Paraneoplastic stiff-person syndrome</td>
<td>5–20</td>
<td>Stiffness predominantly upper limbs, painful spasms precipitated by sensory stimuli</td>
<td>Breast Colon Lung Hodgkin lymphoma Malignant thymoma</td>
<td>Antiamphiphysin</td>
</tr>
<tr>
<td>Chronic intestinal pseudo-obstruction</td>
<td></td>
<td>Weight loss, constipation, abdominal distension, esophageal dysmotility, gastroparesis</td>
<td>SCLC</td>
<td>Anti-Hu Anti-CV2/CRMP5</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>30</td>
<td>Proximal myopathy, heliotrope rash, scaly plaques on dorsal hands</td>
<td>Ovarian Lung Pancreatic Stomach Colorectal Non-Hodgkin lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Present in nearly all patients with the paraneoplastic and nonparaneoplastic form of Lambert–Eaton myasthenic syndrome. Data from references 68, 73, and 74. ANNA = antineuronal nuclear antibody, SCLC = small cell lung cancer, VGCC = voltage-gated calcium channel.
antibody levels can be reduced and thereby ameliorate the damage to the peripheral nervous system in tissues. Plasma exchange can also reduce circulating levels of cytokines and other mediators of inflammation that may contribute to the effectiveness of TPE as immunomodulatory therapy. By comparison, PNS involving the central nervous system do not typically respond to TPE, a fact likely due to the inability of plasma therapy to decrease intrathecal antibody titers.

Patients with acquired neuromyotonia and antibodies directed against voltage-gated potassium channels or paraneoplastic cerebellar degeneration with anti-Tr antibodies may be more likely to respond to TPE; however, many do not have malignancy. In 50% of cases, encephalitis associated with anti–N-methyl D-aspartate receptor antibodies responds to first-line treatment with corticosteroids, IVIG, or TPE. Although immunosuppression with corticosteroids, TPE, and/or IVIG may benefit those with LGI1- and CASPR2-antibody associated syndromes, residual memory impairment is common. However, large case series on long-term outcomes are currently lacking. Even less is known about the treatment and prognosis of other neuronal cell-surface antibody syndromes (eg, γ-aminobutyric acid [B], α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid receptor). Typically, they are treated similar to anti–N-methyl D-aspartate receptor encephalitis. Disorders such as paraneoplastic cerebellar degeneration are generally associated with neuronal loss; because they subacutely evolve and treatment is often delayed, the neurons die, thus making recovery impossible.

Some central nervous system disorders, such as opsoclonus–myoclonus syndrome, may not involve cellular loss and, in fact, may have no identifiable pathological features. Thus, patients with these disorders, like those with the Lambert–Eaton myasthenic syndrome (LEMS), have the potential for recovery.

LEMS is a syndrome that involves the neuromuscular junction and can typically respond well to immunosuppression and, subsequently, to treatment of the underlying tumor. TPE may be useful adjunct therapy for patients whose neurological deficit is severe or rapidly developing or among those who cannot tolerate treatment with IVIG (ASFA category II; grade 2C recommendation).

Reports of benefit are tempered by the observation that responses can be slow and symptoms can worsen following the completion of TPE if additional immunosuppressive therapy is not employed.

The reported TPE regimens for LEMS vary from 5 to 15 regimens of daily TPE over 5 to 19 days to 8 to 10 regimens of TPE carried out at 5- to 7-day intervals. Most reports employed 1.25 plasma volume exchanges. However, the peak effect is usually demonstrated after 2 weeks and largely subsides after 6 weeks. This may be due to the slower turnover of the presynaptic voltage-gated calcium channel compared with the postsynaptic acetylcholine receptor.

The effectiveness of immunosuppressive therapy in non-LEMS PNS with onconeural antibodies is not supported by higher level evidence. Few studies prove efficacy, although several retrospective and small prospective studies support the benefit of immunosuppression for some patients and select syndromes. The ASFA guidelines have assigned a grade 2C recommendation for this category III indication. Procedures are performed daily or every other day for a total of 5 to 6 exchanges over 2 weeks, although the exact number of exchanges should be adjusted for each patient. Some patients will require maintenance therapy on a monthly or less frequent basis. TPE cannot be considered as standard therapy for PNS. Most patients treated with TPE have also received immunosuppressive drugs as well as specific anticancer therapy.

**Hematopoietic Stem Cell Transplantation–Associated Thrombotic Microangiopathy**

Thrombotic microangiopathy (TMA) refers to a histopathological appearance, describing arteriolar thrombi associated with intimal swelling and fibrinoid necrosis of the vessel wall. The microscopic injury results from a variety of insults that can cause the activation of intravascular platelets with the subsequent formation of platelet-rich thrombi within the microcirculation. TMA following allogeneic hematopoietic stem cell transplantation (HSCT), also called transplant-associated TMA, appears to be primarily triggered by mechanisms of endothelial cell injury, including conditioning chemotherapy, irradiation, immunosuppressive agents (eg, mammalian target of rapamycin, calcineurin inhibitor drugs), graft-versus-host disease (GVHD), and opportunistic infections. The damaged endothelial cells release microparticles and von Willebrand factor, which induce platelet adhesion/aggregation and a procoagulant state. This process consumes platelets and induces mechanical damage to RBCs as they impact microthrombi or fibrin strands obstructing the microcirculation.

The clinical hallmarks of TMA include microangiopathic hemolytic anemia and thrombocytopenia, and the associated laboratory findings include schistocytes, increased serum lactate dehydrogenase, decreased serum haptoglobin, and indirect hyperbilsirubinemia. Hemoglobinuria, either frank or microscopic, is frequent. Kidneys are the major target organs of transplant-associated TMA; thus, renal function abnormalities are common. Unlike idiopathic TTP, in which severe deficiency of the von Willebrand factor protease, ADAMTS13 (a disintegrin and metalloprotease with thrombospondin-1-like domains), leads to
the presence of ultra-large multimers of vWF and systemic platelet agglutination, multiple studies in post-transplantation TMA have failed to document a severe deficiency of ADAMTS13.\textsuperscript{109-111}

TMA can occur within the first few weeks following transplantation or as a late complication, particularly in association with GVHD. One-year cumulative incidences of 13% and 15% were reported in patients undergoing nonmyeloablative conditioning and high-dose conditioning, respectively.\textsuperscript{112} Most large, retrospective studies report a prevalence of 10% to 25%,\textsuperscript{113} Transplant-associated TMA carries a poor prognosis. In a literature review of 35 published articles involving more than 5,423 allogeneic HSCT recipients, 447 study volunteers (8.2%) developed transplant-associated TMA and had a median mortality rate of 75% within 3 months of the diagnosis.\textsuperscript{114} Clinical risk factors associated with transplant-associated TMA include high-dose conditioning regimens, acute GVHD, female sex, older age, active infections, receiving transplantations from unrelated donors, and the combination of mammalian target of rapamycin and calcineurin inhibitor drugs.\textsuperscript{115}

Currently, no consensus exists regarding the approach to treatment of transplant-associated TMA, and no randomized clinical trial data exist. Initial management involves the reduction or discontinuation of the mammalian target of rapamycin and calcineurin inhibitor drugs (especially if used in combination) along with aggressive treatment of underlying GVHD and infections. A role for TPE in this disorder remains unclear. Response rates of transplant-associated TMA to TPE are significantly lower (< 50%)\textsuperscript{116} than the high responses in idiopathic TTP (≤ 85%).\textsuperscript{117-119} A systematic review published in 2004 noted an 82% mortality rate among 176 study volunteers with transplant-associated TMA who underwent TPE compared with a 50% mortality rate among 101 study volunteers not treated with TPE, suggesting that the toxicity of the procedure outweighs the potential benefits.\textsuperscript{114} Similarly high cumulative mortality rates were cited by the Blood and Marrow Transplant Clinical Trials Network Toxicty Committee in a consensus statement recommending that TPE not be considered as standard of care for transplant-associated TMA.\textsuperscript{120} The difference seen in mortality rates may partly reflect the significant comorbidity of the post-transplantation state; however, it also supports the available data that indicate that transplant-associated TMA results from mechanisms distinct from those involved in idiopathic TTP.

Because some patients with transplant-associated TMA appear to respond to treatment, a trial of TPE could be considered as salvage therapy for select patients with persistent, progressive, end-organ complications despite a resolution of infections and GVHD (ASFA category III; grade 2C recommendation).\textsuperscript{1} TPE for transplant-associated TMA is usually performed daily until a response is seen and is then either discontinued or tapered off, a process similar to treatment for idiopathic TTP. The therapeutic end point may be difficult to determine because the platelet count, schistocytes, and lactate dehydrogenase levels could be affected by incomplete engraftment and other post-transplantation complications.

Based on the data from anecdotal reports, other salvage treatment options for transplant-associated TMA might include daclizumab, defibrotide, and rituximab.\textsuperscript{121-123} Such anecdotal reports of clinical response to eculizumab suggest that transplant-associated TMA could involve aberrant and autonomous complement activation and include some patients who may have an inherent defect in complement regulation.\textsuperscript{124,125}

**Therapeutic Leukocytapheresis**

The majority of leukocytapheresis procedures are carried out to treat hyperleukocytosis and complications of leukostasis associated with acute leukemias.

**Leukocytapheresis for Acute Leukemia and Leukostosis With Hyperleukocytosis**

Hyperleukocytosis is variably defined as a WBC or leucemic blast cell count above 50,000/µL or 100,000/µL. The incidence of hyperleukocytosis ranges between 5% and 13% in adult acute myeloid leukemia (AML) and between 10% and 30% in acute lymphoblastic leukemia (ALL).\textsuperscript{126} Although hyperleukocytosis does not appear to have a major impact in early mortality in ALL unless the WBC count is more than 250,000/µL, it is associated with an increased likelihood of induction death and reduced likelihood of achieving complete remission in cases of AML.\textsuperscript{127,128}

Hyperleukocytosis with AML and ALL may be associated with disseminated intravascular coagulopathy, tumor lysis syndrome, and leukostasis. Leukostasis refers to end-organ complications due to microvascular leukoaggregates, hyperviscosity, tissue ischemia, infarction, and hemorrhage as a result of high numbers of leukocytes. The pathophysiology of leukostasis is based on the rheological properties of the blasts, which is a function of the deformability of the blasts (rigidity) and the volume of the blasts (cell fraction) in the blood,\textsuperscript{129} and the cytoadhesive interactions between the blasts and the endothelium.\textsuperscript{130} This second mechanism is based on the activation of the endothelium by blasts to secrete cytokines that in turn mediate the expression of specific receptors such as intercellular adhesion molecule 1, vascular cell adhesion protein 1, selectins, and others that promote blast adhesion.\textsuperscript{130} Leukostasis in ALL usually occurs with WBC counts higher than 400,000/µL.\textsuperscript{131} Compared with lymphoid blasts, myeloid blasts are larger, less deformable, and their cytokine products are more
prone to activate inflammation and the molecular expression of endothelial cell adhesion. A blast count above 100,000/μL is a good predictor of leukostasis in the myeloid phenotype AML (FAB M1, M2, M3v). The blast count is less reliable in monocytic lineage AML (FAB M4, M5) in which severe leukostasis can occur with WBC counts above 50,000/μL.  

Central nervous system manifestations of leukostasis can include confusion, somnolence, dizziness, headache, delirium, coma, and parenchymal hemorrhage, and pulmonary complications can include hypoxemia, diffuse alveolar hemorrhage, and respiratory failure with interstitial infiltrates, alveolar infiltrates, or both. Both pulmonary and neurological manifestations are associated with increased rates of mortality in adults and children. In cases of hyperleukocytosis in AML, the mortality rate has been reported to be between 5% and 30%.  

Definitive treatments for hyperleukocytosis in the setting of AML or ALL involve induction chemotherapy with aggressive supportive care. Hydroxyurea, cytarabine, or both are useful in temporizing cytoreductive agents for AML. Hyperuricemia and tumor lysis syndrome are treated with intravenous fluids, electrolyte replacement, allopurinol or rasburicase, alkalization of the urine, and dialysis. Bleeding and coagulopathy are managed with plasma, cryoprecipitate, and/or platelet transfusions. However, RBC transfusions should be deferred to avoid augmenting hyperviscosity and promoting leukostasis. Leukocytapheresis allows for the rapid reduction of the intravascular leukemic cellular burden, thereby resolving leukostatic microvascular occlusion and improving tissue perfusion. No randomized prospective studies of leukocytapheresis for hyperleukocytosis or leukostasis have been published. Published data regarding the clinical value of therapeutic leukocytapheresis are limited, observational, and conflicting. This is partly due to different WBC thresholds prompting leukocytapheresis, patient selection, and therapeutic end points.

Previous multiple retrospective cohort studies of AML demonstrate reduced early mortality; however, leukocytapheresis offers no benefit to overall outcome. Recently, a systematic review and meta-analysis using an intent-to-treat approach evaluated leukapheresis and low-dose chemotherapy interventions in patients with AML and WBC counts above 100,000/μL. Data were reviewed from 15 of the studies in which leukocytapheresis was used. In the analysis, the mean early mortality rate of 20.1% during the first month of induction chemotherapy in patients with hyperleukocytosis was not reduced by leukocytapheresis (or low-dose chemotherapy), suggesting limited benefit. The authors noted limitations of the primary studies: the studies were small, retrospective, observational, and all had a moderate to high risk of confounding bias.

Prophylactic leukocytapheresis remains a consideration for patients with AML and WBC counts above 100,000/μL without overt leukostasis manifestations as a means to rapidly reduce blood viscosity and facilitate safe RBC transfusion as well as to avoid leukostasis that might occur following the start of chemotherapy, particularly with the M4 or M5 subtype.  

Among children and adults with ALL, clinical symptoms of leukostasis develop in less than 3% at WBC counts lower than 400,000/μL. Therefore, prophylactic leukocytapheresis offers no advantage over aggressive induction chemotherapy and supportive care, including among those with tumor lysis syndrome. By comparison, pulmonary and central nervous system complications develop in more than 50% of children with ALL and WBC counts above 400,000/μL, suggesting that prophylactic leukocytapheresis might be beneficial in that setting.

For patients with ALL or AML and clinical leukostasis complications, ASFA category I (grade 1B recommendation) has been assigned and is based on numerous reports and retrospective case series that describe the rapid reversal of pulmonary and central nervous system manifestations following cytoreduction with leukocytapheresis. However, improvement may not be observed if severe end-organ injury or hemorrhage has already occurred. The ASFA category III (grade 2C recommendation) for prophylactic leukocytapheresis probably reflects the limited and conflicting data available in the literature to guide treatment in patients who are asymptomatic.  

A single leukocytapheresis procedure can reduce the WBC count by 30% to 60%. Daily — or, on occasion, twice-daily — procedures for life-threatening cases can be performed by processing 1.5 to 2 blood volumes and using crystalloid or 5% albumin as the replacement fluid. RBC priming may be employed for adults with severe anemia; however, undiluted packed RBCs should be avoided in small children with hyperviscosity. For patients with AML and leukostasis complications, apheresis must be discontinued when the blast cell count is less than 50,000 to 100,000/μL and clinical manifestations are resolved or maximum benefit is achieved. Chemotherapy should not be postponed and is required to prevent the rapid reaccumulation of circulating blasts.

**Leukocytapheresis for Chronic Myeloid Leukemia With Hyperleukocytosis and Priapism**

The incidence of leukostasis as a result of hyperleukocytosis in adults presenting with CML has been estimated to be between approximately 12% and 60% among children with CML. The most recognized features of hyperleukocytosis in CML are constitutional (malaise and fever), cardiorespiratory, neurological,
or vascular, including retinal hemorrhage, myocardial ischemia, and priapism.

Priapism occurs in 1% to 2% of males presenting with chronic phase CML and WBC counts above 500,000/μL.\textsuperscript{140-142} It is characterized by a prolonged, painful erection. Priapism in this setting is a urological emergency with a poor prognosis, and the risk of impotence in adults is 50% despite appropriate management.\textsuperscript{143} The primary mechanism is the aggregation of leukemic cells in the corpora cavernosa and the dorsal vein of the penis.\textsuperscript{144} A contributing factor is the venous congestion of the corpora cavernosa due to mechanical pressure on the abdominal veins by the enlarged spleen. Increased production of cytokines and adhesion molecules by leukemic cells can also be seen and will result in the activation of endothelial cells and lead to the increased sequestration of cells in the microvasculature.\textsuperscript{145}

No standard treatment has been recommended for leukemic priapism. Systemic therapies include cytoreductive agents, such as high-dose hydroxyurea and tyrosine kinase inhibitors, with or without the addition of leukocytapheresis to reduce hyperviscosity.\textsuperscript{138,146} A review of the published literature revealed that 3 of 4 patients with ischemic priapism treated by leukocytapheresis had a resolution of priapism compared with 3 of 15 patients treated with chemotherapy alone.\textsuperscript{147} Some case series have reported on the successful use of therapeutic leukocytapheresis in combination with cytotoxic therapy to treat priapism.\textsuperscript{142,144,146,148,149} Although some of these studies indicated that a conservative approach may be successful in preserving erectile function, a combined modality approach is strongly recommended by the American Urological Association so that systemic treatment for the underlying disorder and intracavernous treatment be concurrently administered.\textsuperscript{147}

**Leukocytapheresis for Other Chronic Leukemias and Leukostasis With Hyperleukocytosis**

Leukostasis complications with other leukemias are rare but may occur with chronic myelomonocytic leukemia\textsuperscript{150} and WBC counts higher than 100,000/μL with a high level of lactate dehydrogenase. In cases of chronic lymphocytic leukemia, leukostasis is rare and is predominantly described in patients with WBC counts above 1,000,000/μL.\textsuperscript{151}

**Extracorporeal Photopheresis**

ECP is an immunomodulating cell therapy whereby a patient’s circulating WBCs are collected via a leukocytapheresis procedure, exposed ex vivo to photo-activatable 8 methoxypsoralen, irradiated with ultraviolet A light, and then rein infused into the patient. ECP was originally introduced in 1987 by Edelson et al\textsuperscript{152} for the treatment of Sézary syndrome, an aggressive form of advanced cutaneous T-cell lymphoma (CTCL). In 1988, ECP was approved by the US Food and Drug Administration (FDA) for the treatment of advanced forms of CTCL, and has since become a recommended first-line therapy for selected patients with advanced stage CTCL (ASFA category I).\textsuperscript{1,153,154}

ECP is also currently utilized for patients with acute and/or chronic skin and nonskin GVHD (ASFA categories II and III, respectively) and for solid organ transplant rejection (ASFA category II).\textsuperscript{1} Its use is also expanding into the treatment of select autoimmune diseases such as pemphigus vulgaris, scleroderma, inflammatory bowel disease, and nephrogenic systemic fibrosis (ASFA category III).

The molecular mechanisms for the therapeutic effects of ECP are not fully understood. The cytotoxic effects and the role of other cell populations, including dendritic cells, T cells, and natural killer cells, continue to be investigated. Detailed discussions of all the cellular mediators in the process described below are beyond the scope of this article but have been reviewed elsewhere.\textsuperscript{155-158}

Cell death by apoptosis appears to be a major mechanism of action that occurs within 24 to 72 hours of photoactivation; however, 5% to 15% of the total lymphocyte population is exposed to treatment during each procedure.\textsuperscript{159} Thus, additional and/or complementary mechanisms of action are also important. Exposed monocytes undergo apoptosis later than lymphocytes but a portion differentiate into immature dendritic cells.\textsuperscript{159} These dendritic cells have been identified as key mediators of peripheral tolerance\textsuperscript{157} and are found in patients treated with ECP for chronic GVHD.\textsuperscript{160} Together with macrophages, these immature dendritic cells are the antigen-presenting cells that recognize, engulf, and display cellular determinants from the apoptotic lymphocytes. After engulfing apoptotic cells, the immature dendritic cells differentiate into semi-mature dendritic cells, migrate to lymph nodes, and present antigenic peptides to T lymphocytes. This brings about a shift from a Th1 to a Th2 immune response, an increase in anti-inflammatory cytokines (eg, interleukin 10, transforming growth factor β), a decrease in proinflammatory cytokines, and the proliferation of T-regulatory cells. These T-regulatory cells down-regulate the GVHD process by inactivating T-effector cells\textsuperscript{158,161-163} and encouraging peripheral tolerance. In the treatment of CTCL, the apoptotic tumor debris is thought to provide target antigens for cytotoxic CD8\textsuperscript{+} lymphocytes.\textsuperscript{164}

**Cutaneous T-Cell Lymphoma**

Cutaneous lymphomas are characterized by the localization of malignant lymphocytes in the skin. Approximately two-thirds of these lymphomas are of T-cell origin. The most common form of CTCL is
mycosis fungoides, which makes up 60% of CTCL cases. By contrast, Sézary syndrome, which is an aggressive form of advanced CTCL, occurs in about 5% of patients. In Sézary syndrome, the prognosis is generally poor and has a median survival rate of less than 3 years. A meta-analysis of 19 studies that utilized ECP for patients at all stages of CTCL showed overall response rates of 55.5% and 55.7% with ECP alone and ECP in combination with other therapies, respectively. Scarsbrick et al concluded that all patients with erythrodermic CTCL (major criteria) are candidates for ECP, and those with a peripheral blood T-cell clone and/or circulating Sézary cells comprising more than 10% of the lymphocytes and/or have a CD4:CD8 ratio higher than 10 (minor criteria) may also benefit from ECP. Response to ECP has been linked to a short duration of disease, the absence of bulky lymphadenopathy or internal organ involvement, a WBC count lower than 20,000/µL, fewer than 20% Sézary cells, normal or mildly abnormal natural killer cell activity, a level of CD8+ T cells above 15%, lack of prior intensive chemotherapy, and plaque-stage disease involving 10% to 15% of the skin surface. Fewer patients with nonerythrodermic CTCL have been treated with ECP and 1 randomized crossover study alone suggested no ECP benefit.

Guidelines from the National Comprehensive Cancer Network recommend ECP as an option for advanced mycosis fungoides and Sézary syndrome (stage 2B, 3, or 4) when the disease is refractory to skin-directed treatment. However, ECP is not expected to increase survival; typically, the treatment delays the progression of disease and improves pruritus.

The standard schedule of ECP for the treatment of CTCL consists of procedures performed on 2 consecutive days every 2 to 4 weeks and generally continued for up to 6 months to assess response. The median time for a response to ECP is 5 to 6 months, although response may take as long as 10 months in some patients. Those who respond after 6 to 8 cycles appear to have an improved long-term outcome. When maximal response is achieved, ECP treatments can be reduced to once every 6 to 12 weeks with the goal of discontinuation if relapses do not occur. If CTCL recurs in more than 25% of the skin, then ECP once or twice monthly should be re instituted. If evidence exists of disease progression after 6 months of ECP alone, combination therapy should be considered. If minimal or no response is seen after 3 months of combination therapy, then ECP should be discontinued.

**Extracorporeal Cellular Therapy in Graft-vs-Host Disease**

GVHD remains a major complication of allogeneic HSCT. Despite an overall improvement in human leukocyte antigen typing, conditioning regimens, supportive care, and post-transplantation immunosuppression, the overall incidence of GVHD has increased because an increasing number of older patients are undergoing allogeneic HSCT and the use of haploidentical, double-cord blood and human leukocyte antigen–mismatched donors are being used. GVHD following HSCT is classified as an acute, chronic, or overlap syndrome. Despite prophylactic therapy with immunosuppressive agents, 20% to 80% of patients develop acute GVHD following allogeneic HSCT. Acute GVHD results from the activation of donor T cells by host antigen–presenting cells, leading to T-cell– and cytokine-mediated tissue injury. Chronic GVHD is due to dysregulated allogeneic or autoreactive T cells, B cells, antigen-presenting cells, and natural killer cells, thus leading to fibrosis, inflammation, sclerosis, and atrophy of affected tissues. Moder ate-to-severe GVHD is the leading cause of impaired immune function, compromised functional status, and transplantation-related deaths. High-dose corticosteroids are first-line therapy for moderate-to-severe acute and chronic GVHD with or without the use of calcineurin inhibitors. Patients with chronic GVHD require prolonged immunosuppressive treatment for an average of 2 to 3 years from the initial diagnosis, with 10% of those surviving for at least 7 years still requiring immunosuppressive treatment at that time or beyond. Severe GVHD unresponsive to treatment carries a high risk of death or severe morbidity due to end-organ complications, infections, or both, and the transplantation-related mortality rate exceeds 40%. To date, the US Food and Drug Administration has not approved a treatment option for GVHD.

Therapies for steroid-refractory acute GVHD include mycophenolate mofetil, denileukin difitox, sirolimus, infliximab, etanercept, pentostatin, horse or rabbit antithymocyte globulin, and alemtuzumab. Evidence does not suggest that any one second-line agent is superior to another. As a result, decisions on which agent to use at individual treatment centers often vary according to the clinical experience of health care professionals, cost, and treatment availability.

ASFA has reviewed the data available on the overall response rates to ECP for steroid-refractory acute GVHD and found that overall response rates in pediatric and adult patients ranged from 52% to 100%, with responses in cutaneous (66%–100%), gastrointestinal tract (40%–83%), and hepatic (27%–71%) acute GVHD. Higher response rates have been reported in early-onset GVHD; however, the strongest predictor for response to ECP in a multivariate analysis was GVHD severity (100% response in grade 2 disease vs 30% in grade 3/4). Complete responses and

January 2015, Vol. 22, No. 1

Cancer Control 71
improved survival rates are often reported among acute GVHD cohorts; however, the nonrandomized and retrospective results for ECP are not superior to results reported for alternative salvage approaches for steroid-refractory acute GVHD.

Therapies for steroid-refractory/dependent chronic GVHD include sirolimus, mycophenolate mofetil, azathioprine, thalidomide, ECP, total lymphoid irradiation, mesenchymal cells, imatinib, pentostatin, various monoclonal antibodies, and others.\textsuperscript{177,178} Approximately 30% to 65% of patients with chronic GVHD and dependent on steroids improve with ECP, but most experience partial responses alone.\textsuperscript{1} Skin, oral, and ocular chronic GVHD manifestations respond in 30% to 100% of cases, whereas liver, joint, and gastrointestinal complications improve in 30% to 80%, 50%, and 0% to 50% of cases, respectively.\textsuperscript{1} A review of 23 studies totaling 735 patients treated with ECP for steroid-resistant, intolerant, or dependent chronic GVHD noted that overall and complete response rates were observed in 64% and 35% of cases with skin involvement, in 56% and 27% cases of oral GVHD, and in 47% to 57% with gastrointestinal tract chronic GVHD.\textsuperscript{181} ECP has also been reported to stabilize lung function with bronchiolitis obliterans syndrome related to chronic GVHD\textsuperscript{182}; however, response rates for lung involvement are typically lower, ranging from 0% to 66%.\textsuperscript{183,184} Patients responding to ECP also have a better probability of survival, both in children (96% vs 58% 5-year survival)\textsuperscript{185} and in adults (88% vs 18% at 2 years; relative risk, 11.6; \(P = .022\)).\textsuperscript{186}

Maximal responses for chronic GVHD usually require 2 to 6 months of treatment. The single, randomized controlled trial using ECP for steroid-resistant skin chronic GVHD observed no statistically significant difference in total skin score at 12 weeks of ECP plus salvage GVHD therapy compared with salvage therapy alone.\textsuperscript{187} However, unblinded assessments recorded 40% complete and partial responses at 12 weeks in the ECP-treated group compared with 10% in the non-ECP group (\(P < .001\)).\textsuperscript{187} More rapid skin improvement was also observed at weeks 12 to 24 of ECP and corticosteroids could be more quickly tapered. Among 29 control patients from this study who crossed over to receive 24 weeks of ECP for refractory disease, objective responses occurred in the skin and extracutaneous tissue in 33% and up to 70%, respectively.\textsuperscript{187}

No national consensus exists on the duration and discontinuation of ECP procedures. For acute GVHD, ECP is recommended on 2 consecutive days (1 cycle) per week until disease response and then tapered to alternate weeks before discontinuation.\textsuperscript{1} Some centers have recommended a minimum of 8 weeks.\textsuperscript{188} For chronic GVHD, 1 weekly cycle (or consider biweekly if treating mucocutaneous chronic GVHD alone) until either a response or for 8 to 12 weeks, followed by a taper to every 2 to 4 weeks until maximal response.\textsuperscript{1} One author has proposed 2 to 3 procedures per week depending on disease severity for 4 weeks or more.\textsuperscript{189} Clinical response should be assessed weekly in acute GVHD and every 8 to 12 weeks in chronic GVHD; ECP should be discontinued in cases of no or minimal response. Some studies indicate that approximately 10% of patients with chronic GVHD given ECP may benefit from treatment longer than 12 to 24 months.\textsuperscript{181}

Clinical practice guidelines and consensus statements addressing the use of ECP for GVHD collectively consider ECP as an established second-line therapy option for steroid-refractory chronic GVHD, particularly involving the skin.\textsuperscript{1,190-192} ECP has also been recommended as an adjunctive first-line modality for bronchiolitis obliterans syndrome and select pediatric patients with acute GVHD.\textsuperscript{1,190-192} More recently, a UK group has provided its consensus statement and guidance on the use of ECP in adult and pediatric patients with acute GVHD.\textsuperscript{188} The proven effectiveness of ECP in both acute and chronic GVHD cases is mirrored in the ASFA guidelines, which recommend ECP for chronic (category II; grade 1B recommendation) and acute (category II; grade 2C recommendation) GVHD.\textsuperscript{1}

### Thrombocytapheresis

**Thrombocytosis Associated With Myeloproliferative Neoplasms**

Thrombocytosis is defined as a peripheral blood platelet count above 350,000 to 400,000/µL. Reactive thrombocytosis is the most common cause of an elevated platelet count and can be caused by iron deficiency, inflammatory conditions, infections, malignancy, acute bleeding, hemolysis, and asplenia. Because the platelets in these conditions are functionally normal, the increased platelet count does not normally predispose to thrombosis or acute bleeding. However, functionally abnormal platelets are associated with the elevated platelet counts seen in patients with myeloproliferative neoplasms (eg, essential thrombocytosis, polycythemia vera, chronic myelogenous leukemia, primary myelofibrosis) and refractory anemia with ringed sideroblasts associated with marked thrombocytosis. Functionally abnormal thrombocytosis is associated with an increased incidence of thrombohemorrhagic events.\textsuperscript{193,194} Accurate diagnoses of thrombocytosis are important for both prognostication and treatment.\textsuperscript{195}

Diagnoses of essential thrombocythemia and polycythemia vera are currently in accordance with criteria from the World Health Organization and are based on a composite assessment of clinical and laboratory (hematological, morphological, and molecular) features.\textsuperscript{196} When evaluating thrombocytosis, the detection of the clonal mutation \(JAK2\ V617F\) confirms
the presence of an underlying myeloproliferative neoplasm. However, the absence of this mutation does not rule out the possibility. Up to 50% of patients with essential thrombocythemia might be JAK2 V617F negative; however, finding a mutation in a newly described genetic marker, CALR, or, less commonly, MPL, can identify the majority of cases that are JAK2 mutation negative.

Current risk stratification in essential thrombocythemia and polycythemia vera is designed to estimate the likelihood of thrombotic complications. High risk is defined by age older than 60 years or history of the presence of thrombosis, whereas low risk is defined by the absence of both of these 2 risk factors. Extreme thrombocytosis (platelet count > 1,000,000/μL) can be associated with acquired von Willebrand syndrome and, thus, a risk for bleeding.

Risk factors for shortened survival rates in both polycythemia vera and essential thrombocythemia include advanced age, leukocytosis, and a history of thrombosis.

Major thrombotic complications with essential thrombocythemia and polycythemia vera include stroke, transient ischemic attacks, myocardial infarction, peripheral arterial thrombosis, lower extremity deep venous thrombosis, pulmonary embolism, and venous thrombosis in unusual sites such as hepatic (Budd Chiari syndrome), portal, and mesenteric veins. The risk of thrombosis in essential thrombocythemia and polycythemia vera exceeds 20% and a substantial portion of patients experience microcirculatory disturbances. The most frequent bleeding events are hemorrhages from the gastrointestinal tract followed by hematuria and other mucocutaneous hemorrhages. Hemarthrosis and large muscle hematomas are uncommon. Patients with essential thrombocythemia and low risk of thrombosis are given low-dose aspirin if microvascular symptoms are present but do not require cytoreductive therapy. High-risk patients are treated with cytoreductive therapy, such as hydroxyurea, interferon α, or, less commonly, anagrelide in conjunction with low-dose aspirin.

Thrombocytapheresis has been used to treat acute thromboembolism or hemorrhage in select patients with essential thrombocythemia or polycythemia vera associated with uncontrolled thrombocytosis. The current ASFA guidelines are based on observational case studies or case reports (category II; grade 2C recommendation).1 Thrombocytapheresis should also be electively considered for cytoreduction in patients at increased risk of hemorrhage in whom hydroxyurea is contraindicated, such as in cases of pregnancy, or if cytoreductive therapy with hydroxyurea is likely to be too slow (eg, urgent surgery is required). Because the beneficial effect of platelet reduction is generally quite brief, repeat procedures are often necessary, and it is generally recommended that platelet-lowering agents be given whenever possible to prevent rapid reaccumulation of circulating platelets.

Each thrombocytapheresis procedure (treating 1.5–2 blood volumes) lowers the platelet count by about 30% to 60%. Pre- and post-platelet counts should be closely monitored to gauge the effectiveness of platelet removal and to guide subsequent treatments. The goal of thrombocytapheresis in acute thromboembolism or hemorrhage is the normalization of the platelet count and maintenance of a normal platelet count until pharmacological cytoreductive therapy takes effect. The goal for prophylaxis in high-risk patients who are pregnant or undergoing surgery or post-splenectomy should be based on the patient’s history of bleeding or thrombosis.

**Erythrocytapheresis**

**Polycythemia Vera/Primary Erythrocytosis**

Polycythemia vera is characterized by bone marrow hypercellularity, atypical megakaryocyte hyperplasia, leukocytosis, thrombocytosis, splenomegaly, and a clinical predilection for thromboembolism, bleeding, hyperviscosity complications, and the evolution to myelofibrosis or AML. The JAK2 V617F mutation is found in more than 90% of cases.

In polycythemia vera, whole blood viscosity increases significantly as the hematocrit level exceeds 50%. Malaise, headache, visual disturbances, pruritus, dizziness, confusion, slow mentation, and myalgia are the most common symptoms. Similar to essential thrombocythemia, 15% to 40% of patients with polycythemia vera may experience major arterial cerebrovascular or cardiovascular thromboembolic events, deep venous thrombosis, pulmonary embolism, or intra-abdominal venous thrombotic events. Thrombotic risk factors with polycythemia vera include uncontrolled erythrocytosis (hematocrit > 55%), age older than 60 years, history of prior thrombosis, cardiovascular comorbidities, immobilization, pregnancy, and surgery.

RBC depletion by manual phlebotomy or by automated therapeutic erythrocytapheresis can correct hyperviscosity complications with uncontrolled polycythemia vera by lowering the hematocrit level, thereby reducing capillary shear and increasing microcirculatory blood flow and tissue perfusion. Classical manual phlebotomy is a simple, safe, and low-cost method. However, it can require a significant number of procedures to reach target values. Adverse events related to hypovolemia with manual phlebotomy occur in a substantial number of patients, and, thus, this treatment modality may not be tolerated in the elderly, those with small blood volumes, and those with cardiovascular compromise. However, with auto-
mated therapeutic erythrocytapheresis, up to 800 mL of RBCs per single procedure can be separated from other blood components and concurrently exchanged with a crystalloid or colloid solution, thus offering a far more efficient method in removing RBCs while maintaining isovolemic conditions.

In the past 2 decades, 1 randomized trial and a number of small case series have described the advantages of automated therapeutic erythrocytapheresis for the treatment of hereditary hemochromatosis and erythrocytosis with improvements seen in treatment efficiency, morbidity, and patient experience. For patients with polycythemia vera and acute thromboembolism, severe microvascular complications, or bleeding, automated therapeutic erythrocytapheresis may be a useful alternative to emergent large-volume phlebotomy, particularly if the patient is hemodynamically unstable. Automated therapeutic erythrocytapheresis can also be successfully utilized with polycythemia vera complicated by thrombocytosis; during the same session, the hematocrit level can be lowered to 42% ± 45% and the platelets reduced to 500,000 to 600,000/μL. Therapeutic erythrocytapheresis may also be appropriate prior to surgery to reduce the high risk of perioperative thrombotic complications in a patient with polycythemia vera and a hematocrit level of more than 55%.

A number of studies have been published supporting the use of therapeutic erythrocytapheresis as maintenance therapy. One study of 76 patients with polycythemia vera saw improvement in platelet function, as measured by thromboelastography, after therapeutic erythrocytapheresis, suggesting that the hemodilution achieved with the procedure may reduce thrombotic risk. A retrospective cohort analysis of 98 patients, including 6 with polycythemia vera and 92 with secondary erythrocytosis, observed that chronic automated therapeutic erythrocytapheresis allowed significantly greater treatment intervals (median, 135–150 days; range, 2–7 months) to maintain the target hematocrit level compared with chronic phlebotomy (median, 40 days; range, 20–60 days). The advantage of therapeutic erythrocytapheresis may be due to the relatively greater loss of iron that is associated with this modality that, in turn, limits the growth of hematopoietic cells.

The ASFA guidelines designate polycythemia vera as a category I indication (grade 1B recommendation) for therapeutic erythrocytapheresis. Decisions to use an automated procedure over simple phlebotomy remain based on clinical urgency, necessity, cost, and consideration of the risk of adverse events that may be associated with automated procedures. Although the costs of a single therapeutic erythrocytapheresis procedure are substantially higher than phlebotomy, cost analysis has shown no significant difference in maintenance treatment costs as a result of the fewer treatment procedures needed to reach recommended target values. One group developed a simple and practical mathematical model for predicting the efficiency of a single cycle of therapeutic erythrocytapheresis compared with a single phlebotomy procedure, which could in daily clinical practice aid in optimizing therapeutic erythrocytapheresis use and selecting a proper treatment modality for the individual patient. For example, the researchers determined that therapeutic erythrocytapheresis would not be optimal for patients with a small blood volume and/or marginal achievable change in hematocrit level.

For patients with polycythemia vera, the goal of therapeutic erythrocytapheresis is rapid normalization of hematocrit (ie, < 45%). A single procedure should be designed to achieve the desired postprocedure hematocrit level. Automated instruments allow the operator to choose a postprocedure hematocrit level and calculate the volume of blood removal necessary to attain the goal. Saline boluses may be required during the procedure to reduce blood viscosity in the circuit and avoid pressure alarms.

Conclusions
Therapeutic apheresis (TA) is an important treatment option utilized in patients to manage specific complications associated with malignancy. TA has been used as an emergent procedure, including as a therapeutic plasma exchange to treat symptomatic hyperviscosity or leukocytapheresis for the treatment of leukostasis. TA can be effective as first-line therapy — as seen in the use of extracorporeal photopheresis for erythrodermic cutaneous T-cell lymphoma — although often TA is attempted as salvage or adjunct therapy for conditions not responding to conventional chemotherapy or immunotherapy. Examples of such circumstances include therapeutic plasma exchange for the removal of antibodies associated with underlying paraneoplastic processes or the use of extracorporeal photopheresis for non–skin-associated graft-vs-host disease.

TA modalities are relatively safe procedures; however, they are not without risk. In order for these modalities to be performed, experienced staff members are required. In all cases, the risks, benefits, and costs must be strongly considered before prescribing. The expert-based practice guidelines from the American Society for Apheresis have been developed to inform hematology/oncology professionals and apheresis physicians about the efficacy and limitations of TA for malignancy-related indications as well as to support clinical decision-making. However, well-designed, prospective intervention trials are still needed to better define the role of TA for a variety of disorders.
References


90. Vigilant MC, Sun Y, Sirici L, Polo P, et al. Paraneoplastic opocinopod-myo-
92. David YB, Warner E, Levitama M, et al. Autoimmune paraneoplastic cereb-
96. Neumann DR, Murray NM, Plasma exchange and immunosuppres-
102. Willems E, Baron F, Seidel L, et al. Comparison of thrombotic microan-
104. Batts ED, Lazarus HM. Diagnosis and treatment of transplantation-as-
106. Willems E, Baron F, Seidel L, et al. Comparison of thrombotic microan-


