Applications of Therapeutic Apheresis in Patients with Malignant Disease

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Key Words. Apheresis · Therapeutic apheresis · Apheresis and malignancy · Clinical applications · Plasma exchange · Cytapheresis

ABSTRACT

Therapeutic apheresis (TA) provides the means for the removal of blood components that are abnormal or that circulate in excessive amounts and have a defined pathogenetic role, or are thought to have one. Multiple disease processes have been treated with TA at one time or another, but scientific assessment of the therapeutic effects of the procedure has lagged behind application of the technology. This led the American Medical Association and the American Society for Apheresis to publish position papers on the proper applications of TA. In the field of oncology, therapeutic plasma exchange (TPE) and related procedures may be the treatment of choice for some conditions (e.g., TPE for thrombotic thrombocytopenic purpura, therapeutic leukapheresis for extreme leukocytosis in acute myelogenous leukemia, etc.), or may represent a promising therapeutic modality whose efficacy needs to be established by randomized controlled trials in the future (e.g., photopheresis for the treatment of cutaneous graft-versus-host disease). Some applications should be considered strictly investigational, and should be offered to patients only if they are part of an approved research protocol (e.g., extracorporeal immunoadsorption with staphylococcal protein A for non-hematologic cancer). Routine use of TA should be restricted to conditions where the benefit has been established by controlled studies or the best available evidence. The Oncologist 1997;2:94-103

INTRODUCTION

Therapeutic plasma exchange (TPE) is the exchange of several liters of “abnormal” patient plasma for an isovolemic amount of a colloid solution, or fresh frozen plasma, or a combination of the two. TPE assures the immediate removal of abnormal substances from the circulation, and can produce rapid improvement in a patient’s signs and symptoms before other therapies can take effect. Paraproteins, autoantibodies, lipids, and toxins or drugs that are tightly bound to plasma proteins can be effectively removed by TPE. When a disease is mediated by one of these four categories of substances, there is at least a theoretical basis for initiating TPE. Other forms of therapeutic apheresis (TA) include therapeutic cytapheresis (for the immediate removal of leukocytes or platelets from the circulation of patients with hematologic malignancies), red cell exchange, photopheresis, and extracorporeal immunoadsorption with the staphylococcal protein A (column treatment) [1].

In a consensus statement revised every few years, the Clinical Applications Committee of the American Society for Apheresis (ASFA) distinguishes four categories of diseases in which TA is indicated (Table 1). TA is most commonly performed for the Category I indications, which are listed in Table 2. Table 3 shows the role of TA in diseases likely to be seen in a hematology/oncology practice. [2] In this review, we will discuss the rationale for the procedure in the most frequently encountered indications in patients with malignant disease, and we will present a brief account of the findings of published studies.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombotic thrombocytopenic purpura (TTP) is characterized by the diagnostic pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms, impairment of renal function, and fever [3]. The signs and symptoms of TTP are the result of thrombotic occlusions of the microvasculature in many organs. The disease is thought to result from an abnormal interaction between vascular endothelium and circulating platelets, but whether the primary event is endothelial cell injury or platelet activation...
has not been established. Vascular specimens from patients with TTP have a reduced capacity to form prostacyclin (PGI₂) [4], and reduced availability of PGI₂ may result in loss of endothelial thromboresistance [5] and increased stability of platelet-fibrin thrombi formed in the microcirculation. Further evidence for endothelial cell injury comes from the detection of unusually large von Willebrand factor (VWF) multimers in the plasma of patients with TTP [6]. These multimers do not normally circulate, but are stored in the endothelial cell Weibel-Palade bodies; therefore, their presence in the peripheral blood may reflect endothelial cell damage. Alternatively, the initiating event in TTP could be the release of a factor causing platelet aggregation and adherence to arterioles [7].

TPE (using fresh frozen plasma [FFP] as replacement fluid) is the major treatment modality for idiopathic TTP. Rossi [8] considered all 486 TTP patients enrolled in 25 reports published in 1982-1994 who had been treated with TPE. Fewer than 20% of the patients (85/486 or 17.5%) were refractory to this treatment [8]. The 82.5% response rate compares very favorably with the 54%-67% response rates observed in patients receiving antiplatelet drugs and the 46% survival rate recorded for TTP patients in the period 1964-1980 [8]. TPE is also superior to plasma infusion, and its superiority was recently confirmed in two randomized controlled trials [9, 10]. FFP infused during TPE may restore PGI₂ and/or inhibit the release of unusually large VWF multimers from endothelial cells or restore normal VWF processing in the circulation [11].

TPE should be instituted as rapidly as possible after making a diagnosis of TTP. Intensive, daily TPE is indicated for a period of one to two weeks, exchanging 1.0-1.5 plasma volumes per procedure. Response to treatment should be monitored by obtaining lactate dehydrogenase (LDH) measurements and platelet counts before each procedure, and treatments should continue until the LDH is near normal and the platelet count exceeds 100,000/µl for at least two days in a row. Response to TPE usually occurs within one to two weeks, although some patients may have a delayed response during the third week of treatment [12]. In 1995-96, seven TTP patients were treated at the Mayo Clinic, and they all responded following 5, 6, 7, 11, 12, 14, and 15 days of TPE treatments. The treatments were then tapered, and were continued every other day for three to six days in four of seven patients, in order to prevent disease relapse. Corticosteroids and/or azathioprine are useful adjuncts to TPE [13, 14], but the benefit from addition of antiplatelet agents is unclear [14]. Platelet transfusions can aggravate TTP [13, 14] and should be avoided.
An important management issue is how long to continue the TPE treatments in cases with prolonged courses [12]. Eldor et al. [15] reported disease remission in two patients who underwent TPE more than 80 times with the infusion of more than 970 units of plasma. Taft et al. [16] described six patients who required plasma support for more than three months before complete remission was achieved. One of these patients underwent more than 100 TPE procedures [16]. On the other hand, Rock et al. [17] considered 18 patients who had failed an average of 7.7 exchanges (range 5-14) as refractory to TPE with FFP as replacement fluid, and as suitable candidates to undergo TPE with cryosupernatant plasma. Criteria for refractoriness in the latter study [17] included a failure of the platelet count to increase to 150,000/µl and/or deterioration in the patient’s neurologic status.

Rock et al. [17] suggested that replacement with cryosupernatant plasma may be more effective as first-line treatment for TTP than FFP. Increased VWF levels are found in patients with active TTP [10] and, although these elevated levels may be secondary to endothelial cell damage, it is also possible that VWF may contribute to the disease [18]. If large multimers of VWF are involved in the thrombi which are deposited in the microvasculature of these patients, plasma depleted of the high-molecular-weight multimers may be preferable as replacement fluid in TTP [17, 18]. Of 18 patients who were considered refractory to TPE with FFP in the study of Rock et al. [17], 11 responded to TPE with cryosupernatant plasma.
Patients with tumor in remission at the time of enrollment into the trial had estimated one-year survival rates of 74%, as compared with 22% for historical controls ($p = 0.0161$) [24]. Patients with stable or progressing tumor had one-year survival rates of 27%, as compared with 25% for historical controls. The authors ascribed the benefit noted in subjects with tumor in remission to an “immunomodulatory” effect of the column [24, 25]. They proposed that “protective” antibody (i.e., antibody directed against a tumor-associated antigen or the idiotope of an autoantibody) is complexed in circulating immune complexes (CICs) in cancer patients, and that immunoadsorption with the staphylococcal protein A column facilitates the release of free protective antibody in treated patient plasma. When protective antibody is released, conditions shift from those of antigen excess to those of antibody excess, and large CICs (19S)—which are readily cleared by macrophages—replace the earlier small (7-10S) CICs, which escape such clearance. Small CICs, formed under conditions of antigen excess, may exercise an immunosuppressive effect in patients with cancer and autoimmune diseases [25]. CICs in patients with CATT/HUS contain platelet-associated antigens [GPIIb/IIIa], and/or tumor-associated antigens [Le$^a$ glycolipids], and/or platelet autoantibody complexed with anti-idiotypic antibody [25]). It is postulated that immunoadsorption may trigger the production of protective antibody, and lead to a change in the patients’ immune response to the culprit antigen, which is maintained after treatments have been completed [25].

**Hematologic Malignancies**

Extreme leukocytosis in the context of acute myelogenous leukemia (AML), usually the M4 and M5 types, may result in a leukostasis syndrome characterized by impaired flow and accumulation of leukemic blasts in the microvasculature, especially the small vessels of the lungs and the brain. The leukocytes cause increased blood viscosity and increased consumption of oxygen, resulting in local tissue hypoxia and organ dysfunction. This manifests as respiratory impairment, headache, dizziness, fainting, altered sensorium, visual disturbances, priapism, tinnitus, etc. Leukocytes may spill into the surrounding tissues at a later stage, after causing damage to the vascular wall. Tumor nodules form in the perivascular white matter of the brain, and may be associated with cerebral hemorrhage when the circulating blast count exceeds 300,000/$\mu$l. Symptoms of leukostasis can develop in AML with blast counts exceeding 50,000/$\mu$l, but they are rare in patients with acute lymphocytic leukemia (ALL) and may appear in chronic myelogenous leukemia (CML) only with exceedingly high white cell counts (>300,000/$\mu$l) [26].
Emergency leukapheresis is warranted, and the reduction in the circulating blast count results in rapid clinical improvement. Whether emergency leukapheresis is also indicated on a prophylactic basis for all AML patients with blast counts exceeding 50,000/µl or 100,000/µl remains controversial. Prophylactic leukapheresis is probably appropriate in patients with the M4 and M5 types, and/or patients in whom the blast count is rapidly rising. Leukapheresis does not affect already-formed tumor nodules in the brain, and irradiation of the brain could be combined with leukapheresis to prevent cerebral bleeding [27]. Chemotherapy should be initiated as soon as possible. Red cell and platelet transfusions should be withheld until the white cell count is reduced by leukapheresis, to prevent worsening of the manifestations of hyperviscosity. A single leukapheresis can reduce the white cell count to 30%-60% of the preprocedure value [28], and is often adequate treatment of the emergency. A second procedure is sometimes needed on the following day.

Extreme thrombocytosis in the context of a chronic myeloproliferative disease may manifest with either bleeding or thrombosis. The combination of symptoms and a platelet count exceeding 1,000,000/µl may warrant emergency plateletpheresis to immediately reduce the platelet count by 45%-70% [29, 30]. A single procedure is usually adequate treatment, providing that chemotherapy is started at the same time. Prophylactic plateletpheresis is probably not indicated in patients with platelet counts exceeding 1,000,000/µl unless a particular patient is especially at risk for bleeding or thrombosis. Arguments have been presented in favor of prophylactic plateletpheresis in pregnant women (to prevent placental infarction and fetal death), in patients scheduled to undergo surgery, in elderly patients with cardiovascular disease, etc.

Unusually high platelet counts can also occur in benign conditions (e.g., acute or chronic inflammatory disorders, postsplenectomy or in the postoperative state, etc.). Benign thrombocytosis is generally asymptomatic and is not an indication for plateletpheresis. However, the underlying condition may not be known when a patient presents with extreme thrombocytosis or leukocytosis. Plateletpheresis or leukapheresis is generally warranted if thrombotic or hemorrhagic manifestations or symptoms of vascular stasis cannot be otherwise explained. The procedure can also be performed as a diagnostic trial to determine whether symptoms are alleviated by a reduction in the platelet or white cell count.

Photopheresis is presently the treatment of choice for newly diagnosed cutaneous T cell lymphoma [31]. Patients having only cutaneous disease have a 60% four-year survival rate if they receive photopheresis, as compared with a 30% survival rate for patients receiving conventional chemotherapy [32]. However, the role of photopheresis is controversial in patients with advanced disease (i.e., cutaneous lesions of the plaque or tumor stages or systemic involvement). Photopheresis consists of removal of >5 billion leukocytes from the patient (via leukapheresis) and extracorporeal exposure of these cells to ultraviolet light inside the separator. A drug (8-methoxy-psoralen) is incorporated in the DNA of the cells prior to their exposure to light. The drug is given to the patient 90 minutes before the procedure and crosses the nuclear membranes of all nucleated cells of the body. (In the future, it is likely that the drug will be delivered directly to the leukocytes inside the separator.) When exposed to light, these leukocytes suffer DNA damage, in that their pyrimidines become covalently linked. It is postulated that treated lymphocytes become capable of mediating antitumor immunity in the host, and they are returned to the patient at the end of the procedure. Newly diagnosed patients with T cell lymphoma have nearly normal immune competence, and they are most capable of mounting an immunologic attack against the tumor.

**Paraproteinemias**

Abnormal proteins, usually immunoglobulins, accumulate in the circulation of patients with multiple myeloma, Waldenström’s macroglobulinemia, cryoglobulinemia, and other disorders (e.g., pemphigus, rheumatoid arthritis, etc.) [33]. Paraproteins increase the plasma viscosity and the
total blood volume, interact with platelets and coagulation factors, infiltrate nerves or produce demyelination, and may precipitate in the renal tubules of patients with myeloma or produce an immune-complex-type glomerulonephritis in patients with cryoglobulinemia.

The hyperviscosity syndrome is an acute medical emergency. It usually presents with neurologic signs and symptoms including headache, vertigo, somnolence, obtundation, seizures, loss of vision, and coma. Paraproteinemic coagulopathy may coexist and manifest with epistaxis, gingival bleeding, gastrointestinal hemorrhage, and purpura. Hypervolemia with a total blood volume up to twice normal, greatly increased plasma volume, and dilutional anemia may also coexist. Most patients become symptomatic when a viscosity of 4-6 (relative to water) is reached. If left untreated, hyperviscosity is fatal.

Emergency TPE should be instituted. One or two procedures are usually sufficient to relieve the neurologic signs and symptoms and the bleeding diathesis, because they remove sufficient paraprotein to reduce the viscosity below the threshold value for appearance of symptoms. The relationship between viscosity and individual paraprotein concentration is exponential rather than linear. Once the symptomatic threshold (viscosity of 4-6) is exceeded, the plasma viscosity increases much faster than does the paraprotein concentration. Accordingly, removal of only a modest amount of paraprotein is sufficient to reduce the plasma viscosity below the cutoff (Fig. 1). Because the culprit paraprotein is usually IgM, it is mostly (93%) distributed in the intravascular compartment and is efficiently removed by TPE. Chemotherapy assures control of the paraprotein concentration after the initial crisis is confronted.

TPE consists of a 1-1.5-volume exchange, using 5% albumin as replacement fluid. It may have to be combined with plasmapheresis to correct the cardiovascular complications of hypervolemia. A second procedure may be indicated one to three days later. Hypervolemic patients may need maintenance therapy with weekly or monthly plasmapheresis removing 500-700 ml of plasma [34].

Patients with myeloma kidney are managed with chemotherapy and alkaline diuresis, along with TPE or peritoneal dialysis intended to reduce the precipitation of plasma paraproteins in the renal tubules. TPE is considered more effective than dialysis for this purpose [35-37]. Intensive TPE performed daily or every other day and using 5% albumin as replacement fluid is indicated for one to four weeks until the acute renal failure is relieved. Maintenance therapy (three treatments over one week every five weeks) may prevent recurrent episodes of renal failure in some patients [38].

Paraproteinemic peripheral neuropathy is primarily managed with chemotherapeutic and immunosuppressive drugs intended to control the production and accumulation of the paraprotein. Small case series and anecdotal case reports have produced conflicting results regarding the efficacy of TPE in treating the neuropathy of patients with paraproteinemia [39]. A controlled trial was conducted in patients with monoclonal gammapathy of undetermined significance (MGUS) and showed a short-lived but significant improvement in the TPE group as compared with the sham pheresis group in patients with monoclonal immunoglobulin of the IgG or IgA class [40]. Patients were not receiving concomitant immunosuppression in that study. Accordingly, TPE two to three times a week for two to four weeks can be offered as a therapeutic option to patients with MGUS, with or without immunosuppression. A prolonged course of TPE at a tapered frequency can also be considered in responding patients.

In the cryoglobulinemias, TPE is performed daily to every other day, and may present special technical challenges, as the temperature of the equipment and replacement fluid used, and even the temperature of the room, may have to be kept as close to body temperature as possible. Rapidly progressing glomerulonephritis and the nephrotic syndrome respond well to TPE [41]. TPE should be initiated promptly if a patient presents acutely with life-threatening or severe organ dysfunction signs and symptoms, or if immunosuppressive therapy has been ineffective.

**Non-Hematologic Cancer**

Cancer patients have been reported to have a worse prognosis in the presence of CICs, as a probable downregulation of the immune response might lead to progression of their disease [42, 43]. In vitro removal of immunosuppressive CICs can result in increased antitumor immune activity [44], and clinical antitumor responses were reported in patients following TPE [42]. Protein A immunoabsorption was subsequently tried in cancer patients as a more specific approach to immune complex extraction than TPE. Using this technology, responses have been demonstrated in induced and naturally occurring tumors in rats, dogs, and cats, and in small series of patients [45, 46].

Messerschmidt et al. [47] reported on 142 patients treated with protein A immunoabsorption for malignant disease unresponsive to conventional therapy. These subjects received a total of 12 treatments (either off-line or online), usually administered three times a week. Patients with stable or regressing disease were permitted to continue treatment beyond the twelfth procedure. Responses to therapy were evaluated based on the criteria established by the International Union Against Cancer. Complete remission (CR) was defined as disappearance of all evidence of disease. Partial remission (PR) was defined as a 50% decrease.
in the product of the two greatest perpendicular diameter measurements of the tumor, and no new lesions. A less-than-partial remission (<PR) was defined as a >25%, but <50%, decrease in tumor size. Stable disease was defined as a <25% reduction in tumor size, but without progression, and no new lesions. Progression was defined as an increase of >25% in the size of any one measured lesion, or as appearance of new lesions. Objective responses to therapy had to be present for at least 30 days to be counted. Patients who received at least seven immunoadsorption treatments were considered evaluable.

Overall, 22 of 101 evaluable patients (21.8%) exhibited a PR or <PR to treatment (Table 4). Partial responses were observed almost exclusively in patients with Kaposi’s sarcoma and breast adenocarcinoma, and these subjects also had the best overall responses to therapy. No complete responses were recorded.

Based on the available data, immunoadsorption could be offered as an option to cancer patients only on an experimental basis. Despite a favorable response in 20%-25% of subjects, the findings cited above remain controversial [2] for the following reasons: A) efficacy has been difficult to establish because of the heterogeneity of enrolled patients and the lack of proper controls; B) the duration of favorable responses has been brief, and C) occasional patients have experienced serious reactions to treatment [48]. Protein A immunoadsorption deserves further investigation to permit an adequate delineation of both efficacy and toxicity, and to elucidate the mechanism of action of the Prosorba® column.

### Table 4. Multicenter trial of the Prosorba® column in patients with cancer refractory to conventional therapy: responses to immunoadsorption

<table>
<thead>
<tr>
<th>Tumor</th>
<th>PR</th>
<th>&lt;PR</th>
<th>&lt;PR/number evaluable (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>12</td>
<td>10</td>
<td>22/101 (21.1%)</td>
</tr>
<tr>
<td>Breast adenocarcinoma</td>
<td>5</td>
<td>3</td>
<td>8/28 (28.5%)</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>6</td>
<td>3</td>
<td>9/23 (39.1%)</td>
</tr>
<tr>
<td>Colon adenocarcinoma</td>
<td>1</td>
<td>1</td>
<td>2/18 (11.1%)</td>
</tr>
<tr>
<td>Other*</td>
<td>0</td>
<td>3</td>
<td>3/32 (9.4%)</td>
</tr>
</tbody>
</table>

*Based on data reported by Messerschmidt et al. [47].

*Including a wide variety of carcinomas, sarcomas, and leukemias/lymphomas. The predominating diagnoses were pulmonary and renal carcinoma, leukemia, and melanoma.

Some authors recommend that patients with unusually high isoagglutinin titer prior to receiving ABO-incompatible BMT undergo intensive, daily, large-volume TPE for reduction of their antibody titers. This treatment should probably be offered only to patients with antibody titers exceeding 1:256 or 1:512, but there is no agreement as to how “high” a titer is dangerous. Several treatments exchanging two to four plasma volumes per procedure and replacing with donor type or group AB FFP may be needed. However, there is no consensus as to the necessity or appropriateness of this treatment [2, 51].

Following the success of photopheresis in the treatment of cutaneous T cell lymphoma, this modality was also used in patients with GVHD, which can be viewed as a T cell dyscrasia with cutaneous manifestations [52, 53]. In a recent study [54], 11 patients with cutaneous GVHD resistant to standard immunosuppressive drugs were treated with photopheresis. Skin lesions were completely cleared in 75% of patients with acute GVHD and in 70% of patients with chronic GVHD. Three patients were refractory to treatment. Photopheresis may benefit patients with cutaneous GVHD, and randomized controlled trials are warranted to establish the efficacy of this treatment.

### Refractoriness to Random-Donor Platelet Transfusions

Bensinger et al. [55] suggested a possible role for TPE in the treatment of platelet refractoriness in an uncontrolled series of 18 refractory patients. Eleven patients demonstrated some response to treatment (in terms of a rise in platelet count), but some of the responses were transient. The possible benefit from TPE remains speculative, as no confirmatory controlled studies have been published.

Extracorporeal immunoadsorption with staphylococcal protein A has produced decreases in platelet autoantibodies, platelet-associated IgG, and CICs in patients with idiopathic thrombocytopenic purpura (ITP) [56]. Encouraged by reports of success of this mode of treatment in ITP [56], Christie et al. evaluated the possible contribution of extracorporeal immunoadsorption to the
management of refractoriness to random-donor platelet transfusions [57]. They reported on 10 thrombocytopenic patients. Nine of these were also refractory to HLA-matched platelets, and nine had been previously treated with steroids, IVIG, and/or other forms of immunosuppressive therapy. Antibodies to HLA class I antigens, ABO antigens, and/or platelet-specific alloantigens could be demonstrated in the serum of 8 of 10 patients. Enrolled subjects received from one to 14 offline or on-line treatments, and six of them responded to therapy. Christie et al. [57] concluded that, although the mechanism of action of protein A column therapy is poorly understood, this treatment may be an effective means of increasing platelet counts and responsiveness to platelet transfusions.

However, another group, which reported on three refractory patients, concluded that protein A immunoadsorption is not beneficial in this situation [58]. Refractoriness to random-donor platelet transfusions is a frequent and important clinical problem in tertiary care medical centers, and any possible benefit from immunoadsorption in this setting needs to be investigated in large, multicenter randomized controlled trials.

**REFERENCES**


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