High-dose cyclophosphamide without stem cell rescue in immune-mediated necrotizing myopathies

ABSTRACT
Objective: To describe the experience managing treatment-refractory immune-mediated necrotizing myopathies (IMNM) with high-dose cyclophosphamide (HiCy) therapy.
Methods: Five patients with severe refractory IMNM who were treated with HiCy without stem cell rescue were identified. Their medical records were reviewed to assess demographic, clinical, and histologic characteristics as well as response to therapy.
Results: Three patients with anti–signal recognition particle (SRP) and 2 patients with anti-HMG-CoA reductase autoantibodies were included. The mean follow-up time after HiCy therapy was 37 ± 28 months. Two patients demonstrated substantial response, evidenced by improved muscle strength and decreased muscle enzymes after HiCy therapy; both of these patients were anti-SRP positive. Four patients experienced febrile neutropenia after HiCy therapy, one of which required a prolonged intensive care unit stay for infectious complications, from which they eventually recovered.
Conclusions: These data suggest that HiCy therapy without stem cell rescue may be considered as an alternative for the treatment of refractory IMNM.

GLOSSARY
ASCT = autologous stem cell transplantation; CK = creatine kinase; HiCy = high-dose cyclophosphamide; IG = immunoglobulin; IMNM = immune-mediated necrotizing myopathy; SRP = signal recognition particle.

Some patients with myositis may be resistant to standard immunosuppressive regimens, including prednisone, methotrexate, azathioprine, IV immunoglobulin (IG), rituximab, and/or other medications. In such patients, especially those with a progressive clinical course, additional therapies may be required. High-dose chemotherapy followed by stem cell rescue through autologous stem cell transplantation (ASCT) has been previously used with some success in patients with refractory myositis.1–3 However, given the risks associated with ASCT, high-dose cyclophosphamide (HiCy) without bone marrow transplantation can also be considered. First used for treatment of severe aplastic anemia,4,5 HiCy has subsequently been applied to several rheumatologic and neurologic diseases.6–10 As HiCy seems to be better tolerated than ASCT and yet induces a high rate of remission in refractory autoimmune diseases,11 we have used it to treat a number of patients with refractory myositis at the Johns Hopkins Myositis Center.12 In this case series, we report the clinical response of 5 patients who underwent HiCy therapy for refractory immune-mediated necrotizing myopathy (IMNM), a particularly severe form of myositis that predominantly affects skeletal muscle.

METHODS This is a retrospective case series review of 5 patients with IMNM who were treated with HiCy at the Johns Hopkins Myositis Center. The Johns Hopkins Institutional Review Board approved this study. All patients had been evaluated as part of routine clinical care between 2009 and 2016. The patients were administered cyclophosphamide at a dose of 50 mg/kg of ideal body weight IV...
Table 1: Summary of demographic, clinical features, and immunosuppressive medications in 5 patients treated with HiCy

| Patient | Age at diagnosis/sex/race | Phenotype (myositis-specific antibody) | Previous treatments | Follow-up period after HiCy therapy, mo |
|---------|---------------------------|---------------------------------------|---------------------|----------------------------------------|
| 1       | 53/M/AA                   | NM (anti-SRP)                          | MEP, PDN, MTX, IVIG, AZA, MMF, ACTH, corticosteroids, RTX | 34                                      |
| 2       | 33/F/C                    | NM (anti-SRP)                          | PDN, AZA, IVIG, RTX | 72                                      |
| 3       | 36/M/AA                   | NM (anti-SRP)                          | PDN, AZA, RTX       | 7                                       |
| 4       | 38/M/CM                   | NM (anti-HMGCR)                        | PDN, IVIG, MTX, RTX, PLEX | 59                                      |
| 5       | 22/F/AA                   | NM (anti-HMGCR)                        | PDN, MTX, MMF, IVIG, RTX, PLEX | 14                                      |

Abbreviations: AA = African American; AZA = azathioprine; C = Caucasian; HiCy = high-dose cyclophosphamide; IG = immunoglobulin; MEP = methylprednisolone; MMF = mycophenolate mofetil; MTX = methotrexate; NM = necrotizing myopathy; PDN = prednisone; PLEX = plasmapheresis/plasma exchange; RTX = rituximab; SRP = signal recognition particle; TAC = tacrolimus.

RESULTS: Table 1 summarizes demographic features, clinical characteristics, and immunosuppressive therapies in 5 patients. Tables 2 and 3 summarize muscle strength, prednisone dose, and creatine kinase (CK) level before and after HiCy treatment. Figure provides the overall change in strength over the first year for each patient after receiving HiCy therapy.

Patient 1: A 53-year-old African American man presented with a 4-month history of progressive upper and lower extremity weaknesses, dyspnea on exertion, and dysphagia. His initial CK level was greater than 9,000 IU/L, and he had muscle strength grade 3/5 in proximal upper and lower extremities. Electromyography demonstrated an irritative myopathy, and muscle biopsy showed severe necrotizing myopathy. Lower extremity MRI showed atrophy and muscle edema. Antibodies against signal recognition particle (SRP) were detected in this patient’s serum. He was treated with corticosteroids and methotrexate with minimal improvement. Azathioprine, mycophenolate mofetil, and IVIG treatment yielded temporary improvement in muscle strength, but worsening dysphagia and muscle pain. He was subsequently treated with ACTH gel (corticosteroids injection), rituximab, and tacrolimus with no substantial improvement in his symptoms. Given the refractory nature of his disease, the patient was treated with HiCy. He tolerated the treatment well, but 9 days after discharge, he was admitted to the hospital with neutropenic fever and treated for pneumonia. In the ensuing 2 months, he experienced marked improvement in muscle strength, and his CK level decreased from 2,000 to less than 500 IU/L. The patient was completely weaned off immunosuppressive therapy, and 3 months later, his muscle strength was graded 5/5 in both upper and lower extremities and his CK level normalized.

Patient 2: A 33-year-old white woman who developed 5 months of progressive lower extremity weakness and dyspnea was evaluated in clinic in March 2007. Her evaluation was notable for proximal muscle weakness, CK of 8,000 IU/L, an irritative myopathy on electromyography, muscle biopsy showing a necrotizing myopathy, and positive anti-SRP antibodies. Her proximal upper extremities were graded 4/5 and lower extremities 4/5. She was initially treated with azathioprine and prednisone 60 mg daily without effect. She subsequently received methotrexate and IVIG (2 g/kg), but despite these therapies, she had persistent weakness, and her CK level remained 2,000–3,000 IU/L. She received rituximab with suppression of her CD19/CD20 cell populations, after which her CK actually increased to 6,000 IU/L.

Table 2: Summary of creatine kinase (CK) value, glucocorticoid dose, and manual muscle strength testing before high-dose cyclophosphamide therapy

| Patient | Peak CK, IU/L | Max prednisone dose, mg/d | Deltoid strength, min | Hip flexor strength, min |
|---------|---------------|---------------------------|-----------------------|-------------------------|
| Before therapy | | | | |
| Definite responders | | | | |
| 1       | 9,000         | 60                        | 3/5                   | 3/5                     |
| 2       | 8,495         | 60                        | 4–/5                  | 2/5                     |
| Nonresponders | | | | |
| 3       | 16,000        | 100                       | 3+/5                  | 2/5                     |
| 4       | 18,000        | 100                       | 4+/5                  | 2/5                     |
| 5       | 22,050        | 80                        | 1–2/5                 | 1–2/5                   |

CK normal range (24–170 IU/L).
She therefore received HiCy in November 2008. She tolerated the therapy well, but 9 days after the infusion, she was admitted to the hospital for neutropenic fever and received broad-spectrum antibiotics. No infection was identified, and she subsequently recovered. In January 2009, her strength was starting to progressively improve. Over the subsequent years, she was able to taper her immunosuppressive regimen while retaining her strength and function. During her most recent follow-up appointment, her CK level trended down to 100 IU/L, her strength had improved to 4+/5 in proximal muscle groups, and she remained in clinical remission off of all immunosuppressive therapies.

**Patient 3.** A 36-year-old African American man presented to our clinic in February 2011 with a 7-month history of proximal muscle weakness accompanied by a 40-lb unintentional weight loss. His evaluation revealed a CK level of 16,000 IU/L, and electromyography showed an irritable myopathy. A muscle biopsy of his right thigh by report showed minimal inflammation. He was subsequently found to have both anti-SRP and anti-Ro autoantibodies. His proximal lower extremities were graded as 2/5 in strength bilaterally. He was treated with high-dose prednisone, 100 mg/d, and azathioprine with initial improvement, but this was transient, despite this therapy, he worsened clinically with a persistently elevated CK level to ~4,000 IU/L and proximal muscle weakness graded 2/5. He was subsequently trialed on methotrexate and 4 doses of rituximab therapy with documented suppressed CD19/CD20 cell counts. However, he did not have any significant improvement. He therefore was referred for and received HiCy in May 2016. His hospital course was complicated by neutropenic fever and fungal pneumonia as well as *Clostridium difficile* colitis. He was hospitalized for a total of 25 days. Within months, his CK level had decreased to 1,000 IU/L; however, at his most recent follow-up, 7 months after HiCy, his CK level again started to rise to 3,500 IU/L with a decrease in strength to pre-HiCy levels.

**Patient 4.** A 38-year-old white man presented with an 11-month history of progressive muscle weakness and myalgia. His initial evaluation was notable for a CK level of 18,000 IU/L, electromyography revealing an irritable myopathy and MRI of bilateral thighs demonstrating muscle edema of all compartments. A muscle biopsy sample showed severe necrotizing myopathy. Serum test revealed antibodies to 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR antibodies), with no history of statin use. The patient was started on prednisone 60 mg daily with worsening muscle weakness in upper extremities grade 4+/5 and hip flexors grade 2/5. IVIG (2 g/kg) and azathioprine treatments were administered, but the muscle

### Table 3 Summary of creatine kinase (CK) value, glucocorticoid dose, and manual muscle strength testing after high-dose cyclophosphamide therapy

| Patient | Nadir CK, IU/L | Most recent CK, IU/L | Current prednisone dose, mg/d | Deltoid strength (at last visit) | Hip flexor strength (at last visit) |
|---------|---------------|---------------------|------------------------------|--------------------------------|-----------------------------------|
| After therapy |               |                     |                             |                                |                                   |
| **Definite responders** |               |                     |                             |                                |                                   |
| 1       | 123           | 494                 | 0                           | 4+/5                           | 5/5                               |
| 2       | 100           | 100                 | 0                           | 4+/5                           | 4+/5                              |
| **Nonresponders** |               |                     |                             |                                |                                   |
| 3       | 1,058         | 3,594               | 10                          | 4+/5                           | 2/5                               |
| 4       | 245           | 714                 | 10                          | 5/5                            | 3/5                               |
| 5       | 663           | 3,923               | 40 every other day          | 1–2/5                          | 1–2/5                             |

CK normal range (24–170 IU/L).

Y-axis is 0–40, where the deltoids and hip flexors were scored on a 0–5 scale, and subsequently transformed to a scale of 0–10 for each of the 4 muscles, resulting in a maximum score of 40. HiCy – high-dose cyclophosphamide.
weakness worsened. He was prescribed 2 doses of rituximab and methotrexate, resulting in slight improvement in muscle strength, but CK levels started to rise again within 6 months. Rituximab was started again, but it was accompanied by an anaphylactic reaction. He then received 5 plasmapheresis treatments without any substantial improvement in strength. The patient was admitted and received HiCy for 4 consecutive days in September 2011. He had 1 episode of neutropenic fever 15 days after HiCy, but he recovered successfully. Within 1 month, strength remained at 4/5 in the proximal upper extremity and 3/5 in the hip flexors (weaker than the grades before HiCy therapy). The patient was started on mycophenolate mofetil without any improvement after 3 months. He underwent desensitization for rituximab and received a dose of rituximab in intensive care unit. Five months after rituximab therapy, muscle strength improved to 5/5 in the upper extremities and 4/5 in the hip flexors, and the CD19/CD20 counts remained suppressed. On his most recent visit, the patient required 10 mg prednisone daily with intermittent rituximab.

**Patient 5.** A 22-year-old African American woman first developed proximal muscle weakness 6 weeks after the delivery of her second child in January 2007. She was evaluated at our clinic in March 2008 and was found to have a CK level of 15,000 IU/L and an EMG showing an irritative myopathy. She underwent a muscle biopsy that revealed a necrotizing myopathy. She was treated with 80 mg/d prednisone and methotrexate without substantial benefit. She was thus transitioned to IVIG, but her CK level actually increased to over 17,000 IU/L. She then received rituximab infusions with minimal improvement and a nadir CK level of 4,800 IU/L. Mycophenolate was added with no appreciable difference. She also received 1 round of plasmapheresis, which resulted in substantial improvement in strength but only lasted a few days and was complicated by bacteremia and pneumonia. Throughout this time, she was unable to decrease her prednisone less than 20–30 mg/d. Serum test revealed antibodies to 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR antibodies), with no history of statin use. Given her refractory nature and poor functional status requiring a wheelchair and family assistance, she received HiCy in April 2015. She tolerated the infusions well and did not have any complications after hospitalization. In May, she started to observe increasing proximal muscle strength, and this continued throughout 2015 (knee flexors/extensors by dynamometry increased from 11–13 to 25–26 lbs bilaterally). Her CK level decreased to ~1,800 IU/L. However, in February 2016, she was noted to start to decline functionally. At her last visit in May 2016, approximately 1 year after HiCy, she was noted to have persistent muscle weakness (hip flexors 2/5) and still required 40 mg/d prednisone every other day.

**TOXICITY** All 5 patients tolerated the HiCy regimen well. All patients experienced mild side effects including nausea and alopecia. Neutropenic fever was observed in 4 patients within 2–3 weeks after receiving HiCy, but all recovered. One patient (patient 3) experienced a prolonged hospital stay of 25 days after HiCy for treatment of *C difficile* colitis and fungal pneumonia. At the time of this report, no patient experienced hemorrhagic cystitis or malignancy. There were no fatalities.

**DISCUSSION** In this study, we have described our experience treating patients with severe refractory IMNM with HiCy without stem cell rescue. The 2 definite responders (patients 1 and 2) had substantial improvement in muscle strength and decreased requirement for corticosteroids after treatment. Nonresponders included patients 3, 4, and 5 who had no improvement in strength or ability to taper immunosuppression. Patient 3 had initial improvement with subsequent return to pre-HiCy status. Patient 4 initially demonstrated partial response but then worsened, prompting treatment with rituximab, after which he demonstrated improvement. In all cases, the adverse effects were manageable and comparable with those observed in previous HiCy studies. Although 4 of the 5 patients required hospitalization for neutropenic fever and/or infection, the high risk of this side effect was anticipated and considered warranted, given the limited additional treatment options and the potential benefit of HiCy. This series suggests that HiCy may be effective in select patients with treatment-refractory IMNM.

IMNM is sometimes associated with unique autoantibodies, including anti-SRP (patients 1–3) and anti-HMGCR autoantibodies (patients 4–5), and a distinct clinical phenotype. Anti-HMGCR myopathy is characterized by prominent myofiber necrosis on biopsy and very high CK levels. Similarily, patients with anti-SRP antibodies frequently present with markedly elevated CK levels and a necrotizing myopathy without primary inflammation. Although it is interesting that both patients who responded to HiCy were anti-SRP positive, the numbers included in this study are too small to conclude whether autoantibody status can predict response to this therapy.

Regarding the 3 patients with anti-SRP antibodies, 2 experienced dramatic improvement, whereas the third had initial improvement with subsequent worsening at the time of this report. Notably, the
patient who worsened also had anti-Ro autoantibodies. Other groups have noted that in rheumatologic conditions such as systemic lupus erythematosus and scleroderma, the presence of anti-Ro autoantibodies portends a poorer prognosis\(^{22,23}\) and in myositis has been associated with earlier and more severe disease.\(^{24–26}\)

A review of the literature suggests that despite an initial response rate, most patients with severe autoimmune disease ultimately relapse following HiCy therapy with only 20% remaining disease free 5 years after treatment.\(^{12}\) However, it should be noted that patients with myositis were not included in those studies. We acknowledge that this therapy carries a higher risk of infection and morbidity, especially when taking into account a potential high relapse rate as seen in other autoimmune conditions treated with this regimen. Furthermore, long-term risk regarding malignancy must be taken into account, given its association with some necrotizing myopathies.\(^{27,28}\) However, for patients who have failed conventional therapies for necrotizing myopathy (i.e., rituximab and IVIG), we believe that this therapy offers another option for the clinician to consider who otherwise has very few options.

Although follow-up of patients with myositis in the current study was limited to an average of 3 years (median 37 ± 28 months, range 7–72 months), the 2 responders have now been followed without relapse for 34 and 72 months, respectively. Additional study and follow-up time will be needed to further assess the true duration of remission.

A strength of this study is that all 5 patients underwent the same HiCy protocol at a single center. In addition, all have had longitudinal follow-up in the same center. Limitations of the study include its retrospective nature and the small number of patients. Furthermore, as this study was not protocol driven, follow-up was not uniform and at the discretion of the treating physician. Additionally, many patients were treated with concurrent medications; however, they were on stable doses for months preceding the administration of HiCy. As such, the likelihood that the patients had a delayed response to their background immunosuppressive medications is unlikely.

Although numerous therapies have been shown to be effective for the treatment of inflammatory myopathies, treatment of refractory cases, particularly IMNM, remains challenging.\(^{29}\) The data presented here reveal that HiCy may represent a potential therapeutic alternative in IMNM patients with refractory disease.

**AUTHOR CONTRIBUTIONS**

C.A. Mecoli: design/conceptualization and drafting/revising manuscript.  
A.H. Lahouti: design/conceptualization and drafting/revising manuscript.

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