LEADING ARTICLE

Efficacy and safety of mycophenolate mofetil in treating immune-related hepatitis induced by immune checkpoint inhibitor use: A retrospective study

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Abstract

Background and Aim: To investigate the outcomes in eight Japanese patients with cancer treated with mycophenolate mofetil (MMF) and corticosteroids for immune checkpoint inhibitor treatment-induced severe immune-related hepatitis (ir-hepatitis) and the efficacy and safety of MMF.

Methods: We retrospectively examined patient background, treatment course, as well as examination and imaging data using electronic medical records.

Results: The ratio of male to female patients was 7:1, and the median age was 60 years (27–72 years). There were five and two cases of kidney cancer and malignant melanoma, respectively, and one case of lung cancer. The median number of days until MMF administration in addition to systemic corticosteroid therapy after the onset of ir-hepatitis was 14.5 (2–42). The patients were categorized as four "good responders" who showed an improvement in the liver function tests following MMF treatment and four "poor responders" who did not. Furthermore, the time from the onset of ir-hepatitis to initial MMF administration was significantly shorter in good responders (median 3 days, range 2–15 days) than in poor responders (median 25.5 days, range 14–42 days) ($P = 0.042$). No significant intergroup difference was observed in other clinical factors. No serious adverse events caused by MMF were observed in any case.

Conclusions: According to these findings, early recognition of corticosteroid refractoriness and the use of MMF may be beneficial in patients with ir-hepatitis.

Introduction

Immune checkpoint inhibitors (ICIs) are promising drugs for treating diseases by strengthening the immune system of patients with cancer. They enhance antitumor effects by blocking endogenous factors such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death-1 (PD-1). ICIs, including nivolumab, pembrolizuab, and ipilimumab, have been approved in many countries, as they prolong the overall survival of patients with various types of cancer. Their use may lead to unique adverse events known as immune-related adverse events (irAEs), and early detection and proper management of irAEs is essential as they may lead to fatal outcomes. The "Cancer Immunotherapy Guidelines" created by the Japanese Society of Medical Oncology (JSMO) and guidelines on ICI-induced irAEs issued by the American Society of Clinical Oncology (ASCO) describe treatments for immune-related hepatitis (ir-hepatitis).[1,2] Both guidelines state that ICI administration can be continued after the occurrence of grade 1 ir-hepatitis with regular monitoring of liver function parameters. In case of deterioration to grade 2, ICI administration should be discontinued and liver function parameters should be monitored. Furthermore, corticosteroids should be administered if abnormal liver function test values persist for more than 5–7 days or worsen further. In case of deterioration of ir-hepatitis to ≥grade 3, ICI administration should be discontinued and 1–2 mg/kg of methylprednisolone (mPSL) or an equivalent amount of corticosteroid should be given as an intravenous injection, and if liver function test values show no improvements for more than 3–5 days or deteriorate further, the combined use of 1 g of mycophenolate mofetil (MMF) twice daily or the use of other immunosuppressants should be considered. Meanwhile, the efficacy of MMF in treating liver dysfunctions occurring after ICI administration has not been established yet, and the use of MMF for this purpose is currently not covered by insurance in Japan.[3] Possible side effects of MMF include diarrhea and hyperuricemia. Side effects that require attention include malignant lymphoma and skin tumor; however, they have been reported to occur very rarely.

To date, there have been many case reports on the treatment of ICI-induced ir-hepatitis using MMF[4–16]; however, we could find no reports that comprehensively describe when and how much MMF should be administered. In this study, we investigated the outcomes of Japanese patients with cancer treated using MMF combined with corticosteroids for ir-hepatitis induced via various ICIs to clarify the efficacy and safety of MMF in ir-hepatitis treatment.

Methods

Subjects. A total of 1227 patients underwent ICI treatment at the Osaka International Cancer Institute (hereinafter our institute) between January 2018 and December 2020. Of them, eight Japanese patients with cancer in whom MMF in combination with corticosteroids was used for treating ICI treatment-induced ir-hepatitis and whose treatment details could be reviewed using electronic medical records were included in this study.

Data collection and evaluation. Patient background, treatment course, and examination and imaging data were retrospectively collected from electronic medical records. Hepatitis was evaluated using the Common Terminology Criteria for Adverse Events ver 5.0. Diagnosis of ir-hepatitis has been described in the previous reports from our instutition.[17] Briefly, it was done by the attending physician and hepatologists after the risk of other liver disorders had been eliminated based on various examinations, such as medical interviews; blood tests, including immunoglobulin G (Ig-G), Ig-M, anti-nuclear antibody, anti-mitochondrial antibody; and serological tests for hepatitis (A, B, C, and E), herpes simplex virus, and cytomegalovirus; or imaging modalities, such as ultrasonography, computed tomography (CT), or magnetic resonance imaging. MMF administration was determined according to guidelines at the discretion of the attending physician and hepatologist. The day of ir-hepatitis onset was defined as day 0. Regarding liver function tests, total bilirubin (T-Bil; normal range, ≤1.5 mg/dL), aspartate transaminase (AST; normal range, ≤30 IU/L), alanine transaminase (ALT; normal

range, ≤30 IU/L), and alkaline phosphatase (ALP; normal range, ≤322 IU/L) were evaluated. In the present study, "good responders" were defined as those showing persistent improvement to grade 1 or less in liver function tests during MMF treatment, whereas "poor responders" were defined as those whose liver function tests did not improve to grade 1.

Ethical considerations. This study was conducted in compliance with the "Declaration of Helsinki" and the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and approved by the Ethical Review Board of our institute (approval number: 20061). This study gave due consideration to personal data protection, and data were handled following anonymization. Information regarding this study is available on our institute's website, and we adopted an opt-out system that can respond to requests of withdrawal from research whenever necessary.

Statistical analysis. Mann–Whitney's U test, chi-square test, and Fisher's exact test were used for intergroup comparisons as appropriate.

Results

Patient background of eight patients and treatment course for ir-hepatitis. Patient background information is summarized in Table 1, and treatment course for ir-hepatitis is summarized in Table 2. The ratio of male to female patients was 7:1. The patients had a median age of 60 years (range: 27–72 years). By cancer type, five patients, two patients, and one patient had renal cell carcinoma, malignant melanoma, and non-small-cell lung cancer, respectively. No patients had a previous history of chronic liver disease. Five patients had received previous cancer treatment before the current ICI treatment, three of whom had been treated with another ICI regimen (cases 3, 4, and 5). In the current ICI treatment, nivolumab, ipilimumab + nivolumab, and pembrolizumab were used in three, three, and two cases, respectively; in the two cases in which pembrolizumab was used, carboplatin and pemetrexed were used in combination in one case (case 6), whereas axitinib was administered concurrently in the other (case 8). The median duration of the ICI treatment was 53 days (range: 21–582 days). The median time from the commencement of ICI treatment to the onset of ir-hepatitis was 63 days (range: 4–721 days). The ir-hepatitis occurred in a median of 36 days (range: 4–426 days) after the final ICI administration. At the onset of ir-hepatitis,

Table 1 Background of eight cancer patients with ir-hepatitis who underwent MMF treatment

	Overall	Good responders	Poor responders	*P*-value
Number of cases	8	4	4	—
Age (years)	60 (27–72)[†]	64 (50–69)	53 (27–72)	0.387
Sex (male/female)	7/1	4/0	3/1	1.000
Type of malignancy (renal cell carcinoma/malignant melanoma/non-small-cell lung cancer)	5/2/1	3/1/0	2/1/1	0.549
History of chronic liver disease (yes/no)	0/8	0/4	0/4	1.000
ICI that caused ir-hepatitis (nivolumab/ipilimumab + nivolumab/pembrolizumab)	3/3/2	2/2/0	1/1/2	0.264
Duration of ICI treatment (days)	53 (21–582)	84 (21–582)	42.5 (21–309)	0.554
Time from the commencement of ICI treatment to the onset of ir-hepatitis (days)	63 (4–721)	134.5 (19–691)	55 (4–721)	0.772
At baseline				
T-Bil (mg/dL)	0.5 (0.3–0.7)	0.4 (0.3–0.6)	0.5 (0.3–0.7)	0.448
AST (IU/L)	21.5 (17–58)	49 (20–58)	20 (17–26)	0.169
ALT (IU/L)	54.5 (12–330)	89 (25–103)	28 (12–330)	0.655
ALP (IU/L)	230 (187–450)	276 (201–450)	230 (187–264)	0.177
At onset of ir-hepatitis				
T-Bil (mg/dL)	1.25 (0.6–2.7)	1.7 (0.6–2.7)	1.0 (0.7–1.9)	0.387
AST (IU/L)	345 (99–1243)	345 (99–686)	318 (128–1243)	0.773
ALT (IU/L)	404 (116–1136)	337.5 (202–606)	423 (116–1136)	0.564
ALP (IU/L)	829.5 (235–2370)	1468 (638–2370)	614 (235–927)	0.083
CTCAE grade of liver injury (3/4)	6/2	3/1	3/1	1.000
Duration from the onset of ir-hepatitis to initial MMF administration (days)	14.5 (2–42)	3 (2–15)	25.5 (14–42)	0.042
Starting dose of MMF (500 mg/1000 mg/2000 mg)	1/1/6	1/0/3	0/1/3	0.368
Duration of MMF administration (days)	59 (29–90)	45.5 (30–69)	77 (29–90)	0.248

[†]Data expressed as median (range).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitor, ir-hepatitis, immune-related hepatitis; MMF, mycophenolate mofetil; T-Bil, total bilirubin.

Table 2   Treatment course of eight cancer patients with ir-hepatitis who underwent MMF treatment

No	Age (years)	Sex	Type of malignancy	Previous cancer treatment	Current ICI treatment	Duration of ICI treatment (days)	Time from the commencement of ICI treatment to the onset of ir-hepatitis (days)	Changes in liver function data after the onset of ir-hepatitis	Dosing method of corticosteroid	Dosing method of MMF	Outcome
1	69	M	Renal cell carcinoma	None	Ipilimumab + Nivolumab	21	19	(see liver function table 1 below)	(see corticosteroid 1 below)	≪MMF≫ day 2–24: 2000mg; day 25–31: 1000mg	Resumption of treatment for the underlying disease using axitinib on day 199.
2	50	M	Renal cell carcinoma	Sunitinib ↓ Everolimus ↓ Pazopanib	Nivolumab	582	691	(see liver function table 2 below)	(see corticosteroid 2 below)	≪MMF≫ day 3–44: 2000mg; day 45–51: 1000mg	Resumption of treatment for the underlying disease using axitinib on day 67.

Patient 1 — Changes in liver function data after the onset of ir-hepatitis

day	AST	ALT	T−Bil	ALP
0	427	202	1.4	1518
2	636	170	2.4	2277
4	851	179	1.5	3894
6	194	141	0.9	2864
7	61	107	1.0	1993
14	20	42	1.4	817
23	12	15	0.9	420
31	13	18	0.6	329
39	14	17	0.6	280
45	13	14	0.5	243
53	14	14	0.4	220
60	13	13	0.4	199
66	15	13	0.4	188
74	14	11	0.5	181
88	16	10	0.5	252
97	16	11	0.4	232

Patient 1 — Dosing method of corticosteroid

≪mPSL (intravenous)≫
day −11–−3: 60mg: Used for cerebral edema and rash
≪DEX (intravenous)≫
day −2–0: 16mg
≪PSL (intravenous)≫
day 1–3: 1000mg: Used for ir-hepatitis
day 4–10: 160mg
day 11–12: 120mg
day 13–15: 80mg
≪PSL (oral)≫
day 16–17: 60mg
day 18–19: 50mg
day 20–22: 40mg
day 23–49: 30mg
day 50–63: 20mg
day 64–66: 15mg
day 67–79: 12mg
day 80–96: 10mg
day 97–122: 7mg
day 123–150: 5mg
day 151–278: 3mg
day 279–306: 2mg
day 307–362: 1mg

Patient 2 — Changes in liver function data after the onset of ir-hepatitis

day	AST	ALT	T−Bil	ALP
0	686	606	2.0	638
2	483	504	1.9	NT
4	351	430	1.6	NT
6	63	230	0.8	NT
8	39	139	0.6	NT
15	14	35	0.4	NT
22	21	43	0.4	NT
29	39	106	0.4	NT
36	33	131	0.4	NT
43	35	104	0.4	NT
50	12	25	0.3	NT
56	9	17	0.2	NT
63	10	20	0.3	NT
71	13	22	0.3	NT
80	21	29	0.2	NT
87	30	37	0.7	772
101	27	31	0.4	554

Patient 2 — Dosing method of corticosteroid

≪DEX (oral)≫
day −625–−593: 1mg: Used for cerebral edema
day −389–−249: 2mg
day −248–−60: 1mg
≪DEX (intravenous)≫
day −59–−55: 4mg
≪DEX (oral)≫
day −54–−12: 4mg
day −11–−1: 2mg
≪mPSL (intravenous)≫
day 0–2: 500mg: Used for ir-hepatitis
day 3–9: 70mg
day 10–16: 60mg
day 17–23: 50mg
day 24–25: 40mg
≪PSL (oral)≫
day 26–38: 40mg
day 39–58: 30mg
day 59–61: 25mg
day 62–69: 20mg
day 70–79: 15mg
day 80–107: 5mg
≪Hydrocortisone (oral)≫
day 45–81: 15mg

									day	AST	ALT	T~Bil	ALP	
									0	263	274	2.7	2370	
									2	316	464	2.1	2502	
									4	146	535	1.2	1912	
									6	85	482	1.1	1432	
									14	48	247	1.0	925	
3	61	M	Malignant melanoma	Pembrolizumab	Ipilimumab + Nivolumab	42	29		21	33	161	1.0	594	
									28	26	98	0.7	382	
									35	**28**	**75**	**0.7**	**304**	
									38	**24**	**68**	**0.7**	**256**	
									52	**23**	**46**	**0.6**	**310**	

Patient 3 treatment:

≪PSL (intravenous) ≫
day 0–1： 120mg： Used for ir-hepatitis
≪mPSL (intravenous) ≫
day 2–4： 1000mg
≪PSL (intravenous)≫
day 5–8： 120mg
day 9–12： 100mg
day 13–17： 80mg
day 18–21： 60mg
day 22–26： 50mg
day 27–31： 40mg
≪PSL (oral)≫
day 32–36： 30mg
day 37–43： 20mg
day 44–50： 10mg
day 51–57： 5mg

≪MMF≫
day 3–71： 2000mg

Hospital discharge on day 39 in the treatment plan of best supportive care.

									day	AST	ALT	T−Bil	ALP	
									0	99	401	0.6	1418	
									2	58	345	0.6	1351	
									4	56	290	0.6	NT	
									6	52	337	0.5	1226	
									14	17	90	0.6	532	
4	67	M	Renal cell carcinoma	Ipilimumab + Nivolumab	Nivolumab	126	240		21	23	94	0.4	606	
									28	**22**	**36**	**0.9**	**346**	
									35	108	115	0.5	1541	
									42	14	72	0.5	1819	
									48	**11**	**24**	**0.5**	**760**	
									54	**15**	**16**	**0.4**	**564**	
									60	**13**	**26**	**0.8**	**395**	
									70	**11**	**6**	**0.4**	**444**	

Patient 4 treatment:

≪mPSL (intravenous) ≫
day −91–−89： 1000mg： Used for cytokine storm
≪PSL (intravenous) ≫
day −88–−84： 80mg
day −83： 60mg
day −82–−75： 50mg
day −74–−68： 40mg
[day −67–−8： Change hospital for rehabilitation]
≪PSL (intravenous) ≫
day −7–−4： 70mg： Used for kidney disorder, thrombocytopenia and rash
day −3–−1： 50mg
day 0–4： 140mg： Used for ir-hepatitis
≪mPSL (intravenous) ≫
day 5–7： 1000mg
day 8–11： 500mg
day 12： 250mg
≪PSL (intravenous) ≫
day 13–17： 140mg
day 18–21： 120mg
day 22–25： 100mg
day 26–29： 80mg
day 30–33： 60mg
day 34–37： 40mg
day 38–45： 140mg
day 46–50： 120mg
day 51–57： 100mg
day 58–65： 60mg
day 66–72： 40mg

≪MMF≫
day 15–26： 500mg
day 35–37： 500mg
day38–56： 1000mg

Death on day 73 by the underlying disease.

								day	AST	ALT	T−Bil	ALP			
5	27	M	Malignant melanoma	Nivolumab	Ipilimumab + Nivolumab	21	13	0	147	116	0.9	732			

≪mPSL (intravenous)≫
day −1： 60mg： Used for hepatitis and cytokine storm
day 0–11： 120mg： Used for ir-hepatitis
day 12–18： 100mg
≪mPSL (oral)≫
day 19–20： 80mg
day 21： 100mg
≪mPSL (intravenous)≫
day 22–42： 100mg
day 43–53： 90mg
day 54–69： 80mg
day 70–74： 70mg
day 75–78：： 60mg
day 79–82： 50mg
day 83–91： 40mg
day 92–95： 30mg
≪mPSL (oral)≫
day 96–104： 20mg

≪MMF≫ day 35– 104： 2000mg

Change hospital on day 104 in the treatment plan of best supportive care.

day	AST	ALT	T−Bil	ALP
0	147	116	0.9	732
2	203	228	0.4	585
4	81	214	0.6	462
6	56	159	0.6	458
12	38	128	0.5	306
18	31	100	0.5	238
25	50	151	0.6	214
34	41	128	0.6	179
42	26	105	0.6	157
49	23	108	0.6	151
56	**19**	**79**	**0.7**	**124**
63	23	95	0.7	108
67	**21**	**84**	**0.6**	**111**
74	**17**	**79**	**0.5**	**114**
82	22	91	0.5	112
89	42	104	0.6	153
99	41	135	0.8	182
102	35	120	0.8	217

| 6 | 72 | M | Non-small cell lung cancer | None | Pembrolizumab + Carboplatin + Pemetrexed | 64 | 97 |

≪PSL (oral)≫
day −39–−17： 30mg： Used for fever
day −18–−1： 25mg
day 0–4： 60mg： Used for ir-hepatitis
day 5–9： 50mg
day 10–21： 40mg
day 22–36： 30mg
day 37： 20mg

≪MMF≫ day 16–37： 1000mg

Change hospital on day 37. for the treatment of tuberculosis.

day	AST	ALT	T−Bil	ALP
0	128	439	1.1	235
2	75	331	1.0	227
4	61	234	1.0	238
7	51	213	1.0	201
9	53	199	1.1	224
16	70	198	0.9	226
23	33	93	1.0	213
28	**43**	**81**	**0.8**	**174**
35	60	102	1.0	239

| 7 | 59 | F | Renal cell carcinoma | Sunitinib ↓ Axitinib ↓ Temsirolimus | Nivolumab | 309 | 721 |

≪PSL (oral)≫
day −700–−694： 20mg： Used for immune–related neuropathy
day −693–−687： 15mg
day −686–−673： 10mg
day −672–−666： 20mg
day −665–−659： 15mg
day −658–−652： 20mg
day −651–−645： 15mg
day −644–−553： 10mg
day −552–−411： 7.5mg
day −410–−404： 40mg
day −403–−364： 20mg
day −363–−334： 15mg
day −333–−316： 30mg
day −315–−134： 25mg
day −133–−106： 20mg
day −105–9： 25mg： Used for hepatitis
≪mPSL (intravenous)≫
day 10–13： 1000mg
day 14–17： 80mg
day 18–37： 70mg
day 38–42： 60mg
day 43–48： 50mg
day 49–55： 40mg
day 56–64： 30mg
≪PSL (oral)≫
day 65–75： 30mg
≪mPSL (intravenous)≫
day 76–90： 30mg

≪MMF≫ day 14–89： 2000mg

Death on day 93 by the underlying disease.

day	AST	ALT	T−Bil	ALP
0	1243	1136	1.9	927
1	471	854	3.6	789
2	270	610	4.3	729
3	202	550	6.5	858
6	137	315	8.2	2077
13	126	174	16.4	1777
20	161	215	21.0	2905
27	128	156	16.4	2881
35	59	54	9.4	2176
42	50	29	5.2	1465
48	36	13	4.2	1049
56	38	11	2.6	1163
65	39	14	1.9	1678
72	29	9	1.5	1757
83	30	11	1.3	2052

Case: 8   Age: 47   Sex: M   Primary disease: Renal cell carcinoma   (None)   ICI: Pembrolizumab + Axitinib   21   4

day	AST	ALT	T−Bil	ALP	≪PSL (intravenous)≫
0	489	407	**0.7**	496	day 0–1 ： 160mg ： Used for ir-hepatitis
2	1145	1130	1.1	463	day 5–7 ： 160mg
4	961	1560	2.6	464	day 8–10 ： 80mg
6	243	909	1.8	554	day 11–14 ： 70mg
12	**48**	291	**0.7**	561	day 15–17 ： 60mg
19	73	161	**0.9**	**359**	day 18–21 ： 50mg
25	**42**	**90**	**0.6**	**253**	day 22–24 ： 40mg
32	**33**	**20**	3.0	**167**	day 25–29 ： 30mg
39	**50**	94	6.5	426	day 33–37 ： 100mg
46	224	1030	12.8	519	day 38–42 ： 80mg
53	77	196	12.8	566	day 43–44 ： 60mg
60	70	343	12.1	884	day 50–52 ： 80mg
67	615	1282	10.2	1209	day 53–55 ： 70mg
74	176	863	9.3	1224	day 56–63 ： 60mg
81	**67**	253	4.7	874	day 64–65 ： 50mg
88	**53**	133	2.3	850	day 66–67 ： 70mg

day 68–81 ： 140mg
day 85–87 ： 120mg
≪mPSL (intravenous)≫
day 2–4 ： 1000mg
day 30–32 ： 1000mg
day 61–63 ： 250mg
day 82–84 ： 250mg
≪PSL (oral)≫
day 45–46 ： 60mg
day 59–61 ： 60mg

≪MMF≫ day 42–87 ： 2000mg

Commencement of tacrolimus for ir-hepatitis on day 87.

Negative numbers denote the steroid administration before the onset of ir−hepatitis.

Liver function data of the grade 1 or less are shown in bold.

M ： male, F ： female, ICI ： Immune checkpoint inhibitor, ir−hepatitis ： Immune−related hepatitis, BSC ： Best supportive care, NT ： not tested

AST ： Aspartate transaminase, ALT ： Alanine aminotransferase, T−Bil ： Total bilirubin, ALP ： Alkaline phosphatase

mPSL ： Methylprednisolone, PSL ： Prednisolone, DEX ： Dexamethasone sodium phosphate, MMF ： Mycophenolate mofetil

median T-Bil, AST, ALT, and ALP were 1.25 mg/dL (range: 0.6–2.7 mg/dL), 345 IU/L (range: 99–1243 IU/L), 404 IU/L (range: 116–1136 IU/L), and 829.5 IU/L (range: 235–2370 IU/L), respectively. Six and two patients presented with the CTCAE grade 3 and grade 4 liver injury.

Concerning the medication for ir-hepatitis, corticosteroid administration was started before the onset of ir-hepatitis for treating irAEs other than ir-hepatitis or other diseases in six cases (cases 1, 2, 4, 5, 6, and 7); the median number of days from the start of corticosteroid administration until the onset of ir-hepatitis was 65 days (range: 1–700 days). In the remaining two cases (cases 3 and 8), corticosteroid administration was started at the onset of ir-hepatitis. The median dosing period of corticosteroids after the onset of ir-hepatitis was 88.5 days (range: 37–361 days). MMF was added after the patients were considered non-responsive to corticosteroids. The median number of days until the start of MMF administration after the onset of ir-hepatitis was 14.5 (range: 2–42 days). The daily MMF dose at introduction was 2000 mg/day in six cases, 1000 mg/day in one case (case 6), and 500 mg/day in one case (case 4), out of the total of eight cases. The duration of MMF administration was 47.5 days (range: 22–76 days).

Effectiveness and safety of MMF for ir-hepatitis.
Changes in the liver function tests in each of the eight cases before and after the MMF administration are shown in Table 2. In cases 1–4, MMF was effective and led to alleviation up to CTCAE grade 1 of all four laboratory tests, namely T-Bil, AST, ALT, and ALP. In these four cases, the number of days required for ir-hepatitis improvement to grade 1 following MMF administration was 23 in case 1, 50 in case 2, 35 in case 3, and 48 in case 4. The treatment of the primary disease through the next regimen was resumed in cases 1 and 2. The best supportive care (BSC) was then established in case 3. Case 4 died of exacerbation of the primary cancer disease. Therefore, these four cases (cases 1–4) who had ir-hepatitis were regarded as "good responders" to MMF treatment.

However, the remaining four cases (cases 5–8) did not present with a good response to the MMF treatment; MMF did not result in sufficient decrease in the levels of T-Bil, AST, ALT, and ALP to CTCAE grade 1 during follow-up. These patients with ir-hepatitis were regarded as "poor responders" to MMF treatment. As for the outcome of these patients, BSC was subsequently given in case 5. Case 6 was transferred to another hospital to treat the tuberculosis that occurred accidentally. Case
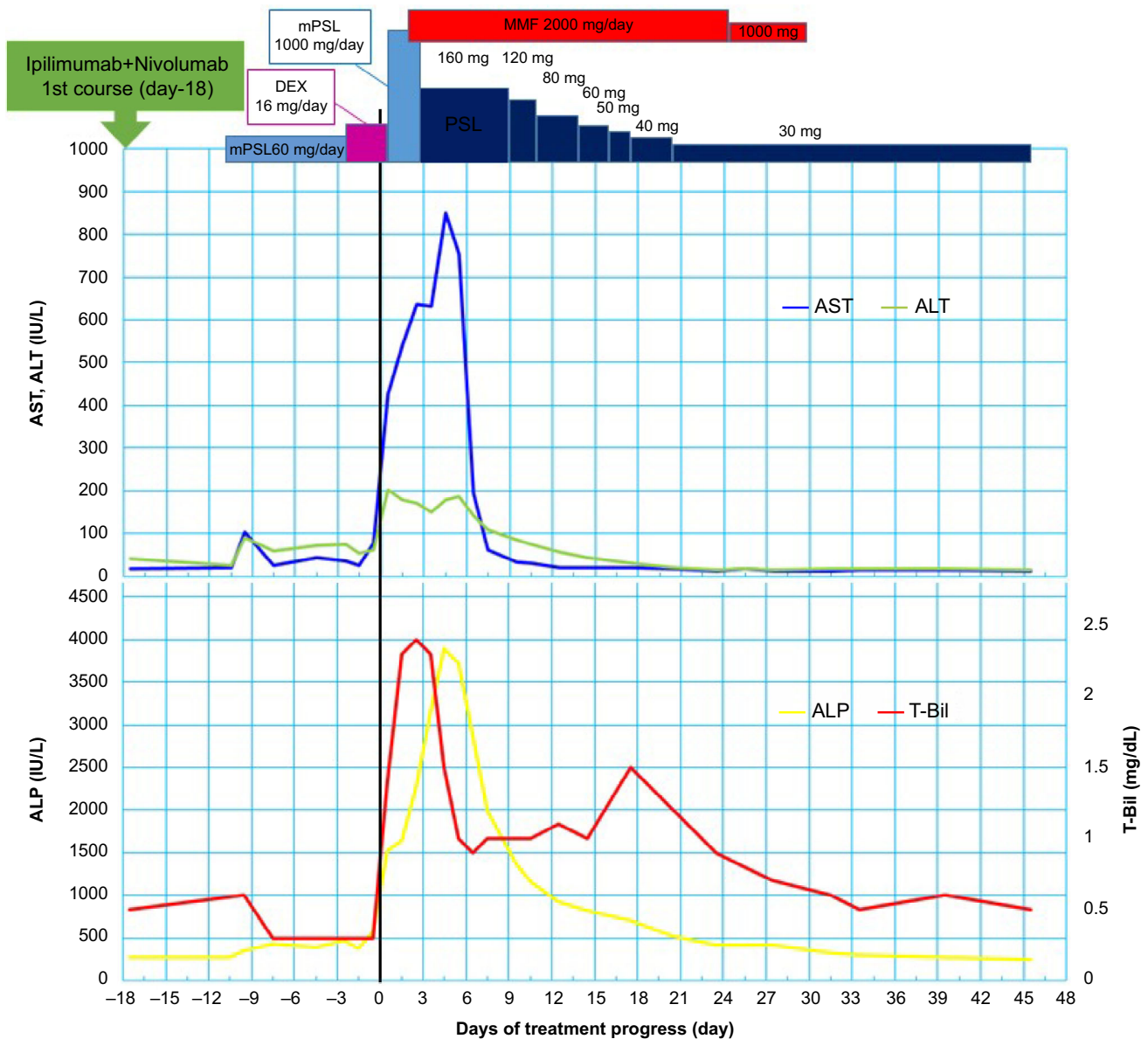
Figure 1 Clinical course after first course of ipilimumab + nivolumab combination therapy in case 1. The day of ir-hepatitis onset was defined as day 0. The patient was diagnosed with immune-related dermatologic disorder on day 11, and 60 mg/day of mPSL was administered intravenously. On day 0, fever persisted, and abnormal blood test results were observed: AST, ALT, and ALP levels were 427, 202, and 1518 IU/L. On days 1–3, a steroid pulse treatment (mPSL, 1000 mg/day) was given; furthermore, MMF administration was commenced on day 2. On day 2, fever subsided, and on day 3, the dose was changed from 1000 mg/day mPSL to 160 mg/day PSL. After day 9, ir-hepatitis rapidly improved, and PSL was gradually reduced. MMF was administered at a reduced dose of 1000 mg/day on day 25 and then discontinued on day 31. Since then, PSL dose was gradually reduced and there was no recurrence of ir-hepatitis.

7 died of exacerbation of the primary cancer. In case 8, in which MMF was ineffective in treating ir-hepatitis, tacrolimus was administered in addition to prednisolone (PSL) and MMF on day 87, and the treatment is still going on.

When the clinical factors were compared between the four "good responders" and four "poor responders" to the MMF treatment (Table 1), the duration from the onset of ir-hepatitis to initial MMF administration was significantly shorter in good responders (median 3 days, range 2–15 days) than in poor responders (median 25.5 days, range 14–42 days) ($P = 0.042$). No significant difference was observed in the other clinical factors between good and poor responders.

As for adverse events of MMF, no serious adverse events were noted in any of the eight patients with ir-hepatitis except for two patients who presented with infectious diseases (cases 4 and 6); however, the direct causal relationship with MMF remained unclear.

In case 4, cytomegalovirus and aspergillus developed after the administration of corticosteroid and MMF, and treatment was performed in our facility. In case 6, tuberculosis developed after the administration of corticosteroid and MMF; therefore, tuberculosis treatment was given in another hospital.

Case presentation. Figure 1 shows the detailed clinical course of case 1 with right renal cell carcinoma along with multiple lung and brain metastase; the day of ir-hepatitis onset was defined as day 0. The patient suddenly became unable to speak fluently and underwent a detailed head examination at another hospital on day 32. Since multiple brain metastases were found, gamma knife radiosurgery was performed, and the speech disorder improved. Subsequently, on day 21, the patient was transferred to our hospital for systemic treatment. The first course of ipilimumab + nivolumab combination therapy was performed. After 8 days, he was sent to our hospital on an emergency basis because he showed consciousness disorder, systemic rash, and fever. He was diagnosed with immune-related dermatologic disorder, and 60 mg/day of mPSL was administered intravenously. The skin rash was ameliorated, whereas high fever continued, probably because of a thermoregulation disorder caused by irradiation-related brain edema. mPSL was subsequently replaced by 16 mg/day of dexamethasone along with the administration of concentrated glycerin and fructose. On day 0, fever persisted, and abnormal blood test results were observed; AST, ALT, and ALP levels were 427, 202, and 1518 IU/L. Although lumboabdominal CT scan showed no abnormality in the liver and biliary tract, the patient was diagnosed with ir-hepatitis based on the clinical symptoms and blood test results. On days 1–3, a steroid pulse treatment (mPSL, 1000 mg/day) was performed; furthermore, MMF administration was commenced on day 2. On day 2, fever subsided, and on day 3 the dose was changed from 1000 mg/day mPSL (i.v.) to 160-mg/day PSL (i.v.). After day 9, ir-hepatitis rapidly improved, and PSL was gradually reduced. MMF was administered at a reduced dose of 1000 mg/day on day 25 and then discontinued on day 31. Since then, PSL dose was gradually reduced and there was no recurrence of ir-hepatitis. Treatment was resumed in the patient with the underlying disorder (axitinib was started on day 199). The patient subsequently continued to undergo the treatment for the primary disease, but died of respiratory failure caused by an exacerbation of the primary disease on day 1233.

Discussion

ICIs, including nivolumab, pembrolizuab, and ipilimumab, are currently used for treating malignant melanoma, non-small-cell lung cancer, and various other carcinomas, and a wide variety of irAEs have been reported. As the use of ICIs is expected to increase further, the incidence of ≥grade 3 hepatitis as a serious irAE is also likely to increase. Based on the results of clinical trials of ICIs involving patients with melanoma, the incidence of ir-hepatitis, including all grades, was less than 5% in patients undergoing monotherapy with the anti-PD-1 antibody nivolumab but increased to about 20% in patients receiving nivolumab in combination with ipilimumab.[18–20]

Based on its mechanism of pathogenesis, ir-hepatitis is expected to cause a chronic liver disorder similar to autoimmune hepatitis (AIH), but it has been found to differ from AIH in terms of clinical course and pathological features.[21] Zen and Yeh,[22] Sue *et al.*,[23] and Kleiner and Berman.[24] compared ir-hepatitis with AIH in terms of pathological features and reported that while centrilobular hepatitis lesions with mild inflammation in the portal area were observed, the proliferation of CD4- and CD20-positive cells in ICI-related hepatitis was less than in AIH and infiltrating CD8-positive cells were mainly found. These findings suggest that activated T lymphocytes damage hepatocytes and cause liver dysfunction in ir-hepatitis and AIH; however, the types of lymphocytes responsible are different, including CD4- and CD20-positive cells or CD8-positive cells. Accordingly, MMF, which is a drug frequently used as an immunosuppressant and has been reported to be effective for treating AIH,[25,26] could also be effective in treating irAEs.

MMF is an antimetabolite that inhibits DNA synthesis by reversibly and noncompetitively inhibiting inosinate dehydrogenase in the purine biosynthesis pathway.[27] MMF inhibits the proliferation and activation of T and B lymphocytes, which depend mainly on the de novo purine synthesis pathway, and interferes with antibody production, cellular immunity, and cytokine production. Therefore, MMF can be expected to improve ir-hepatitis by impairing lymphocyte function.[28] Various guidelines recommend corticosteroid administration when ir-hepatitis of ≥grade 2 persists without improvement or is exacerbated.[1,2] In cases when the liver function test values do not improve after corticosteroid treatment, the combined use of MMF should be considered. In the present study, MMF was administered at doses of 500–2000 mg/day in addition to the corticosteroid in the eight patients with grade-3 or higher ir-hepatitis according to the dosage and administration criteria provided in the JSMO and ASCO guidelines. The median number of days until the start of MMF administration after the diagnosis of ir-hepatitis was 14.5 days (range: 2–42 days). It is of particular interest to note that, among our patients, patients who received MMF treatment immediately after the onset of ir-hepatitis showed a tendency to have a better response to the MMF treatment. Indeed, the median duration from the onset of ir-hepatitis to initial MMF administration was 3 days (range, 2–15 days) in the "good responders," compared with median 25.5 days (range, 14–42 days) in the "poor responders." According to this, it would be better to start MMF treatment earlier in patients with ir-hepatitis who do not respond to the preceding corticosteroid treatment. In three of our four "good responders" to MMF, corticosteroid was already administered before the onset of ir-hepatitis. In such "steroid-refractory" ir-hepatitis patients, the treatment plan for MMF administration would be easier to decide. However, patients in whom ir-hepatitis developed under the non-administration of corticosteroid, both early recognition of refractoriness to the preceding corticosteroid treatment and the use of MMF may be useful.

When the MMF treatment together with corticosteroids does not show sufficient effectiveness for ir-hepatitis, other drugs, such as antithymocyte globulin (ATG),[29] azathioprine,[30] and tacrolimus,[31] have been suggested to be used as third-line treatment, although the priority of use of these drugs has not been established in any of the guidelines. In this study, oral tacrolimus administration was done in case 8, in whom the irAE was refractory to corticosteroids and MMF. In future, it will be necessary to investigate when

to switch from MMF to next-line treatment and evaluate the efficacy of next-line treatment while treating ir-hepatitis in patients non-responsive or intolerant to MMF.

Adverse events of MMF, such as the development of secondary malignant tumor, progressive multifocal leukoencephalopathy, BK virus nephropathy, blood disorder, malignant tumor, gastrointestinal disorder, severe diarrhea, thrombosis, heart disorder, liver dysfunction, pulmonary edema, and convulsions, among others, have been reported. None of the above-mentioned adverse events of MMF was observed.in our patients, suggesting the safety of the MMF treatment in ir-hepatitis to some extent. However, serious infectious diseases, tuberculosis, and infection with cytomegalovirus and aspergillus developed during MMF treatment in two cases. Such infectious diseases may be induced through not only the direct immunosuppressive effect of MMF but also the cancer-bearing condition and the systemic cancer treatment using ICIs and other drugs. During MMF treatment for ir-hepatitis, it is imperative to exercise caution in terms of the development of infectious diseases that may be caused by the complex factors.

This study has some limitations. First, it included a small number of cases observed in a single institution. Second, this was a retrospective study conducted using electronic medical records. Thus, there could have been various biases due to the insufficient statistical power of the tests performed. A multicenter study is necessary to include more cases and perform more accurate evaluations.

Conclusion

In conclusion, we represented the case of eight patients having ir-hepatitis who underwent MMF treatment in addition to corticosteroid in the present study. Better treatment response was found in patients in whom MMF was administered more promptly after the onset of ir-hepatitis. Our results suggest that early recognition of corticosteroid refractoriness and the use of MMF in line with the guidelines[1,2] may be beneficial in patients with ir-hepatitis. Further large-scale studies should offer better understanding concerning the optimal use of MMF in ir-hepatitis.

Ethics Statement

The present study was approved by the Ethical Review Board of the Osaka International Cancer Institute (Osaka, Japan) and conducted in accordance with the ethical guidelines on clinical research (approval no. 20061). Information regarding the present study is available at the institution's website.

Patient Consent Statement

Due consideration was given toward protecting personal information, and patient data was handled after ensuring anonymization. Informed consent was obtained from all patients included in the study. The patients could withdraw their consent for participation at any period throughout the study.

Data availability statement. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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