REVIEW

Therapeutic Plasma Exchange: For Cancer Patients

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Abstract: Therapeutic plasma exchange is used as a trial method for the treatment of cancer patients. Therapeutic plasma exchange uses in vitro technology to remove pathogenic factors in the plasma, returning the replacement and remaining components to the patient to facilitate cure. In the effort to explore new methods of cancer treatment, the introduction of therapeutic plasma exchange brings new hope for cancer treatment; however, the current evidence supporting therapeutic plasma exchange is controversial, and most of the evidence comes from observational studies, lacking large prospective randomized trials. Therefore, this review attempts to focus on the main indications of therapeutic plasma exchange for the treatment of tumors and their complications, including hematological tumors (multiple myeloma cast nephropathy and hyperviscosity syndrome), nervous system tumors (myasthenia gravis associated with thymoma, paraneoplastic neurological syndrome, Lambert–Eaton myasthenia syndrome, and anti-N-methyl-D-aspartate receptor encephalitis), overdose of chemotherapy drugs. In addition, the issues of side-effects and safety in the use of therapeutic plasma exchange are also discussed. However, well-designed prospective trials are needed to better define the role of therapeutic plasma exchange in cancer.

Keywords: therapeutic plasma exchange, plasma exchange, double-filtration plasmapheresis, plasma adsorption, indications, complications

Introduction

Cancer is becoming the second most common cause of death in the world. Traditional treatment methods include surgery, chemotherapy, radiotherapy, and hormone therapy, as well as various combination therapies.[1] Modern treatment approaches are multi-model, including emerging molecular and targeted therapies,[2] but these methods have limited effectiveness in improving survival. New ways to slow the progression of cancer and even to cure it are being sought. Therapeutic plasma exchange (TPE) therapy is one such way. Plasma replacement therapy has been in development for more than 50 years and has become a common and relatively safe treatment.[3,4] It can be used as a treatment of first choice in some diseases such as thrombotic thrombocytopenic purpura,[5,6] but is usually used as an adjunct to treatment.

TPE is a blood component apheresis technology used mainly for symptomatic treatment; it is used to remove pathological plasma while supplementing a certain amount of normal plasma or solution to treat patients with cancer and related complications.[7] TPE can eliminate macromolecular proteins and antibodies, and it is precisely because of this immunological property that it is useful in the treatment of patients with malignant tumors.[8]

TPE therapy plays an important role in the treatment of a variety of tumors, such as multiple myeloma and Waldenström macroglobulinemia, and can also be used to eliminate paraneoplastic syndromes and excessive levels of chemotherapeutic drugs.[9–11] The TPE process involves removing or reducing the concentration of harmful substances in the plasma. First, the whole blood is passed through an external filter to separate the plasma and cellular components. After the removal of part of the harmful or pathological components in the plasma, the cellular components and replacement fluid are mixed on returning the remaining plasma to the body. The most commonly used TPE types are plasma exchange (PE), double-filtered plasmapheresis (DFPP), and plasma adsorption (PA).[12]

This review briefly summarizes these three methods, examines the application of TPE in tumor treatment to understand its therapeutic effects, and speculates that TPE alone or in combination with other therapies can replace or

Table 1 The Different Ways of Therapeutic Plasma Exchange

Modalities	The Molecular Weight of the Removed Component	Indication	Alternative Solution	Efficiency	Specificity
Plasma exchange (PE)	Small and large molecules no larger than a few million Daltons	·Thrombotic microangiopathy (TMA) ·Acute liver failure ·Diseases of the nervous system ·Myeloma cast nephropathy	• Fresh frozen plasma (FFP) • 4–6% Albumin solution	High	Low
Double-filtration plasmapheresis (DFPP)	A relatively large molecule in plasma	Hyperviscosity syndrome (HVS)	Usually a solution of albumin	Middle	Middle
Plasma adsorption (PA)	Selective adsorption, such as autoantibodies, immune complexes, etc	·Myasthenia gravis (MG) ·Guillain Barre syndrome (GBS)	–	Low	High

improve current tumor treatments. In addition, the side-effects of TPE have also been included in the scope of this review.

TPE Modalities

The most commonly used TPE methods include PE, DFPP, PA.[13] Each of these three methods has advantages and disadvantages, depending on the principle and specificity of the removal of the target substance. Table 1 illustrates the differences in molecular weight of the removed components, indications, replacement solutions, and removal efficiency and the specificity of the three methods.

Plasma Exchange (PE)

After the introduction of DFPP, PE was also known as single-filter plasmapheresis (SFPP).[14] It is a method of treating isolated blood and replenishing a replacement solution of the corresponding component, which is primarily used to eliminate pathogenic material and provide the necessary ingredients.[12] The PE principle is shown in Figure 1.

The sieving coefficient of PE for most plasma proteins is 0.9–1.0, and the selectivity is low, so both large and small molecules can be filtered out.[15] In addition to removing pathological solutes, PE may also have immunomodulatory effects, such as removing immune-related molecules in the circulation and enhancing the sensitivity of cells to immunosuppressive agents.[16]

Although desirable properties of PE replacement fluids have been proposed, it is difficult for the actual replacement fluids to meet these standards.[12] For this reason, in practical applications, fresh frozen plasma (FFP) or a 4–5% human albumin solution that meets the patient's pathophysiological conditions is often used as an alternative liquid.[17] In addition, the choice of vascular access is related to the physiological condition of the patient as well as the frequency and velocity of the PE.

Double-Filtration Plasmapheresis (DFPP)

DFPP does not remove all plasma but semi-selectively removes high molecular weight components such as immuno-globulins, immune complexes, and lipoproteins in the plasma.[18] Therefore, DFPP selectively removes macromolecules while reducing the use of replacement fluids.

As shown in Figure 2, DFPP requires the passage of the patient's blood through two filters.[19] The two filters have different pore sizes. The first filter is the same as the plasma separator in PE and is used to separate the tangible components of blood and plasma. The second filter is the plasma fractionator, which filters the plasma components according to their molecular weights. The concentrated plasma portion containing relatively high molecular weight proteins (such as immunoglobulins) is discarded while the plasma rich in albumin is filtered and returned to the patient with the required volume of replacement fluid.
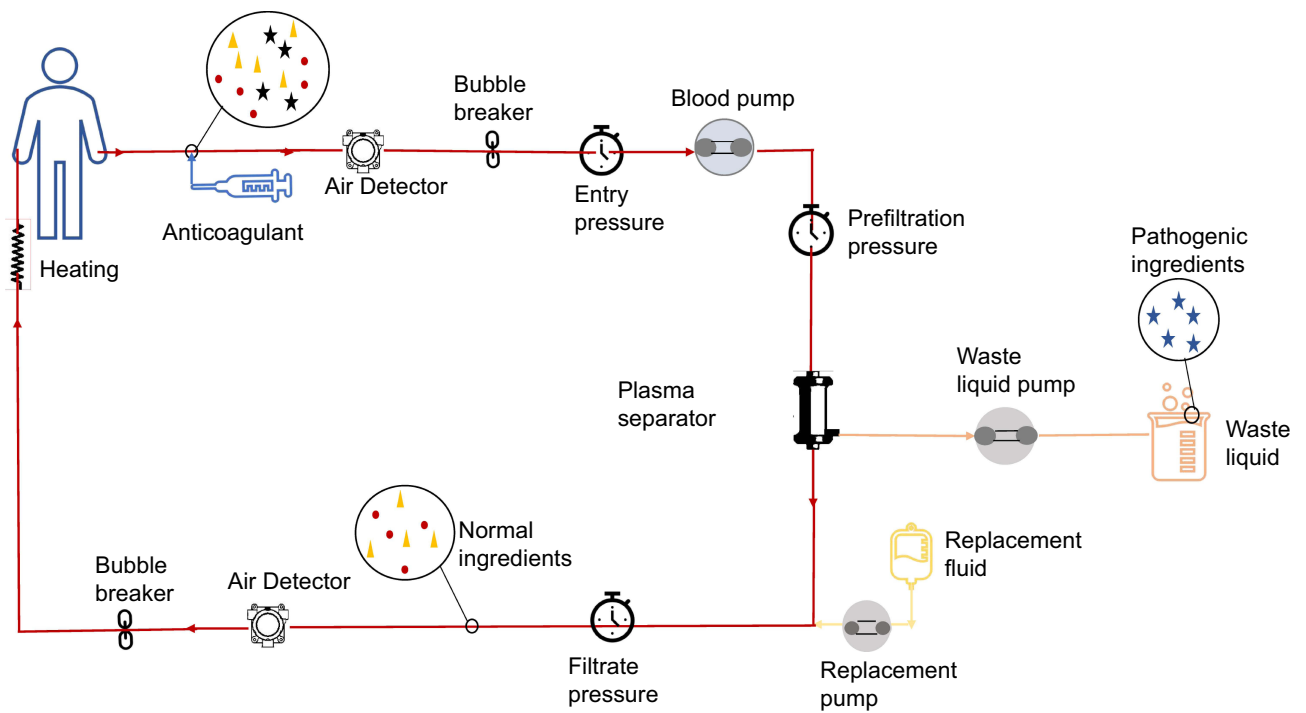
Figure 1 The principle of plasma exchange (PE). The blood is separated from the body, processed and then passed through a single plasma separator. The filtered blood components are returned to the body together with the replacement fluid.
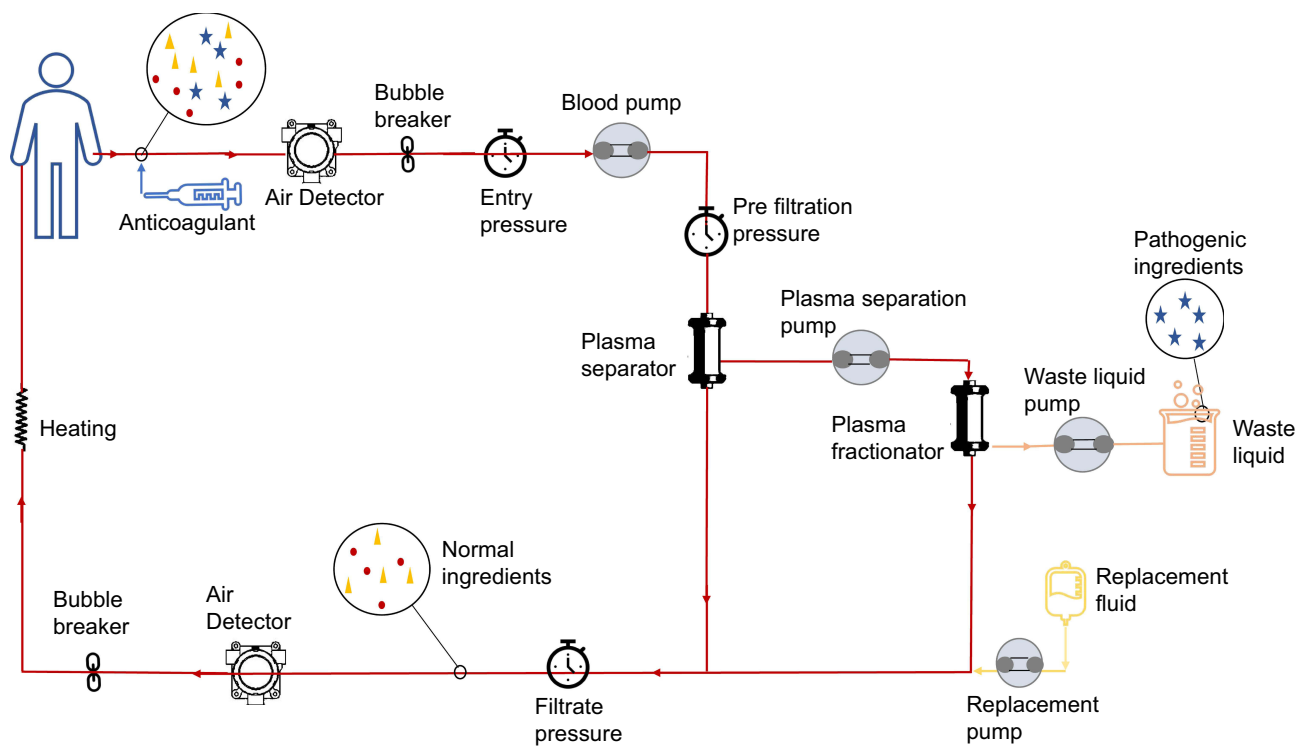

Figure 2 The principle of double filtration plasmapheresis (DFPP). The blood passed through the plasma separator and then passed through the plasma fractionator, and the filtered components were also returned to the human body after being combined with the replacement solution.

Because DFPP can greatly reduce the levels of autoantibodies in the circulation, it has obvious efficacy in reducing the titers of autoantibodies and immunoglobulins.[20] In addition, DFPP may also have the ability to regulate the function of regulatory T cells (Tregs) and increase the proportion of these cells in the plasma.[21]

Plasma Adsorption (PA)

PA is a process of selective adsorption and removal of pathological substances using adsorbents.[22] It does not require the addition of replacement fluids, thus minimizing the loss of useful plasma proteins and avoiding the possibility of viral infections or allergic reactions to albumin, Figure 3.

There are two types of PA adsorbents, biological and non-biological adsorbents.[23] The affinity of biosorbents is higher than that of non-biosorbents because biosorbents rely on biological reactions for adsorption while non-biosorbents rely on physical and chemical binding forces. However, biosorbents are difficult to sterilize and are biochemically unstable whereas non-biosorbents are not only stable but also suitable for sterilization.

PA is widely used in nervous system diseases,[24] including Guillain-Barre syndrome (GBS),[25] chronic inflammatory demyelinating neuropathy (CIDP),[26] multiple sclerosis (MS),[27] neuromyelitis optica (NMO),[28] rheumatic diseases (such as lupus nephritis),[29] and other refractory diseases. In addition to eliminating pathogenic agents, PA is thought to result in alterations in the balance of cytokines associated with autoimmunity by clearing antibodies in large quantities, such as stimulating the upregulation of anti-inflammatory cytokines (such as interleukin - 10 (IL-10)) and reducing pro-inflammatory factors (for example, interleukin - 18 (IL-18) and interleukin - 17 (IL-17)).[30]

Application of TPE in Tumor Therapy

Due to its ability to eliminate pathological molecules, TPE has played a major role in the treatment of a variety of tumors including hematological and neurological tumors. Table 2 shows the ASFA staging and classification of the diseases discussed in this review.[31]
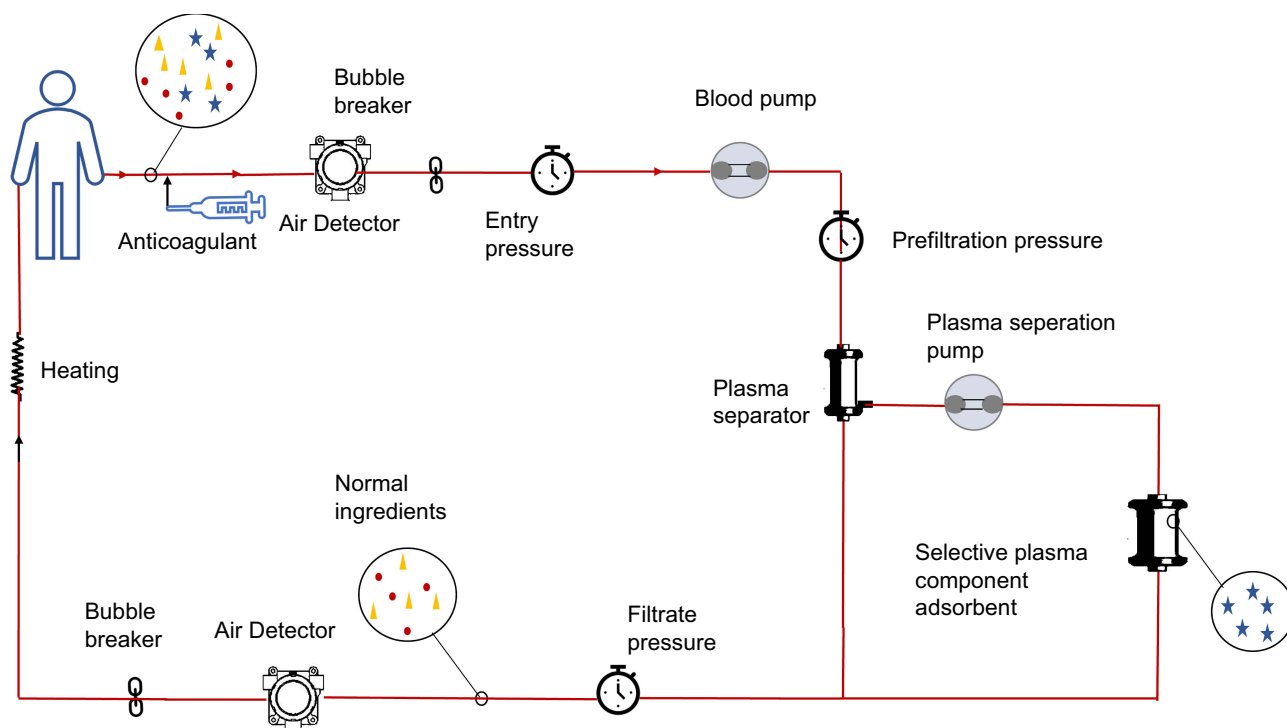

Figure 3 The principle of plasma adsorption (PA). Blood that has gone through a plasma separator is washed out of the blood with selective adsorbents and returned directly to the body.

Table 2 Indications for TPE in Patients with Cancer

Disease	Indication	Category	Grade[a]
MCS		II	2B
HVS	Symptomatic	I	1B
	Prophylaxis for rituximab	I	1C
MG	Acute, short-term treatment	I	1B
	Long-term treatment	I	2B
PNS		III	2C
LEMS		II	2C
NMDAR		I	1C

Notes: [a]Digital representation the strength of recommendation: strong 1 vs weak 2; the letters denote the strength of evidence support, A, B, C respectively represents high, middle and low evidence support.

Hematological Tumors
Myeloma Cast Nephropathy

Multiple myeloma (MM) is a malignant disease of plasma cells characterized by abnormal myeloid plasma cell proliferation and the development of monoclonal or excessive free light chains (FLCs, or M proteins). More than 50% of patients with multiple myeloma develop renal insufficiency and the prognosis of these patients is closely related to the reversibility of the renal failure.[32,33] Cast nephropathy is a potentially reversible cause of renal failure. It is usually caused by increased renal tubular filtration of FLCs.[34]

Supportive treatment for multiple myeloma is the most common indication of TPE in hematology. In addition to correcting hypercalcemia and immediate reduction in the blood volume,[35] TPE also plays an important preventive role in the management of multiple myeloma patients. Removal of the FLCs and recovery of renal function are key to the treatment of renal failure caused by cast nephropathy. TPE therapy has been shown to reduce renal damage caused by FLCs, reduce tube formation, and prevent the progression of renal failure in patients with myeloma. It was first used in 1976 to treat acute renal failure caused by multiple myeloma.[36] However, three randomized controlled trials on the efficacy of TPE in multiple myeloma cast nephropathy have provided conflicting results. These three randomized controlled trials studied the effect of PE on cast nephropathy. Two of the trials involved 29 and 21 participants, but produced conflicting results.[37,38] A subsequent relatively large randomized controlled trial (97 participants) conducted by Clark et al did not find a substantial advantage of TPE in multiple myeloma.[39]

Leung et al demonstrated that TPE restored renal function solely by reducing the levels of circulating light chains in patients with biopsy-confirmed cast nephropathy.[40] It is worth noting that none of these three randomized controlled trials confirmed tubular nephropathy by biopsy and nor measured the FLC levels. Since the most important factor in determining survival continues to be a patient's response to chemotherapy, renal biopsy is recommended to determine whether each patient should be treated with TPE in combination with chemotherapy.[41] TPE does not reduce the tumor burden and does not have a clear benefit in extending survival, so it is only recommended for specific subgroups such as patients with very high circulating light chain levels and patients with severe renal failure and is not recommended for the routine treatment of multiple myeloma.[42,43] At present, it is accepted that concurrent chemotherapy and TPE can improve the prognosis before the blood FLC level is significantly reduced. The improved outcomes and survival of patients with cast nephropathy were significantly associated with reduced FLCs. Although it remains controversial whether TPE alters renal outcomes at present, it is well established that TPE significantly reduces FLCs and that the decrease is more profound as the number of TPE increases. This allows TPE to improve kidney function when combined with chemotherapy, thus prolonging the patient's survival.[44,45] Proteasome inhibitors improve cast nephropathy through anti-inflammation of renal interstitium and thus have an extremely important role in the treatment of myeloma patients with renal failure.[46,47] We can hypothesize that in combination with plasma exchange, which removes the light chain, the kidney damage of myeloma is further alleviated. However, systematic studies and relevant guidelines in this area are

lacking so far. Therefore, in the following studies, we can conduct relevant preclinical and clinical experiments to verify this conjecture.

Hyperviscosity Syndrome

Hyperviscosity syndrome (HVS) refers to the physiological changes and clinical sequelae associated with impaired blood flow caused by hyperviscosity of the plasma.[48] Since Waldenstrom first described macroglobulinemia, symptoms of high viscosity have been observed in patients.[49,50] The most common monoclonal proteins that cause high viscosity are IgG, IgA, and IgM. IgM has a profound effect on blood cells and blood flow. Although serum viscosity initially increases linearly with increasing IgG levels it increases exponentially when the IgM concentration exceeds 3g/dL, leading to symptoms associated with high viscosity.[48,51,52] Waldenstrom macroglobulinemia (WM, also known as the lymphatic plasma cell lymphoma, LPL) is a monoclonal lymphatic proliferative disease that occurs in about 2% of non-Hodgkin's lymphoma cases and is characterized by the synthesis and secretion of large amounts of monoclonal IgM.[53,54] WM accounts for between 10% and 30% of cases of symptomatic high blood viscosity, while multiple myeloma accounts for between 2% and 6%.[55]

TPE can not only control symptomatic HVS in patients by the rapid reduction of paraprotein levels but can also be used for the prevention and long-term treatment of the condition.[56] The immediate treatment of symptomatic HVS is aimed at reducing blood viscosity to control the symptoms while long-term treatment is aimed at controlling the underlying disease to prevent the production of monoclonal proteins.[57] The treatment strategy for symptomatic HVS should be guided by a target serum viscosity. Since 70–80% of macromolecular proteins are present in blood vessels, a single exchange can remove up to 65% of these proteins in the body, typically 1–1.5 plasma volumes per course of exchange, reducing viscosity by 20%-30%, and two to three TPE sessions can reduce the serum IgM levels by 30%-60%.[52,56,58] In addition, the decrease in IgM was associated with a decrease in the incidence of infusion reactions, primarily allergic reactions, in rituximab therapy for lymphoplasmacytic lymphoma.[59,60] Therefore, in the treatment of lymphatic plasmapheresis lymphoma, the combination of rituximab and plasmapheresis can be regarded as a new treatment method. Because TPE does not affect the underlying cause of the disease, chemotherapy is usually begun at the same time as TPE. Usually, it is only necessary to control the viscosity below the symptom threshold in patients, rather than to reduce it to normal. Keeping the serum viscosity below the threshold of symptoms in each patient can effectively prevent the recurrence of HVS.[48,61]

Neurological Tumors

Thymoma-Related Myasthenia Gravis

Thymoma is a rare malignant tumor of the thymus epithelium and is a common primary tumor of the mediastinum. Myasthenia gravis (MG) is the typical autoimmune manifestation of thymoma.[62] About 35% of thymoma patients have myasthenia gravis.[63] MG is frequently caused by autoantibodies against the components of nicotinic acetylcholine receptor (AChR) on the postsynaptic membrane of the neuromuscular junction and is characterized by fatigue and muscle weakness.[64–66] Apart from acetylcholine receptor autoantibodies (AChR-Ab), presynaptic membrane antibodies (PRSM-Ab) and anti-titin antibodies (Titin-Ab) may also be involved.[67]

TPE has become the standard treatment for MG. The indications for TPE include MG crisis, acute exacerbation of MG, and optimization of clinical status before thymectomy.[68] Since TPE can relieve symptoms by reducing the titer of AChR-Abs in MG patients, plasma exchange has since been recommended for the treatment of thymoma-associated MG as well as for myasthenic crisis.[69,70] TPE is also used as a preoperative preparation for thymoma resection, reducing the likelihood of myasthenic crisis and reducing the duration of mechanical ventilation (MV) and intensive care unit (ICU) hospitalization.[71,72]

However, the available evidence indicates that TPE should only be used as a short-term therapy for MG since it can only improve the redistribution of AChR-Abs but cannot prevent their resynthesis.[73] T lymphocytes (such as thymocytoma-derived CD4+T cells) and B lymphocytes as well as cytokines (such as IL-8 and IL-10) are involved in the occurrence and development of MG.[21,30,74,75] In addition to the elimination of pathological autoantibodies, TPE can also up-regulate immune tolerance and eliminate cytokines involved in MG development to achieve therapeutic

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effects.[76] In addition, a study has shown that when DFPP is used to treat MG caused by thymoma, it can more effectively increase the expression of Treg cells, thereby benefiting MG patients through immunomodulatory effects.[21]

Notably, in one case report, TPE not only reduced the size of the thymoma lesion in the patient but also restored the patient's muscle strength.[77] Munakata and Nagane Y observed the efficacy of combined therapy with methyl-potent (HMP) MG (TPE+HMP) immediately after TPE.[78,79] In the absence of sufficient large randomized controlled trials to evaluate the long-term outcomes of TPE in MG patients, due to the efficacy of this method has been proven, the feasibility of TPE for combination therapy in MG patients has become a new consideration.

Paraneoplastic Neurological Syndrome

Paraneoplastic neurological syndrome (PNS) is a malignancy-associated syndrome that has been shown to be immune-mediated, yet affects any part of the nervous system, from nerves to muscles.[80,81] About 50% of PNS patients possess anti-neurogenic autoantibodies that react with tumor antigens.[82] The disease is caused by cross-reactions between the circulating antibodies and antigens expressed by the tumor cells. The most important relevant antibodies are anti-Hu (ANNA1) and anti-Yo (PCA1).[83] PNS can be associated with any type of malignancy, and the most common tumor associated with PNS in adults is small cell lung cancer (SCLC).[84]

Since the effectiveness of TPE in reducing autoantibodies and immunoglobulin titers has been confirmed by many reports, TPE has been attempted as a treatment for PNS; the therapeutic effect of TPE on PNS, however, is mixed. There are individual cases showing the therapeutic effect of TPE on PNS and some researchers believe that TPE may mitigate the rapid development of PNS in patients without anti-neuronal antibodies, but most scholars believe that TPE cannot influence paraneoplastic symptoms.[85–89] At present, the best treatment for PNS symptoms is to identify and eradicate potential malignant tumors. Nevertheless, patients with PNS symptoms should consider early active immunosuppression before malignant tumors are confirmed and TPE is often used to initiate immunosuppression.[81,90] Interestingly, human chorionic gonadotropin (hCG) may be able to change the process of Hu-PNS, because hCG may have immunomodulatory activity.[91]

Lambert–Eaton Muscle Weakness Syndrome

Lambert–Eaton myasthenia syndrome (LEMS) is an autoimmune disease that occurs in the neuromuscular junction and belongs to the paraneoplastic syndromes. The disease is mainly caused by autoantibodies against the presynaptic anti-P/Q type voltage-gated calcium channel preventing the release of acetylcholine-containing vesicles, resulting in muscle weakness.[92,93] Fifty to sixty percent of LEMS cases are tumor-related, the most important of which is small cell lung cancer (SCLC).[94] When LEMS and SCLC coexist, the treatment of SCLC is the priority.[95] The second is to choose 3,4-diaminopyridine (3,4-DAP) to strengthen neuromuscular transmission as a symptomatic treatment.[96] TPE and other immunomodulatory treatments mainly participate in the comprehensive treatment of LEMS after the failure of symptomatic treatment by reducing the autoantibody titer.[97]

However, TPE is not the standard treatment for LEMS. There are only a few studies that have demonstrated the efficacy of TPE in LEMS,[98–100] and no prospective controlled evaluation has been published to date. Therefore, future work can be devoted to the evaluation of the efficacy of TPE on LEMS.

Anti-N-Methyl-D-Aspartate Receptor (Anti-NMDAR) Encephalitis

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was first reported as a paraneoplastic syndrome.[101,102] It is currently believed that the disease is an immune-mediated encephalitis and the cause of the disease is the development of autoantibodies against the synaptic NMDA receptor NR1 subunit on the cell surface.[103–105] Ovarian teratomas have been shown to express NMDA receptors and, therefore, have a strong correlation with anti-NMDAR encephalitis.[106] Thirty-five to sixty percent of anti-NMDAR encephalitis patients have potential tumors, 96% of which are ovarian or extra-ovarian teratomas and tumors.[107,108]

In addition to removing the tumor to eliminate the autoantibody production, TPE is usually the first-line treatment for anti-NMDAR encephalitis. Although some case reports have indicated that TPE treatment is ineffective for the disease,

a large number of studies have proved its efficacy. In addition, based on the therapeutic efficacy of TPE, ASFA classifies TPE as a Class I indication.[31]

Application of TPE in the Case of Cisplatin Overdose

Cisplatin is the first heavy metal-based compound to have demonstrated anti-tumor activity.[109] Its anti-cancer activity relies on the induction of apoptosis in cancer cells. The platinum-based compound is widely used in treating a variety of human cancers including cancers of the bladder, head and neck, lung, ovary, and testis.[110] Ninety percent of the cisplatin that enters the body binds to circulating proteins, and most of this binding is irreversible. Although the reactivity of protein-bound cisplatin is lower than that of the unbound state, there is an exchangeable platinum pool that leads to additional toxicity. Occasionally, excessive cisplatin can cause toxic manifestations including vomiting, bone marrow suppression, and organ toxicity.[111] Due to the dose-dependent nature of cisplatin, the severity of toxicity (including nephrotoxicity, gastrointestinal toxicity, neurotoxicity, ototoxicity, and myelotoxicity) of cisplatin is directly related to dose and time.[112,113] Therefore, in the treatment of cisplatin in humans, the balance between anti-tumor efficacy and toxicity is always pursued to avoid more toxic and side effects. To alleviate the toxic side effects of cisplatin, scholars are conducting continuous research.

Due to its ability to clear plasma, TPE may be beneficial for the treatment of cisplatin excess. Clinical data have shown that TPE can significantly reduce the cisplatin serum concentration, reducing and eliminating the toxicity caused by excessive cisplatin.[114]

Guidelines and large randomized trials on the use of TPE for the treatment of cisplatin overdose are lacking, but there is already practical evidence that PE can be used for the treatment of cisplatin overdose, and we collected the cases published to date (Table 3). In seven cases, including a 13-year-old girl, although cisplatin overdose produced a series of toxic side-effects such as impaired renal function and hearing loss, most of the symptoms were reduced or even eliminated after TPE and other symptomatic treatments. In all cases, only one patient died.[115] This patient was found to have renal insufficiency within 48 hours of the poisoning, and severe sepsis and apnea occurred on the eighth and eleventh days. During the autopsy, high concentrations of cisplatin were found in the patient's heart and peripheral blood. Regrettably, no studies related to DFPP and PA have been found in this regard.

Table 3 Report on TPE for Cisplatin Overdose

Age	Sex	Cancer Types	Dosage	Treatment	IC	FC	Outcome	Reference
59	M	Esophageal carcinoma	300 ng/m^2	TPE+ GM-GSF	2979 ng/mL	185 ng/mL	Renal function recovered and partial remission of esophageal cancer was achieved	[116]
68	F	Ovarian cancer	280 ng/m2	TPE+HD+ GM-GSF+ Prednisone	2900 ng/mL	200 ng/mL	Hearing loss, no signs of recurrence of ovarian cancer	[117]
48	M	Laryngeal carcinoma	400 ng/m2	TPE+HD	2470 ng/mL	216 ng/mL	Full recovery without sequelae	[118]
63	M	Lymphoma	Total 750mg	TPE+HD+ N-acetylcytosine	–	–	Death	[115]
46	F	NSCLC	225 ng/m2	TPE+ Supportive care	–	–	Full recovery without sequelae	[119]
67	M	Esophageal carcinoma	240 ng/m2	TPE+ Intravenous hydration+ Chemical protectant	2350 ng/mL	110 ng/mL	There were no significant complications and only moderate hearing loss	[120]
13	F	Osteosarcoma	240 ng/m2	TPE+Chemical protectant	8500 ng/mL	110 ng/mL	He regained impaired kidney function and hearing	[121]

Abbreviations: IC, initial concentration, the initial plasma concentration of cisplatin; FC, final concentration, the final plasma concentration of cisplatin; M, male; F, female; HD, hemodialysis; GM-GSF, granulocyte macrophage colony stimulating factor; NSCLC, non-small cell lung cancer.

Adverse Events of TPE

Although there is currently a lack of relevant trials and guidelines, the current evidence provides us with a new therapeutic idea: to increase the dose of cisplatin in the target area without increasing the concentration of cisplatin in the peripheral blood in the treatment of cancer patients with conventional dose of cisplatin combined with TPE, to enhance the therapeutic effect without increasing the side-effects.

The overall incidence of TPE clinical adverse events is relatively low and serious complications are rare, but the treatment is not completely risk-free and may even be fatal in severe cases. The severity of adverse events is divided into four levels (Table 4).

Although the incidence is low, TPE complications may appear at each step, including the primary disease, the choice and amount of anticoagulants, the type of replacement fluid, the choice of vascular access, and the choice of TPE method.[122,123]

Among all patients undergoing TPE, patients with anti-NMDA receptor encephalitis have the highest risk of complications.[124]

There are also differences in the incidence of adverse reactions caused by different anticoagulants. Commonly used anticoagulants include citrate and heparin. When using sodium citrate, attention should be paid to monitoring the citric acid concentration to prevent citrate poisoning. At the same time, because citrate combines with calcium ions resulting in anticoagulant properties, the use of citrate can also cause hypocalcemia. The main problems related to heparin are bleeding and protamine neutralization.[125]

Albumin solutions and FFP are commonly used during the TPE process to maintain plasma volume and prevent hypotension and edema. Adverse reactions are usually mild to moderate and serious complications are rare. Although FFP is more effective than albumin in replenishing normal body fluids and immune components, it also leads to a higher incidence of adverse reactions, often resulting in anaphylaxis. As albumin solutions are inactivated, the incidence of anaphylaxis is lower than FFP but the risk of hypotension and metabolic alkalosis is higher.[124,126–128]

Peripheral venipuncture sites may cause peripheral soft tissue damage, bleeding, infection, catheter blockage, thrombosis, and even embolism. Related complications such as bleeding or hematoma caused by central venous access are also inevitable. In addition, the patient's anxiety during puncture may even induce a vasovagal response.[123,129,130]

Different TPE choices have different chances of causing adverse reactions. Centrifugation and filtration are the two main technologies used for plasma separation. Filtration results in almost twice the incidence of adverse reactions than centrifugation.[123,131] In addition, since there are fewer separators that can separate albumin, which has a similar molecular weight to the immunoglobulins present in autoimmune disorders, insufficient albumin supplementation during DFPP can easily lead to a loss of albumin and a decrease in blood volume.[132] Because DFPP can selectively remove

Table 4 Severity of Adverse Events

Grade	Severity	Treatment Requires	Classical Symptom
Grade I	Mild	No intervention required	Week of mouth sting
Grade II	Moderate	Need intervention but can complete treatment	·Paresthesia, ·Mild hypotension, ·Nausea, ·Urticaria
Grade III	Severe	Procedure interrupted or abandoned	·Prolonged vagal response time, ·Decreased level of consciousness, ·Muscle contractions, ·Hand and foot convulsions, ·Seizures, ·Arrhythmia
Grade IV	Fatal	Lethality	No response to treatment

macromolecular immunoglobulins, high molecular weight coagulation factors cannot be spared. According to reports, DFPP can significantly reduce the concentration of FXIII and fibrinogen, leading to the risk of bleeding.[133,134] In comparison, the adverse reaction rate of PA is significantly lower than that of PE and DFPP. Adsorbents are needed in the PA process, including both biosorbents and non-biosorbents. Although the affinity of biosorbents is higher than that of non-biosorbents, they are difficult to sterilize, resulting in a higher risk of infection.[23] Although their incidence is relatively minor, complications such as hypotension, headache, and nausea, as well as fibrinogen depletion, anticoagulation, and catheter-related bleeding are inevitable,[123] of which the most common complications are hypotension and fibrinogen depletion.[135] However, antithrombin and most other coagulation factors are not easily reduced.[136]

Due to the large amount of fluid in and out, serious cardiovascular events such as dehydration, congestive heart failure, pulmonary edema, and pulmonary embolism, as well as serious complications such as cerebrovascular accidents and deaths, are extremely low, but they cannot be ignored. Therefore, an unstable hemodynamic state and severe infection are listed as a contraindication for TPE.[137]

Although the most common TPE complications are mild, the risk of severe complications should be taken seriously. For the potential complications that may occur during the TPE process, symptomatic measures can be taken to prevent their occurrence and reduce their incidence. If conditions permit, a more appropriate TPE method or PA with fewer complications can be selected. In addition, medical staff should be vigilant in identifying the symptoms of complications during the TPE process to prevent the development of serious or even life-threatening conditions.

Conclusions

TPE is a relatively safe blood purification method, which is widely used for treating various systemic diseases. Nowadays, although some cancers can be cured, there are others that do not respond to traditional treatment methods, and the temporary treatment of cancer is relatively limited. The development of new treatment methods has, therefore, become a top priority. TPE treatment, because of its ability to remove pathological components, has become an important treatment option for complications related to malignant tumors. However, there is currently a lack of sufficiently strong evidence to prove that TPE can reduce the tumor burden and improve the survival of patients with malignant tumors. Therefore, TPE tends to be used more for the control of symptoms caused by malignant tumors and the prevention of certain symptoms, such as reversing renal failure in patients with multiple myeloma by removing circulating light chains, controlling and preventing symptoms in patients with HVS, and removing autoantibodies to reduce and prevent complications and paraneoplastic syndromes in patients with nervous system tumors. It is important that the role of traditional treatment methods is not ignored when TPE is used for treatment. It is worth noting that the immune effects of TPE include regulating immune cell activity, clearing immune factors, and reducing autoantibody titers and immunoglobulin concentrations.

This review lists the advantages and disadvantages of the various TPE methods. Medical staff can avoid unnecessary side-effects and maximize the therapeutic effect of TPE by considering the specific characteristics of the TPE method used. Only a few of the diseases applicable to TPE treatment mentioned in this review are included in the ASFA guidelines, with the rest not having been approved by ASFA due to a lack of evidential support. Therefore, in future work, we need more prospective randomized controlled trials to define application of TPE in various diseases. In addition, this review introduces the application of TPE to a typical chemotherapeutic drug, cisplatin, overdose. Many reports have shown that TPE has a significant effect in eliminating the toxic side-effects caused by cisplatin overdose without producing new sequelae, thus TPE may become a way of reducing these side-effects besides chemical antidotes. Although TPE is relatively safe, various complications are inevitable. With careful operation and timely treatment of minor complications, we should be alert to the presence of serious complications and the evolution of mild to moderate complications and develop appropriate treatment plans. Careful inspection and monitoring is thus an effective prerequisite for the successful execution of TPE.

With the diversity of cancer treatments, new therapeutic approaches are imminent. Since the advent of TPE, this modality has been used in the treatment of many diseases. With the development of medicine, TPE is still the first-line treatment for some diseases, although other better treatment strategies are already available for some indications of TPE. In this paper, we introduce the use of TPE in tumor treatment, summarize its therapeutic effects, and speculate that TPE can be used individually to replace or in combination to assist existing methods of tumor treatment, thus demonstrating

the safety and clinical efficacy of TPE in the treatment of tumors and their complications. This may play a guiding role for the use of TPE in malignancy.

In our conclusion, TPE is not a separate treatment, it is part of a patient-centered comprehensive treatment. In addition, due to the limited number of analyzed articles, different research methods, and possible publication deviations, the above conclusions should be interpreted more cautiously.

Abbreviations

TPE, Therapeutic plasma exchange; PE, plasma exchange; DFPP, double-filtered plasmapheresis; PA, plasma adsorption; SFPP, single-filter plasmapheresis; FFP, fresh frozen plasma; GBS, Guillain-Barre syndrome; CIDP, chronic inflammatory demyelinating neuropathy; MS, multiple sclerosis; NMO, neuromyelitis optica; IL-18, interleukin – 18; IL-17, interleukin – 17; MM, Multiple myeloma; FLCs, free light chains; HVS, free light chains; WM, Waldenstrom macroglobulinemia; LPL, lymphatic plasma cell lymphoma; MG, myasthenia gravis; AChR, acetylcholine receptor; AChR-Ab, acetylcholine receptor autoantibodies; PRSM-Ab, presynaptic membrane antibodies; Titin-Ab, anti-titin antibodies; MV, mechanical ventilation; ICU, intensive care unit; PNS, paraneoplastic neurological syndrome; SCLC, small cell lung cancer; hCG, human chorionic gonadotropin; LEMS, Lambert–Eaton myasthenia syndrome; 3,4-DAP, 3,4-diaminopyridine; anti-NMDAR, Anti-N-methyl-D-aspartate receptor.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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