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Treatments for TAFRO syndrome in Japan

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ABSTRACT

TAFRO syndrome is a systemic inflammatory disorder of unknown etiology characterized by thrombocytopenia, anasarca, fever, reticulin myelofibrosis, renal dysfunction, and organomegaly, and frequent lymphadenopathy with Castleman disease-like histology. In this study, we explored optimal treatments for this syndrome using a patient cohort registered in a retrospective registry in Japan. Among 81 patients with TAFRO syndrome, 68 received corticosteroids as the first-line treatment, and as the second-line treatment, 21 received tocilizumab (Toc), 14 received cyclosporine A (CsA), and 8 received rituximab (Rit) in addition to corticosteroids. We compared these second-line treatment groups by setting the primary endpoint as time to next treatment or death (TTNT). Kaplan-Meier analysis showed that the median TTNT in the Toc, CsA, and Rit groups were 2.8 months, 9.2 months, and not reached, respectively. The TTNT of the Rit group was significantly longer than that of the Toc group. In contrast, there were no significant differences in overall survival between groups. Approximately 30% died within 1 year, and the major causes of death were infections. Further studies are warranted to establish the optimal treatment strategies for this syndrome. (In this poster, a part of results published in Int J Hematol 2021,113:73-80 will be presented)

INTRODUCTION

TAFRO syndrome is a systemic inflammatory disorder of unknown etiology characterized by thrombocytopenia (T), anasarca (A), fever (F), reticulin myelofibrosis (R), renal dysfunction, and organomegaly (O) [Kawabata H, et al. J Clin Exp Hematop. 2013,53:57-61]. Patients with this syndrome frequently present with generalized lymphadenopathy with Castleman disease-like histology. Because the disease usually progresses rapidly, rapid diagnosis and initiation of appropriate therapeutic interventions are essential. In most patients with TAFRO syndrome, corticosteroids, including methylprednisolone pulse therapy, have been used as first-line treatments. However, only a small proportion of patients can achieve disease remission by this therapy alone. If it fails, secondary immunosuppressive treatments, including tocilizumab (Toc), an anti-interleukin 6 (IL-6) receptor antibody; siltuximab, an anti-IL-6 antibody; calcineurin inhibitors, such as cyclosporine A (CsA) and tacrolimus; rituximab (Rit), an anti-CD20 antibody; and rapamycin, in combination with corticosteroids, are subsequently used in most cases. However, the objective efficacies of these agents are unknown. In this study, to explore the optimal treatment strategy for TAFRO syndrome, we compared the efficacies of commonly used second-line immunosuppressive agents utilizing a multicenter retrospective registry database in Japan.

METHODS

Patient cohort

Since October 2013, patients with suspected multicentric Castleman disease (MCD) and TAFRO syndrome have been registered to the Multicenter Collaborative Retrospective Study for Establishing the Concept of TAFRO Syndrome registry (UMIN000011809) from 89 collaborating centers in Japan. The inclusion criteria for this study were as follows: (1) patients diagnosed with TAFRO syndrome according to our criteria [Masaki Y, et al. Int J Hematol. 2020,111:155-158]; (2) the first-line immunosuppressive treatment was corticosteroids; and (3) the second-line immunosuppressive treatment was Toc, CsA, or Rit in addition to corticosteroids. Non-immunosuppressive treatments, including blood transfusion, hemodialysis, and administration of intravenous immunoglobulin and thrombopoietin receptor agonists, were not considered as major treatments. Because there are no standardized response criteria for TAFRO syndrome, we set the primary endpoint to be the time to next immunosuppressive treatment or death (TTNT) after initiation of second-line treatments, and the secondary endpoint was the overall survival (OS) after initiation of second-line treatments. This study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Kanazawa Medical University as well as the ethics committee of each participating institution.

Statistical analysis

Fisher's exact tests were used to compare binary variables, and Kruskal-Wallis or Mann-Whitney U tests were used to compare continuous data between groups. TTNT was defined as the interval between the initiation of second-line treatment and the next immunosuppressive treatment or death, and patients who were alive without receiving the third-line treatment at the last follow-up were censored. OS was defined as the interval between the initiation of the second-line treatment and death, and patients who were alive at the last follow-up were censored. The Kaplan-Meier method was used for survival analyses, and log-rank tests were used for comparisons between groups. Results with *P* values less than 0.05 were considered statistically significant.

RESULTS

Patient cohort

In total, 229 patients were registered in the database by the end of December 2019. Those with unicentric Castleman disease (n=3), iMCD without TAFRO syndrome (n=89), HHV-8-associated MCD (n=6), EBV-associated lymphadenopathy (n=3), malignant lymphomas (n=5), collagen diseases (n=13), and other diseases (n=21) were excluded, and 89 patients were diagnosed with TAFRO syndrome (Fig. 1). Among them, follow-up data were available for 81 patients. Treatment profiles of these 81 patients were shown in Table 1. As the first-line treatment, 4 patients were treated with Toc, 9 were treated with combination therapies, and the remaining 68 were treated with corticosteroids. Forty-seven patients subsequently received some second-line treatments; 21 received Toc, 14 received CsA, 8 received Rit in addition to corticosteroids, and 4 were treated with combination chemotherapies. In this study, we compared patient groups receiving Toc, CsA, and Rit as second-line treatments.

Patient characteristics

Clinical profiles and laboratory data at the time of diagnosis for these 3 groups are shown in Table 2. There were no significant differences in age, sex, or laboratory data at diagnosis between groups. The median time periods from initial presentation to second-line treatments in the Toc, CsA, and Rit groups were 0.5 (range, 0.2–3.7), 0.8 (range, 0.2–88.4), and 0.8 (range, 0.3–29.5) months, respectively (P=0.074).

TTNT and OS of the second-line treatment groups

The median follow-up period of the survivors after initiation of second-line treatment was 50.5 months. Among those who received Toc (n=21), CsA (n=14), and Rit (n=8) as second-line treatments, third-line treatments were performed in 11, 7, and 2 patients, respectively. Kaplan-Meier analysis showed that the median TTNTs in the Toc, CsA, and Rit groups were: 2.8 months, 9.2 months, and not reached, respectively. Additionally, the 1-year survival ratios without receiving subsequent treatments in the Toc, CsA, and Rit groups were 23.8%, 35.7%, and 75.0%, respectively (Fig. 2a, P=0.030). The TTNT of Rit group was significantly longer than that in the Toc group (P=0.048). In contrast, there were no significant differences in OS curves between groups (Fig. 2b). The 1-year OS ratios from the initiation of second-line treatment in the Toc, CsA, and Rit groups were 71.4%, 64.3%, and 87.5%, respectively (P=0.31). Seven of 21 patients in the Toc group, 7 of 14 patients in the CsA group, and 1 in 8 patients in the Rit group died during the follow-up period. The major causes of death were infections (n=7) followed by worsening of the primary disease or multi-organ failure (n=3).

DISCUSSION

Van Rhee et al. analyzed therapies performed in 49 patients with iMCD-TAFRO from published case reports and small series studies [Blood. 2018,132:2115-2124]. According to this analysis, 25 patients were treated with corticosteroid monotherapy; the response rate was 36%, and treatment failure occurred in 72% of cases. Additionally, 20 patients were treated with Toc, 8 were treated with CsA, 10 were treated with Rit, and 14 were treated with cyclophosphamide-based cytotoxic chemotherapy, which may include the use of Rit. Response rates for these therapies were 75%, 75%, 90%, and 93%, respectively, and treatment failure eventually occurred in 50%, 25%, 40%, and 29% of cases, respectively. Based on these data, the authors recommended anti-IL-6 monoclonal antibody therapies with or without corticosteroids as the initial therapy and CsA for anti-IL-6 refractory cases, particularly to improve persistent ascites and thrombocytopenia. However, because this study was essentially based on published cases, there may be publication bias. In addition, the follow-up periods of these patients were unknown, and the criteria for responses and failures have not been standardized.

In the current study, to avoid publication bias, we used a retrospective multicenter registration to analyze treatments for TAFRO syndrome. Because it was difficult to objectively evaluate the treatment responses, we used TTNT as an objective marker of treatment efficacy and set it as the primary end point. As a second-line treatment, Rit appeared to be better than Toc in terms of superior TTNT. In contrast, no significant difference was observed in terms of OS between the second-line treatment groups. It is likely that subsequent therapies rescued a large proportion of patients who failed the second-line treatments.

There were several limitations to our study. First, the number of enrolled patients was small. Second, the second-line treatments were selected by attending physicians; therefore, the selection may have reflected physician preference. Due to the possible renal toxicity of CsA, physicians may have not chosen this agent for patients with severe renal dysfunction. Because the use of Toc was approved for iMCD in Japan in 2005, physicians may have preferred to use this agent for those with lymphadenopathy. Rit was approved for the treatment of immune thrombocytopenia in Japan in March 2017; physicians may have begun to preferentially use this agent after its approval. Third, owing to the nature of the multicenter surveillance study, detailed clinical courses, including information on the dosages of these agents, were not available.

In summary, the results of the current study indicated that Toc, CsA, and Rit were commonly used for the treatment of patients with corticosteroid-resistant TAFRO syndrome in Japan. Among them, Rit seemed to be a promising agent. Infections were the major causes of death in our cohort. To establish optimal treatment strategies for TAFRO syndrome, further studies are warranted.

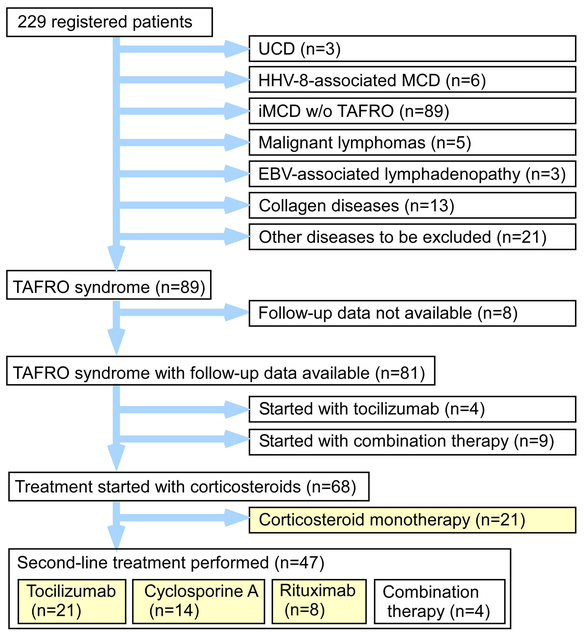

Fig. 1. Selection of patients with TAFRO syndrome treated with corticosteroids as first-line therapy and either tocilizumab, cyclosporine A, or rituximab as second-line treatment from the Multicenter Collaborative Retrospective Study for Establishing the Concept of TAFRO Syndrome Registry in Japan.

Table 2. Patient characteristics at diagnosis

Parameters	Reference ranges	Second-line treatment after corticosteroid therapy			
		Tocilizumab (n=21)	Cyclosporine A (n=14)	Rituximab (n=8)	P-values
Median age [range]		47 [20–85]	51 [30–72]	50 [46–64]	0.78
Male:female		16:5	5:9	2:6	0.016
WBC (×1,000/μL)	3.0–9.1	11.8 (7.4–15.4)	9.3 (7.0–13.0)	9.0 (5.8–16.6)	0.77
Hb (g/dL)	12.9–9.1	10.3 (7.9–12.0)	8.0 (6.8–10.3)	8.1 (6.7–9.7)	0.12
PLT (×1,000/μL)	143–333	31 (18–68)	23 (12–56)	16 (9–33)	0.13
BUN (mg/dL)	8–22	56 (22–71)	33 (20–52)	29 (12–81)	0.42
Creatinine (mg/dL)	0.60–1.10	1.66 (1.10–2.50)	1.30 (0.90–1.90)	1.40 (0.75–3.45)	0.62
Total protein (g/dL)	6.7–8.3	5.4 (5.1–6.2)	5.2 (4.9–6.3)	5.8 (5.1–6.3)	0.91
ALB (g/dL)	4.0–5.0	2.3 (1.8–2.4)	2.3 (2.0–2.5)	2.0 (1.3–2.6)	0.41
CRP (mg/dL)	≤0.3	13.6 (10.4–18.4)	18.3 (9.6–28.5)	19.0 (16.3–25.2)	0.32
LDH (IU/L)	119–229	221 (172–253)	236 (193–467)	212 (178–294)	0.38
ALP (IU/L)	115–359	660 (432–1,194)	965 (360–1,568)	413 (216–1,066)	0.35
γ-GTP (IU/L)	9-32	122 (73–265) (n=20)	139 (61–250) (n=13)	111 (61–141)	0.68
AST (IU/L)	13–33	27 (16–38)	27 (18–86)	24 (17–65)	0.70
ALT (IU/L)	8–42	18 (10–31)	21.5 (12–85)	23 (9–47)	0.64
IgG (mg/dL)	870–1,700	1,179 (1,060–1,501) (n=19)	1,377 (1,142–1,880)	1,569 (1,460–1,637) (n=7)	0.13
IgA (mg/dL)	110–410	190 (171–260) (n=19)	223 (175–254)	232 (186–436) (n=7)	0.58
IgM (mg/dL)	86–160	75 (61–90) (n=19)	60 (40–88)	81 (52–141)	0.21
IL-6 (pg/mL)	≤4.0	23.0 (16.0–34.0) (n=20)	18 (8.2–37.4) (n=10)	13.2 (11.6–142.4) (n=5)	0.40
sIL2R (U/mL)	145–51	1,608 (992–2,301) (n=20)	1,341 (1,026–2,656) (n=13)	1,500 (996–1,979)	0.91
D-dimer (μg/mL)	≤1.0	15.4 (7.9–23.5) (n=18)	11.4 (5.0–13.5) (n=11)	9.6 (5.0–15.0) (n=7)	0.92
FDP (μg/mL)	≤5.0	35.0 (17.4–55.7) (n=16)	27.3 (18.5–36.6) (n=12)	19.5 (8.7–41.1) (n=7)	0.18

For laboratory data, median values (25–75th percentiles) are shown. Numbers of evaluated patients are indicated if not all the patients were examined.

Table 1. Treatment profiles of our cohort (n=81)

- Number of patients who received immunosuppressive treatments (some patients sequentially received multiple therapies.)
  - Corticosteroids 81
  - Tocilizumab 32
  - Cyclosporine 31
  - Rituximab 18
  - CPA (alone or with Combination CT) 8
  - Tacrolimus 1
- Number of patients who received non-immunosuppressive treatments
  - Hemodialysis 26
  - Plasma exchange 10
  - TPO receptor agonists 10
  - IVIG 2

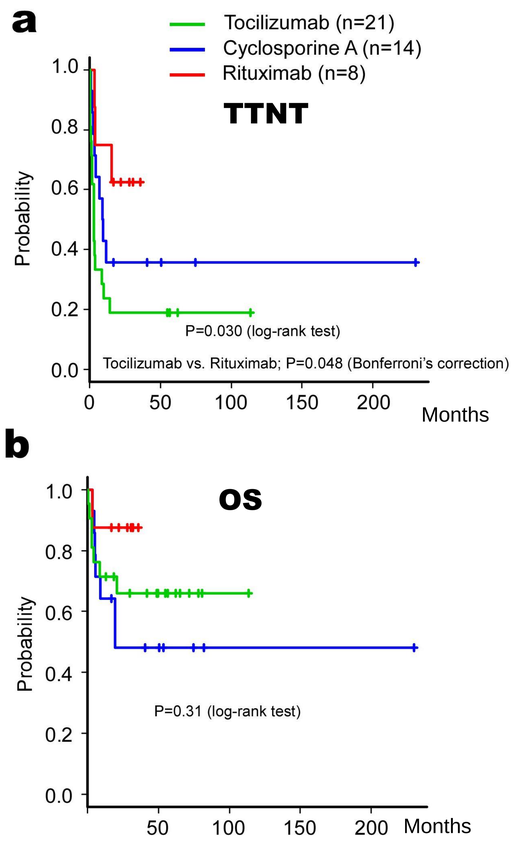

Fig. 2. (a) Time to next treatment or death after initiation of second-line treatment. (b) Overall survival after initiation of second-line treatment.

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Conflict of interest

Dr. AOKI reports personal fees from AbbVie GK., and Janssen Pharmaceutical K.K, outside the submitted work; Dr. Masaki reports grants from Eisai Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Astellas Pharma Inc., Ono Pharmaceutical Co. Ltd., and Pfizer Seiyaku K. K. during the conduct of the study.