

High-dose Cyclophosphamide Without Stem Cell Rescue in Autoimmune Diseases: A Systematic Review

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Abstract

High-dose cyclophosphamide without stem cell rescue is a radical therapy for refractory autoimmune diseases. The objective was to review the results of high-dose cyclophosphamide without stem cell rescue in autoimmune diseases. PubMed, Scielo, and Embase databases were systematically searched for articles on high-dose cyclophosphamide without stem cell rescue treating autoimmune diseases between 1966 and September 2022. Twenty-nine studies were identified, including a total of 404 patients. The diseases most studied were systemic lupus erythematosus (n = 113), multiple sclerosis (n = 99), aplastic anemia (n = 86), and myasthenia gravis (n = 33). Most authors used the posology of 50mg/kg/day over four days of cyclophosphamide associated with Mesna, prophylactic antibiotics, G-CSF (granulocyte colony-stimulating factor), and support of red blood cells, and platelet transfusion. The most common side effects were febrile neutropenia, alopecia, and gastrointestinal complaints. Regarding outcomes, most of the studies demonstrated improvement of the underlying autoimmune disease, some long-lived, but relapses and failures were also identified. In conclusion, high-dose cyclophosphamide without stem cell rescue is an effective option for treating severe autoimmune diseases. This procedure is relatively safe when the appropriate supportive care measures are taken.

Keywords: Cyclophosphamide, high-dose cyclophosphamide, autoimmune diseases, rheumatic diseases

Introduction

Cyclophosphamide (CYC) is widely used in internal medicine to treat severe autoimmune diseases.^{1,2} This drug interferes with cellular DNA synthesis in rapidly dividing cells, leading to cell death; targeting immune cells offers a rationale for its use in autoimmune conditions.³

Due to its potent immunosuppressive activity, this drug is the backbone of the conditioning regimen in autologous stem cell transplantation. However, it has been successfully used without stem cell rescue in autoimmune diseases. This is possible because CYC has a peculiar metabolism that allows it to cause lymphoablation, eliminate autoreactive cells, and spare the hematopoietic stem cells responsible for the reconstitution of bone marrow.^{4,5} CYC is inactivated by aldehyde dehydrogenase, an intracellular enzyme that converts CYC into carboxyphosphamide, a product without pharmacological properties. This enzyme is found in high concentrations in hematopoietic stem cells but not in lymphocytes, explaining the differential action of this drug in these two cell populations.^{4,7} Lymphoid cells, including natural killer cells, B and T lymphocytes, are rapidly destroyed by high doses of CYC; bone marrow reconstitution usually occurs within two weeks of infusion.⁴

The use of high-dose CYC without stem cell rescue started in patients with severe aplastic anemia⁸ and was gradually extended to other autoimmune diseases. Patients with systemic lupus erythematosus (SLE),² rheumatoid arthritis (RA),^{8,9} myasthenia gravis (MG),¹⁰ systemic sclerosis (SSc),¹¹ multiple sclerosis (MS),⁵ and several forms of pemphigus,¹²⁻¹⁴ among others, have benefited from this form of treatment.

Herein, a review of the CYC use without stem cell rescue is done, aiming to collect data on used regimens, safety, and efficacy.

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Methods

Literature Review

A systematic search of articles published in PubMed/MEDLINE, EMBASE, and Scielo from 1966 to August 2022 using the following MeSH entry terms: "high-dose cyclophosphamide without stem cell rescue" OR "immunoablative high-dose cyclophosphamide" AND "autoimmune diseases" OR "rheumatic disease" was done. High-dose CYC was at least 50 mg/kg/day for 4 days in all included studies.

No language restriction was established. The reference lists in the selected articles were examined to detect other publications. Two authors (JFC and TLS) initially executed the literature search and independently selected the study abstracts. In the second stage, the same reviewers independently read the full-text articles selected by abstracts. A third reviewer resolved divergences arising in consensus meetings. The authors followed PRISMA guidelines.¹⁵

Animal experiments, in vitro studies, revisions, and opinion papers were excluded. A standardized form to obtain the following information from selected articles was designed: authors, year of publication, number of studied patients, indication, demographic data, study design, cyclophosphamide posology, outcomes, adjuvant therapies, and side effects.

This article is based on previously conducted studies and does not contain new studies with human participants or animals performed by any of the authors.

Results

The search results are demonstrated in Figure 1.

Twenty-nine papers showed the experience of high-dose CYC without stem cell rescue treatment in 404 patients. Table 1 shows the

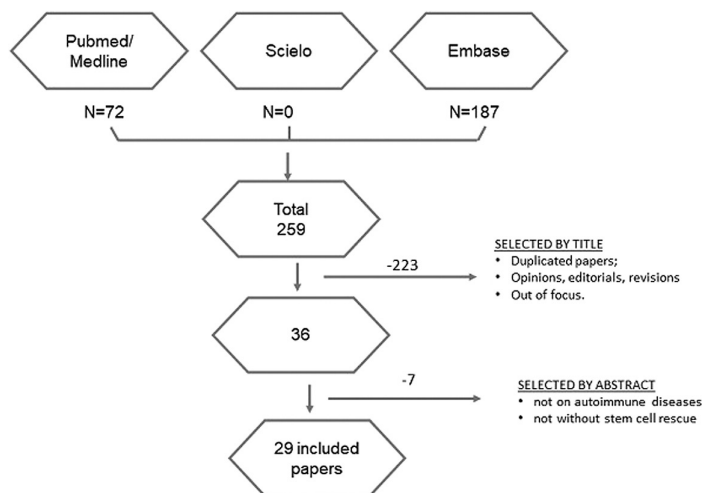


Figure 1. Flowchart showing the selection of the articles for the review.

distribution of studied individuals according to the different diseases. The most studied disease was SLE, followed by MS and aplastic anemia.

Seventeen case reports, case series,^{5,9,10,12-14,16-26} seven prospective open-label,^{8,11,27-31} uncontrolled studies, three retrospective studies,³²⁻³⁴ and two prospective randomized case-control studies: one with monthly infusion of high dose intravenous CYC, at regular doses,³⁵ and another that compared high dose CYC with and without association with cyclosporine,³⁶ were found.

Table 1. Autoimmune Diseases with High-dose Cyclophosphamide Treatment Without Stem Cell Rescue Were Studied

Disease	No. of Patients
Systemic lupus erythematosus	113
Multiple sclerosis	99
Aplastic anemia	86
Myasthenia gravis	33
Hemolytic anemia/Evans syndrome	19
Scleroderma	14
Polyneuropathies	12
Pemphigus	12
Autoimmune thrombocytopenia	5
Rheumatoid arthritis	6
Gastrointestinal disorders (collagenous gastroenteritis and autoimmune enteropathy)	3
Polymyositis	1
Granulomatosis with polyangiitis	1
Total	404

Figure 2 displays the distribution of these papers according to the year of publication.

Table 2 shows the summary of case reports, and Table 3 the main findings of the studies. The oldest patient that used high-dose CYC treatment was a 70-year-old male with paraneoplastic pemphigus,¹² and the youngest was a 6-year-old female with aplastic anemia;²⁷ the most extended follow-up was of 17.8 years described by Brodsky et al.³⁶

With rare exceptions, CYC was applied at the dose of 50 mg/kg/day for 4 days, associated with prophylactic antibiotics, G-CSF (granulocyte colony-stimulating factor), and red packed cells and platelets transfusions according to the patients' needs. Some authors described using trimethoprim-sulfamethoxazole or dapsone for *P. jirovecii* infection prophylaxis.^{5,9,10,32-34} Mesna, a thiol compound designed to function as a regional detoxicant of urotoxic oxazaphosphorine cytostatics,^{37,38} was also administered in most cases to reduce the chances of hemorrhagic cystitis caused by CYC. Despite this, 5 descriptions of that complication were identified: two by Brodsky et al.³³ and three cases by DeZern et al.³⁴

Most authors did not detail ovarian failure, which concerns those using CYC. Petri et al.³⁵ addressed this complication in their case-control study and found it present in 30% of their patients using high-dose CYC versus 43% of those using monthly infusions of this drug at a lower dosage. Cases of pregnancy after this form of treatment were described: one in a 29-year-old woman with SLE by Gladstone et al.¹⁸ 22 weeks after the treatment; another by Petri et al.,³⁰ also in a lupus patient, 3 years after treatment; and the third case by Drachman et al.¹⁰ in a female with MG.

Main Points

- High-dose cyclophosphamide without stem cell rescue is a radical therapy for refractory autoimmune diseases.
- Twenty-nine studies were found on systemic lupus erythematosus, multiple sclerosis, aplastic anemia, and myasthenia gravis.
- Most studies demonstrated improvement in the underlying autoimmune disease, some long-lived, but relapses and failures were also identified.

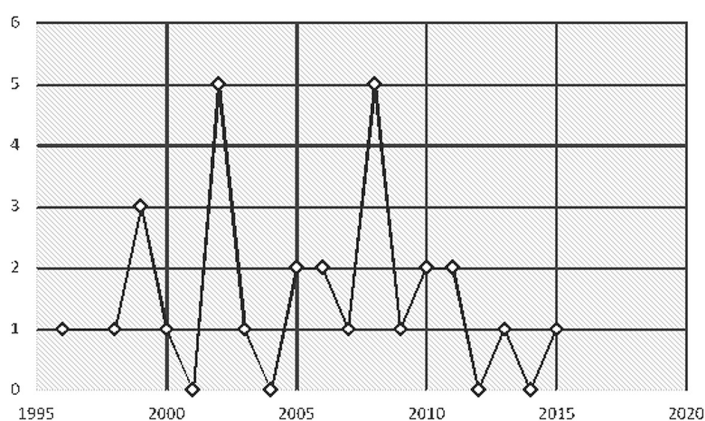


Figure 2. Publications on high-dose cyclophosphamide without stem cell rescue for autoimmune diseases according to the publication year (1996-2020).

The most common side effects were alopecia, gastrointestinal complaints, and infections, but cardiac and renal failure,^{16,18,20} transient hepatitis,¹⁶ and veno-occlusive liver disease¹⁸ were also reported. Moreover, the adjuvant treatment also led to complications such as a case of methemoglobinemia caused by dapsone³⁰ and AIDS acquired by blood transfusion.¹⁶

Few cases of deaths were identified; early in the treatment, they were secondary to infections^{11,34} and later, usually from complications of the underlying disease.^{8,34} Eight out of 29 studies described patients who needed intravenous antibiotics to treat severe infections during hospitalization.

In one of the studies, six patients measured tetanus and diphtheria antibodies after treatment, and the level was found to be low at 5, but the revaccination restored the immunity.¹⁰ Autoantibodies were also measured in this context: Cohen et al¹⁴ showed a decrease in their titer in the case of pemphigus foliaceus, and Drachman et al¹⁰ demonstrated a reduction in the titer of acetylcholine receptor (AChR) antibody levels and the anti-muscle-specific kinase (anti-MuSK) antibodies in myasthenia patients. Reductions in anticardiolipin antibody levels³⁴ were seen in lupus patients. Petri et al³⁰ observed that in 9/14 SLE patients, the anti-dsDNA titer decreased; in one, it was unchanged, but curiously, in 4 of them, the titer increased (1 with complete response; 2 with partial response and one with no response to the treatment).

DeZern et al³² addressed 8 cases treated with high-dose CYC more than once and described that all their patients responded to the first and second treatments; one patient treated three times failed in the third treatment.

Regarding treatment effectiveness, most cases had long-lasting remission of the underlying autoimmune disease^{10,18,20-23} or at least partial improvement, decreasing the need for glucocorticoid and immunosuppressive drug.^{12,13,19,25,31} However, relapses^{8,9,11,14} and even treatment failures^{16,28,30} were also noted.

Discussion

CYC is a potent alkylating agent that was initially developed and is still used to treat some kinds of cancer. It also has immunosuppressant properties that decrease the immune response to self and non-self antigens. This drug is used to treat several autoimmune diseases, usually orally or in intravenous pulses every 15 days to 3 months intervals.² Although efficient, these schemes have the disadvantage of favoring the appearance of side effects due to prolonged and repeated exposure to the drug. Hemorrhagic cystitis, infertility, and cancer induction are some of the most feared side effects of CYC.⁴ In this context, it is possible to speculate if the exposure to a single very high dose of CYC (with good management of acute toxicities) would not be safer than the repetitive monthly pulsed CYC.

The degree of immunological tolerance to the high dose of CYC and the determinants of a good response are unknown. While some patients have long-lasting remission, others achieve only partial remission or no remission. CYC acts through the ‘rebooting’ of the immune system; changes in the production of antibodies and autoantibodies have been demonstrated, although they are not universal.^{10,14,34} Petri et al. described one SLE patient in whom the anti-dsDNA titer was higher after the treatment, with the patient achieving a good response.³⁰

The use of high doses of CYC without stem cell rescue has been considered advantageous in autoimmunity compared to the regimen with autologous cells, as it avoids the risk of re-infusing autoreactive cells with the autograft—which could favor the autoimmune disease relapse.⁴ It is less toxic as patients do not undergo total-body irradiation or busulfan administration, which may destroy the stem cells and cause more profound immunosuppression.⁴ It also avoids the risk of GVHD (graft-versus-host disease), which is more common in allogeneic stem cell transplantation but may also occur in autologous transplantation. Auto GVHD is usually a mild disease that requires no treatment but, in selected cases, may be severe and ultimately fatal.³⁹ Finally, it also significantly reduces the cost of the procedure.⁴

Figure 2 shows that most papers on high-dose CYC without stem cell rescue were published between 2000 and 2010. None were identified in the last five years. The appearance of more potent drugs for treating autoimmune diseases, such as biologics, may have reduced the need for this therapy, as it is usually reserved for the most severe and recalcitrant cases. However, the long-lasting benefit, like those described by Brodsky et al,³³ is an attractive advantage rarely offered by the available alternative drugs. Therefore, studies showing how to select the cases that will respond to this therapy are welcome and could increase the future use of this treatment.

Regarding infection, Petri et al.³⁵ compared high-dose CYC with regular-dose monthly CYC use in 51 patients with lupus and found no difference between the two groups.

This review included only studies that treated autoimmune conditions with high-dose CYC without stem cell rescue and did not address oncological or hematological cases to properly evaluate the safety and efficacy of this therapeutic regimen in this context. In addition, it included all kinds of study designs, except reviews or editorials. Therefore, it is possible to assume that almost all published cases in this field were collected.

Limitations were also observed. Most of the identified papers were cases and series of case reports, precluding any definitive conclusions. In addition, only one study by Petri et al³⁵ compared high-dose CYC treatment with the classical treatments used in autoimmune diseases. Therefore, future studies are warranted,

Table 2. High Dose Cyclophosphamide Without Stem Cell Support in Autoimmune Diseases: Case Reports and Case Series

Author, Year	Study Design	n/Sex/Age	Indication	Dose	Side Effects	Outcome
Nousari et al., 1999 ¹²	Case report	n = 1; male; Age 70 years	Paraneoplastic pemphigus	Cy—50 mg/kg/day for 4 days + G-CSF started on day 10	Day 14: fever was treated with vancomycin, gentamicin, piperacillin, and doxycycline. Prophylactic acyclovir, norfloxacin, dapsone, and fluconazole were added.	Partial healing of his oral lesions; Required use of cyclosporine later
Breban et al., 1999 ⁹	Case series	n = 4; Sex NA; mean age 48 years	Seropositive and erosive RA. 1 patient with scleritis; 1 patient with vasculitis	Cy—4.0 g/m ² + Mesna; + G-CSF starting day 6 as needed; + Prophylactic antibiotics; + SMT-TMP → six months	3 patients—uneventful; 1 patient—flare of lung vasculitis—day 3	Initial improvement. Relapse in all patients 4-6 months (but milder than before Cy)
Mittal et al., 1999 ¹⁶	Case report	n = 1 female; age 21 years	SLE	Cy—5000 mg once	Alopecia; pancytopenia without complications	Remission. Able to discontinue all medication Follow up—9 years
Hayag et al.; 2000 ¹³	Case report	n = 1; male; age = 33 years	PV	Cy—50 mg/kg/day for 4 days; + mesna; + methylprednisolone (40 mg—8/8 hours); + vancomycin + ceftazidime (2 days prior CYC); + G-CSF; + platelet transfusions	Day 6: fever—ticarcillin clavulanate, gentamicin, and fluconazole. Blood cultures— <i>Pseudomonas aeruginosa</i> ; antibiotics changed to imipenem-clastatin and amikacin	Complete healing Followed 15 months
Gladstone et al., 2002 ¹⁷	Case series (n = 4)	n = 1; female; age = 51 years	SLE (vasculitis, mucous ulcers, cognitive deficits, proteinuria, and creatinine of 2.9 mg/dL)	Cy—200 mg/kg, over 4 days + mesna; + prophylactic antibiotics + amphotericin + red blood cells + platelets transfusion as needed	Nonoliguric renal failure requiring hemodialysis; veno-occlusive liver disease; Bacteremia: <i>S. epidermidis</i>	SLAM-2: 19 → 9 SLEDAI: 26 → 6 Follow-up: 38 months
		n = 1; female; age = 50 years	SLE (vasculitis, arthritis, rash, fatigue, headaches, and lymphopenia)	200 mg/kg over 4 days; + mesna; + prophylactic antibiotics + amphotericin; + red blood cells + platelets transfusion as needed	Neutropenia during 15 days → antibiotics and amphotericin B	SLAM-2: 11 → 3 SLEDAI: 26 → 14 Flare at 26 months → arthritis and proteinuria
		n = 1; female; age = 29 years	SLE (mucocutaneous, cranial neuropathy, cognitive impairment, serositis, articular and hematological manifestations)	200 mg/kg, over 4 days; + mesna + prophylactic antibiotics; + red blood cells + platelets transfusion as needed	Neutropenia—6 days → broad-spectrum antibiotics	SLAM-2—12 → 4 SLEDAI—28 → 2 Pregnancy 5 months after → complicated with thrombocytopenia + rash + arthralgias. Delivery of 2 healthy babies Follow-up—18 months
		n = 1; female; age = 38 years	SLE (glomerulonephritis + arthralgias, cognitive impairment, anemia, and thrombocytopenia + antiphospholipid antibody syndrome (with cardiac complications)	200 mg/kg over four days; + mesna; + prophylactic antibiotics + amphotericin; + red blood cells + platelets transfusion as needed	Neutropenia for ten days; cellulitis associated with a catheter;	SLAM-2—20 → 9 SLEDAI—t21 → 9 Improvement of cognition Follow-up—12 months.

Cohen et al., 2002 ¹⁴	Case report	n = 1; female; age = 51 years	PF	Cy—50 mg/kg/day for 4 days; + dexamethasone (20 mg/day); + granisetron; + mesna	Day 6—oral thrush; Day 6—started on GM CSF and erythropoietin; Day 11—gram-negative sepsis (<i>Klebsiella pneumoniae</i> and <i>Enterobacter cloacae</i>); Day 12—acute renal failure; Day 11—platelet transfusion complicated with pulmonary edema	PF relapsed 10 months later (milder)
Drachma et al., 2002 ⁵	Case series (n = 3)	n = 1; female; age 32 years	MG	Cy—50 mg/kg of ideal body weight—4 days; + Prophylaxis <i>P. carinii</i>	Day 5—WBC=0 (normalized in 18 days)	Improved. Follow-up 3.5 years
Brannagan et al., 2002 ²⁰	Case series	n = 1 Female; Age 36 years	MG + SLE + Hashimoto thyroiditis	Cy—50 mg/kg of ideal body weight—4 days; + Prophylaxis <i>P. carinii</i>	Day 6—WBC=0—treated with G-CSF Herpes simplex infection treated successfully with valacyclovir	Improvement. Follow-up 2 years.
Brannagan et al., 2002 ²⁰	Case series	n = 1; male; age—53 years	MG	Cy—50 mg/kg/day for 4 days; + Prophylaxis <i>P. carinii</i>	Day 7 WBC = 0 (normalized in 13 days); Neutropenic fever treated with cefepime	Improvement. Follow up 7 months.
Bittencourt et al. 2005 ²¹	Case report	n = 4; 3 (75%) males; age from 39 to 61 years	CIDR	Cy—200 mg/kg over 4 days; + mesna; + day 10—G-CSF	Neutropenic fever; transient amenorrhea (7 months), renal failure, congestive heart failure, alopecia, mucositis, diarrhea	Improvement in strength and functional status; immunomodulatory medications stopped (all patients)
Shammo et al., 2006 ²²	Case series	n = 1; female; age = 48 years	MS	Cy—3800 mg	Alopecia	Remission for 7 years
Lin et al., 2006 ²³	Case report	n = 4; sex NA; mean age 26 years	MS	Cy—50 mg/kg/day for 4 days + G-CSF, as needed; + blood and platelet transfusion	3 patients—nausea; 3 patients with neutropenic fever; 2 patients—diarrhea; 1 patient with hematuria; 1 with oral herpetic lesion; 1 mild stomatitis	All had improvement of neurologic function (dramatic in 2); 3 patients with improvement in MRI findings.
Brannagan et al., 2006 ²⁴	Case report	n = 1; female; age 45 years	MMN + Crohn's disease	Cy—50 mg/kg daily for 4 days	Day 9: neutropenia Bacteremia—Enterobacter and Pseudomonas successfully treated	Clinical remission. Follow-up—18 months
				Cy—200 mg/kg over 4 days. Day 6: prophylactic antibiotics (fluconazole, acyclovir, and Bactrim); Day 10: filgrastim	Transient alopecia Supraventricular tachycardia after filgrastim infusion	Strength improvement; Regained the ability to write; Follow-up: 27 months

(Continued)

Table 2. High Dose Cyclophosphamide Without Stem Cell Support in Autoimmune Diseases: Case Reports and Case Series (*Continued*)

Author, Year	Study Design	n/Sex/Age	Indication	Dose	Side Effects	Outcome
Luo et al., 2008 ²⁵	Case series	n=4; 100% females; mean age of 13 years	Juvenile lupus Patient 1: hemolytic anemia and GNF class 4; Patient 2: arthritis + GNF class 4; Patient 3: hemolytic anemia, psychiatric symptoms, proteinuria; Patient 4: arthritis, GNF class 4, thrombocytopenia	Cy—1.2 g/m ² /day for days 1-4 + fludarabine 30 mg/m ² /day for day 1-4 + antilymphocyte globulin—25 mg/kg on days 5-7 Blood cultures and antibiotics when fever > 38°C; Packed red blood cell transfusions if hemoglobin < 7.0 g/L; Platelet transfusion if count < 20 × 10 ⁹ /L.	No details	Patient 1: one episode of hemolysis (18 months after) with good response to MP; Follow-up: 28 months; using 10 mg PDN/day/good response. Patient 2: one episode of interstitial pneumonia with renal flare (5 months after) with good response to 60mg/ PDN/day. Follow-up: 23 months; using 10 mg/ PDN/day. Patient 3: two episodes of hemolytic anemia (6 and 13 months after) with good response to PD. Follow-up: 17 months—partial remission; using 10 mg PDN and 50 mg of 6MP/day. Patient 4: one episode of herpes zoster (7 months after) with renal flare treated with acyclovir, IVIG, and 60 mg PDN/day. Maintenance on 10 mg/ PDN/ day.
Mok et al., 2008 ¹⁶	Case report	n=1; female; age= 40 years	SLE with neuromyelitis optica	2 g Cy/day for 4 days + G-CSF	Alopecia + transient gastrointestinal upset	No further deterioration Follow-up 18 months.
Drachman et al. 2008 ¹⁰	Case series	n=12; 9 (75%) females; mean age 34.7 years.	MG	Cy—50 mg/kg/day for 4 days; + mesna; + ondansetron; + transfusion of packed red blood cells and platelets as needed; + prophylactic antibiotics; + TMP-SMT for 6 months (<i>P. carinii</i> prevention)	Seven patients: neutropenic fever (diverticulitis, axilla abscess, line infection, and mycoplasma pneumoniae). Six patients with tetanus and diphtheria antibodies measured → antibody levels did not ↓ in just 1 patient.	Improvement in 9 patients (short-lived in 2); 2 patients in complete remission for 7.5 and 5.5 years. 1 patient received new treatment with a high-dose Cy; another was planned to receive it.
Gladstone et al., 2011 ¹⁹	Case series	n=15; sex NA; age: NA	MS: - 7 with RRMS - 8 with SPMS	Cy—200 mg/kg/4 days	NA	No one had a disease worsening; Improvement in 5/7 (71%) of those with RRMS and 5/8 (62%) of SPMS; 4 patients required additional immunotherapy. Follow-up 2 years
Lahouti et al., 2015 ¹⁸	Case report	n=1; female; age= 30 years	Idiopathic inflammatory myopathy	Cy—50 mg/kg/day, for 4 days	Neutropenic fever—9 days; no transfusions needed	Clinical remission off corticoids; follow-up 6 years

CIDP, chronic inflammatory demyelinating polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; GNF, glomerulonephritis; MG, myasthenia gravis; MS, multiple sclerosis; NA, not available; PDN, prednisone; PF, pemphigus foliaceus; PPMS, primary progressive MS; PV, pemphigus vulgaris; RRMS, relapsing remitting MS; SLAM, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; SPMS, secondary MS; TMP-SMT, trimethoprim-sulfamethoxazole; IMMN, multifocal motor neuropathy; WBC, white blood cells.

Table 3. Summary of Studies on High-Dose Cyclophosphamide Without Stem Cell Rescue for Autoimmune Disease Treatment

Author, Year	Study Design	n/Sex/Age	Indication	Dose	Side Effects	Outcome
Brodsky et al., 1996 ⁵	Randomized case-control	n = 10; 6 (60%) males; mean age 19 years	Severe and super severe aplastic anemia	Cy: 45 mg/kg/day for 4 days with (n = 5) or without (n = 5) cyclosporine	All patients—febrile neutropenia; Transient hepatitis (presumed viral)—n = 4; Renal dysfunction—n = 2 (1 required dialysis); Hypertension—n = 2 (cyclosporine group); Transient congestive heart failure—n = 1	Complete remission—n = 7 (70%); The addition of cyclosporine did not influence the response; 1 patient died 44 months after—of AIDS acquired from a blood transfusion; 3 non-responders died of baseline disease. Median follow-up—10.8 years.
Brodsky et al., 1998 ⁸	Prospective/open trial	n = 8; 50% females; from 23 to 64 years	2: RA (Felty syndrome); 2: SLE 1: Evans syndrome; 1: thrombocytopenic purpura; 1: autoimmune hemolytic anemia 1: chronic inflammatory demyelinating polyneuropathy	Cy: 4.0 g/m ² + G-CSF starting day 6 as needed + red blood cells + platelets transfusion as needed	Complete alopecia in 100%; 6 patients—febrile neutropenia—treated with antibiotics	5: Complete remission; 2: partial remission; 4 patients remained in complete remission for 3-21 months; 2 patients died of baseline disease complications in the follow-up.
Moyo et al., 2002 ²⁹	Prospective, open-label, uncontrolled	n = 9 4 (44.4%) females; median age = 52 years	Autoimmune hemolytic anemia - 8 with warm DAT - 1 with cold agglutinin	Cy: 50 mg/kg ideal body weight/day for 4 days + mesna + G-CSF; initiated on day 6	1 patient was treated empirically with amphotericin B for febrile neutropenia; Median stay at the hospital—21 days	6 complete remission; 3 partial remission. 15 days—platelet transfusion independent; 19 days—RBC transfusion independent; All but 2 became GC independent; 2 on GC → low dose. Median follow-up—15 months
Petri et al., 2003 ³⁰	Prospective open	n = 14 12 (85.7%) females; Mean age of 35 years	SLE (moderate to severe; refractory to corticoid and ≥ 1 immunosuppressor) • 9 with renal; • 3 with CNS (1 cerebellar ataxia, 2 encephalopathies); • 2 with severe skin rash (1 with 60% of body surface area and another with severe pyoderma gangrenosum)	50 mg/kg/day for 4 days + mesna + G-CSF + prophylactic antibiotics: fluconazole + norfloxacin + valacyclovir. + prophylaxis <i>P. carinii</i> —dapsona + blood and platelet transfusion	Bacterial sinus infection—1 patient Methemoglobinemia (by dapsone)—1 patient No premature ovarian failure (1 patient became pregnant 3 years after treatment)	Renal: 4 complete response; 3 partial; 2 no response. No relapse for 29 months → in those with response CNS—patient with ataxia—complete response; 1 encephalopathy—good response; 3 years after—renal flare; 1 encephalopathy—partial response. Skin—patient with a severe rash—partial response that relapsed at 2 years. Response to MTX. Pyoderma gangrenosum—good initial response followed by relapse treated with cyclosporine

(Continued)

Table 3. Summary of Studies on High-Dose Cyclophosphamide Without Stem Cell Rescue for Autoimmune Disease Treatment (*Continued*)

Author, Year	Study Design	n/Sex/Age	Indication	Dose	Side Effects	Outcome
Savage et al., 2007 ²⁷	Open prospective study	n = 5 4 (80%); females; mean age—14 years	Aplastic anemia (hepatitis induced); 1 patient with features of autoimmune hepatitis	Cy: 50 mg/kg/day for 4 days; + mesna + G-CSF—day 6 + prophylactic- fluconazole and TMP-SMT	3 patients with fungal infections; 4 episodes of bacteremia in 3 patients; 2 sepsis in 1 patient; 2 urinary tract infections; 1 sinusitis 1 cellulitis	Hematologic recovery: 4 patients; 1 patient had a liver biopsy, with histological improvement
Krishnan et al., 2008 ³¹	2-year open-label trial	n = 9; 6 (66.6%) males; mean age 35 years	MS	Cy: 50 mg/kg/day for 4 days + mesna; + Day 6—G-CSF; + Prophylactic: norfloxacin, fluconazole, valacyclovir	All had neutropenia that recovered by day 15; mean transfusions—red blood cells = 2 packs; platelets = 1 pack; 2 patients with febrile neutropenia (infection documented in 1) 4 hospital admissions: • 1 (admitted twice) for suspected MS exacerbation—not confirmed • 1 with exacerbation at 18 months • 1 with problems unrelated to MS	EDSS 5.17 → 3.06 2 patients worsened; 4—no change; 5—improved MSFC scores—average improvement in 87% GEL—6.5 → 1.2 Mean follow-up—23 months
Tehirian et al., 2008 ¹¹	Open-label, single-site, uncontrolled study	n = 6; 4 (66.6%) males; age from 19 to 60 years	Diffuse scleroderma	Cy: 50 mg/kg/day for 4 days + mesna + G-CSF + prophylactic antibiotics: fluconazole, norfloxacin, valacyclovir + <i>P. carinii</i> /prophylaxis: dapsone or TMP-SMT + Packed red blood cell and platelet transfusion as needed	1 patient died in the early treatment phase (infection)	Reduction in the skin score (m Rodnan) of—60%; 55%; 41%; 31%, 0%, 37%. PGA scores improved 47%, 69%, 56%, 59%, 80% 2 patients had worsening skin and PGA after initial improvement.
Schwartzman et al., 2009 ³⁸	Prospective, open-label	n = 23 patients, 19 (82.6%) females; mean age = 47.2 years	MS: • 3 with PPMS • 11 with SPMS; • 9 RRMS	Cy: 50 mg/kg—4 days; + Lasix, Diamox, anti-emetics; + Day 11–12: G-CSF; + prophylactic antibiotics	1 patient had a reactivation of CMV hepatitis; 2 patients with pleural and pericardial effusions (both required thoracentesis); Fever, nausea, vomiting, alopecia, and cellulitis	16 reached endpoint (≥ 1 point in EDSS for 6 months); 7 reached secondary endpoint (time to EDSS progression); Significant reduction of flare frequency; Improvement in mental and physical QoL: (data on 16 patients); Treatment was ineffective for SPMS and failed in the 2 PPMS patients

Brodsky et al., 2010 ³³	Retrospective	n = 67; 37 (55.2%) females; the median age of treatment naive-32 years, of refractory patients—34 years	SAA - 44 treatment naive, - 23 refractories to treatment)	Cy: 50 mg/kg/day for 4 days; + mesna; + day 10: G-CSF; + prophylactic antibiotics: fluconazole, norfloxacin, valacyclovir + <i>P. carinii</i> /prophylaxis (TMP-SMT); + Packed red blood cell and platelet transfusion as needed	All patients: alopecia; Febrile neutropenia in most patients; 2 hemorrhagic cystitis; Treatment naive group: 8 severe fungal infections (3 patients died); Treatment refractory group: 10 fungal infections (5 of them died)	Results in 10 years: Overall actuarial survival—88%; response rate-71% Actuarial event-free survival: 58% of treatment naive 27% in the refractory group
Petri et al., 2010 ³⁵	Prospective randomized	n = 47; 42 (89.3%) females. age: n = 27n = 27 between 18 and 39 years and 20 between 40 and 59 years of age.	SLE patients: - 22 with renal involvement; - 14 with neurological involvement.	Cy: 50 mg/kg/4 days (HDIC) (n = 21) vs Cy: 750 m2/month for 6 months followed by quarterly Cy (n = 26n = 26) (MIC)	HDIC: pneumonia, zoster, neutropenic fever, pyelonephritis, staph bacteremia, genital herpes, and <i>C. difficile</i> . 1 death. Ovarian failure in 30%. MIC: pneumonia, line infection, BK virus, bronchitis, zoster, abscess, cellulitis, oral candida, meningococemia, and otitis Ovarian failure in 43%	6 months—52% of HDIC and 35% of MIC had a complete response; 30 months—48% of HDIC and 65% of MIC had a complete response; 6 patients crossed from MIC to HDIC due to a lack of response
DeZem et al., 2011 ³³	Retrospective	n = 140; 62.1% females; median age = 40 years.	14 MG 47 MS 5 CIDP/POEMS 7 scleroderma 40 SLE 1 vasculitides 3 gastrointestinal autoimmune diseases 9 hemolytic anemia/Evans 4 thrombocytopenia 1 pure red cell aplasia 9 pemphigus vulgaris	Cy 50 mg/kg/day for 4 days + mesna; + day 6—G-CSF; + prophylactic antibiotics: fluconazole, norfloxacin, valacyclovir. Antifungal therapy for second fever; + <i>P. carinii</i> /prophylaxis (TMP-SMT or dapsone); + packed red blood cell and platelet transfusion as needed	All patients—alopecia and pancytopenia; Febrile neutropenia—53 patients Hemorrhagic cystitis—3 patients; 1 patient (scleroderma) died of pneumonia—51 days after treatment; 1 patient committed suicide. 7 patients died—12 months after treatment (most of the underlying disease)	The overall response rate was 95%; - 44% of responders remain progression-free during a median of 36 months.
DeZem et al., 2013 ³²	Retrospective (high-dose Cy done more than once)	8 patients (7 treated twice, 1 treated 3 times); 50% females; Mean age 34 years at second treatment	3 MG 3 Aplastic anemia 1 Scleroderma 1 MS Patients treated twice (median interval of 40 months)	Cy: 50 mg/kg/day for 4 days; + mesna; + Day 6—G-CSF; + Prophylactic antibiotics: fluconazole, norfloxacin, valacyclovir; + <i>P. carinii</i> /prophylaxis (TMP-SMT or dapsone); + Packed red blood cell and platelet transfusion as needed.	Alopecia. Febrile neutropenia requiring hospital admission in 7 patients;	All responded after the 1st and 2nd treatments; The patient (with MG) was treated 3x and did not respond to the 3rd treatment.

CIDP: chronic inflammatory demyelinating polyneuropathy; CMV, human cytomegalovirus; CNS, central nervous system; Cy, cyclophosphamide; DAT, direct antiglobulin test; EDSS-Expanded Disability Status Scale; GC, glucocorticoid; G-CSF, granulocyte colony-stimulating factor; Gel, gadolinium-enhancing lesion; HDIC, high dose intravenous cyclophosphamide; MIC, monthly intravenous cyclophosphamide; MMN, multifocal motor neuropathy; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; PGA, physician global assessment; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin abnormalities; PPMS, primary progressive MS; RA, rheumatoid arthritis; RBC, red blood cells; RRMS, relapsing remitting MS; SAA, severe aplastic anemia, MTX, methotrexate; SLE, systemic lupus erythematosus; SPMS, secondary MG, myasthenia gravis; TMP-SMT, trimethoprim-sulfamethoxazole.

including larger samples and more extended observations. This would enable a better understanding of this therapy in autoimmune conditions.

Conclusion

Most studies on high-dose cyclophosphamide without stem cell rescue are case reports or series of cases. However, the analysis of available data suggests that this is an effective option for treating severe autoimmune diseases and that this procedure is relatively safe when the appropriate supportive care measures are taken.

Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – J.F.C.; Design – J.F.C.; Supervision – J.F.C.; Resources – J.F.C., T.L.S.; Materials – J.F.C.; Data Collection and/or Processing – J.F.C., T.L.S.; Analysis and/or Interpretation – J.F.C., T.L.S.; Literature Search – J.F.C., T.L.S.; Writing Manuscript – J.F.C., T.L.S.; Critical Review – J.F.C., T.L.S.

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