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Systematic review of survival outcomes for relapsed or refractory adult T-cell leukemia-lymphoma

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Abstract

Introduction: Adult T-cell leukemia-lymphoma (ATL) is a mature T-cell lymphoprolif-erative neoplasm caused by human T-cell leukemia virus type-1 infection. There is no standard treatment for relapsed or refractory (r/r) ATL, and clinical outcomes are poor. This systematic review examined the survival outcomes for r/r ATL treated with various systemic therapies.

Methods: EMBASE and PubMed were searched for studies on r/r ATL, published be-tween January 2010 and January 2020. The main outcome of interest was overall survival (OS). Median OS and an exploratory 30% OS time were assessed based on published data and Kaplan-Meier curves.

Results: There were 21 unique treatment subgroups (from 14 studies), that met the eligibility criteria. Nine subgroups were mogamulizumab treatment, two were moga-mulizumab prior to allogenic hematopoietic stem cell transplantation (allo-HSCT), five were allo-HSCT, and five were other chemotherapy. Respectively, the median OS and 30% OS varied considerably in range for mogamulizumab treatment (2.2–17.6 months and 8.7–27.1 months), allo-HSCT (3.8–6.2 months and 7.5–19.8 months), and other chemotherapy arms (4.1–20.3 months and 7.1–17.0 months).

Conclusion: Mogamulizumab was the most frequently studied treatment regimen and can potentially provide longer survival compared with chemotherapy alone. Future comparisons with synthetic or historical control arms may enable clearer insights into treatment efficacy.

KEYWORDS
adult T-cell leukemia-lymphoma, drug therapy, hematopoietic stem cell transplantation, recurrence, survival, systematic review

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1 | INTRODUCTION

Adult T-cell leukemia-lymphoma (ATL) is a mature T-cell lymphopro-liferative neoplasm caused by the human T-cell leukemia virus type-1 (HTLV-1) infection.[1,2] This peripheral lymphoma was first described in Japan,[3,4] where there is a high incidence in the Kyushu-Okinawa area.[5] The geographic distribution of ATL corresponds with that of HTLV-1 carriers, with high incidence rates of ATL in HTLV-1 endemic regions.[6,7] For example, ATL accounts for ~25% of peripheral T-cell lymphomas in Asia compared with 2% in North America and 1% in Europe.[8]

Patients with ATL have poor survival outcomes despite intensive chemotherapy.[9] ATL can be classified into four clinical subtypes: acute, lymphoma, chronic, and smoldering[10]; two large retrospective studies found a range of 4-year overall survival (OS) rates for each of these respective subtypes: 11–17%, 16–20%, 36–37%, and 52–60%.[11,12] Disease resistance to anti-cancer agents and the increased susceptibility of patients to various infections contribute to low OS rates with conventional chemotherapy (5–13 months).[13,14] Even for those who respond to treatment, the proportion of patients who relapse can exceed 40%,[15] which often occurs within months of stopping treatment.[16]

Relapsed or refractory (r/r) ATL has extremely poor prognosis, with a median OS of less than 4 months after the first salvage therapy with conventional chemotherapy[17] and an OS of 9 months in patients with intensive chemotherapy.[18] However, treatment guidelines and therapeutic algorithms for r/r ATL are not well defined. According to NCCN guidelines, depending on the disease subtype, the recommended treatment options for r/r ATL include experimental therapy in a clinical trial, zidovudine and interferon, chemotherapy, as well as allogeneic hematopoietic stem cell transplantation (allo-HSCT).[19]

Mogamulizumab, a defucosylated humanized monoclonal antibody against C-C chemokine receptor 4 (CCR4) is another promising salvage targeted therapy for patients with r/r ATL, first approved in Japan in 2012 and not yet approved in other countries for r/r ATL.[20] CCR4 is not common in other cancers, but is expressed in more than 90% of ATL patients[21]; its expression is a poor prognostic factor.[22] Mogamulizumab monotherapy has been studied in r/r ATL patients with positive results.[23] A recent study at a single center in Japan demonstrated a median OS and 1-year OS rate with mogamulizumab initiation to be 7.7 months and 42.0%, respectively.[24]

Another treatment option for r/r ATL, lenalidomide, is an oral im-munomodulator with both antiproliferative and antineoplastic activity in B-cell lymphomas in preclinical studies.[25] It was first approved in the United States in 2005 for myelodysplastic syndromes, and in 2017, its indication was expanded to r/r ATL in Japan. The median OS and median progression-free survival with lenalidomide treatment were 20.3 and 3.8 months, respectively.[26] Several studies have assessed treatment outcomes for available therapies for r/r ATL, but there is a lack of consistency across studies in patient characteristics and survival outcome definitions for r/r ATL patients.

The primary objective of this study was to conduct a systematic literature review to synthesize the available evidence on survival outcomes for patients with r/r ATL treated with various systemic therapies.

2 | METHODS

2.1 | Literature search strategy

Articles published on r/r ATL treatment outcomes in English or Japanese between January 1, 2010, and January 31, 2020, were screened from PubMed and EMBASE literature databases. A detailed description of the search terms can be found in Tables S1, S2. This review was planned, conducted, and reported in adherence with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines for quality in reporting systematic reviews.[27]

2.2 | Study selection criteria

The predefined eligibility criteria for inclusion were comprised of r/r ATL patients who received an approved systemic interventional therapy for r/r ATL. Prospective and retrospective observational studies, as well as randomized control trials (RCT), were assessed. Animal studies, in vitro/ex vivo studies, gene expression/protein expression studies, PCR/laboratory studies, editorials, non-systematic reviews, conference minutes, and case studies were excluded. Only studies that reported OS were included. Identified articles were assessed for eligibility by two researchers (WK and TM) independently using a two-step screening process to examine article titles and abstracts and then relevant full texts. Due to the small number of articles identified, especially the lack of available RCTs, no statistical integration, head-to-head comparisons, nor superiority testing was conducted to avoid biases and interpretation challenges. Instead, the eligible studies were synthesized as a systematic literature review with parameters extracted individually and described in the results.

2.3 | Data extraction

Available data were extracted from the included articles into a predefined evidence summary template. Extracted data included: the reasons for exclusion (if applicable), characteristics of the included studies, target population, treatment characteristics, survival outcomes (including OS rate, median OS, and Kaplan-Meier [KM] plots), overall response rate (ORR), complete response (CR), partial response (PR), and adverse events. Data extraction was conducted by two independent researchers (TM and WK).

As part of an exploratory analysis, 30% OS was calculated to obtain estimates of comparative survival. Because eight KM curves from

six studies showed a long tail below 30% survival probability, this statistic was selected for exploratory purposes. For 30% OS and studies without median OS reported, time-to-event outcomes were summarized using pseudo-individual patient data extracted from published KM survival curves. Graph Grabber (v2.0.2, Quintessa, Henley-on-Thames, UK) software application, a tool that enables users to extract data points from a graph image, was used to accurately reconstruct KM curves to obtain precise curve coordinates. The number of patients at risk for each arm during the follow-up was also extracted from identified studies, either presented beneath the published KM curves or extrapolated based on algorithms published in a prior study that assumes constant rate of censoring.[28] Analyses were performed using R (version 4.0.1) with a published reconstruction algorithm.[29]

3 | RESULTS

3.1 | Search results

The systematic search identified 43 studies for title and abstract screening (Figure 1). An additional four studies were identified through a targeted literature search. After removal of duplicates and screening of the full-text articles, 14 studies were ultimately deemed eligible for extraction, which included a total of 21 treatment subgroups.

3.2 | Characteristics of studies and patients

As listed in Table 1, the final articles were 10 retrospective cohort studies, two single-arm phase II studies, one phase II RCT, and one prospective post-marketing surveillance study. Sample sizes ranged from 14 to 723 patients. Only the RCT evaluated r/r ATL patients from the United States/Europe/Latin America regions, whereas all other studies investigated patients in Japan. Eight studies included a mogamulizumab treatment arm: five were single-arm studies, and three were two-arm studies. One mogamulizumab single-arm study reported a subgroup analysis of mogamulizumab treatment prior to allo-HSCT.[30] In each two-arm study, mogamulizumab treatment was compared with chemotherapy without mogamulizumab. Five studies examined allo-HSCT treatment, one single-arm study and four multiple-arm studies.[15,31-34] One multiple-arm study examined survival outcomes of allo-HSCT as well as with mogamulizumab prior to allo-HSCT.[31] Another reported survival outcomes based on patient-level data for several treatment regimens,[32] and two multiple-arm studies reported survival outcomes with and without donor

Records identified through databases searching
n=43
(EMBASE, n=20;
PubMed, n=23)

Additional records identified through targeted review (n=4)

Duplicates (n=7)

Records after duplicates removed
n=40

Records screened
n=40

Excluded by abstract and title (n=6)
- Not population of interest (n=3)
- Not study design of interest (n=3)

Full-text articles assessed for eligibility
n=34

Excluded after full-text review (n=20)
- Not population of interest (n=15)
- Not reporting outcome of interest (n=4)
- Not study design of interest (n=1)

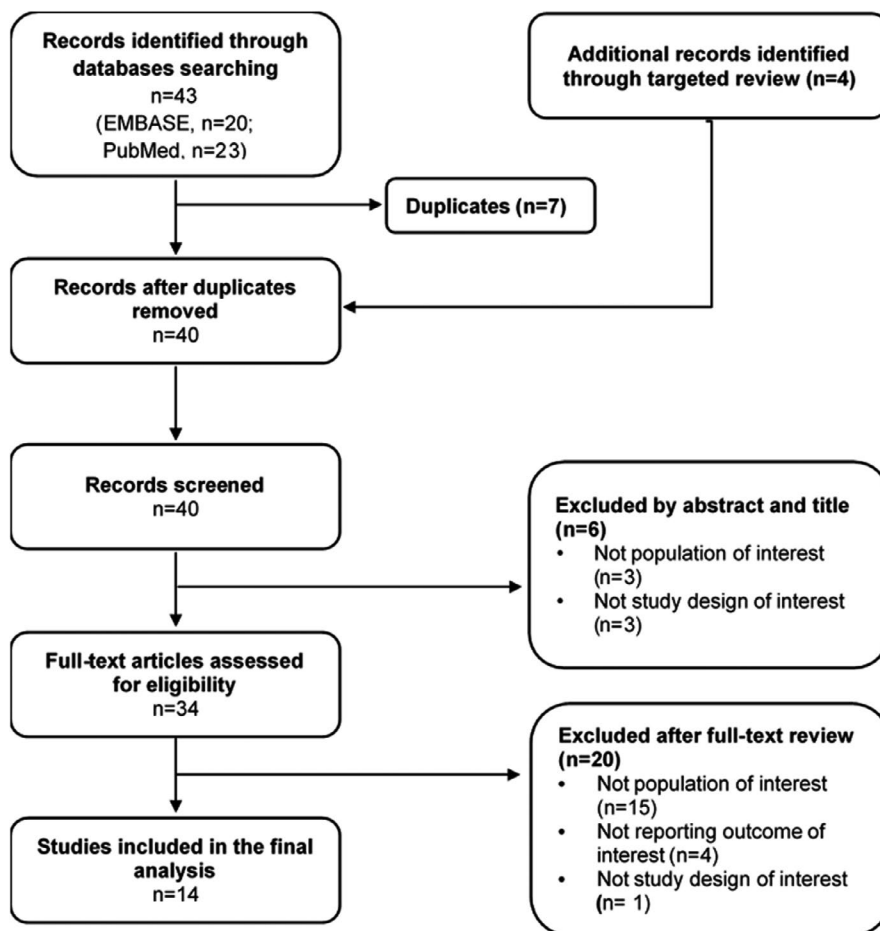**Studies included in the final analysis**
n=14

FIGURE 1 PRISMA flow diagram

lymphocyte infusion (DLI) among patients who received allo-HSCT.[15] One study assessed lenalidomide as a single treatment arm,[26] and one examined EPOCH regimen as a single treatment arm.[35]

The acute subtype was the most common classification of r/r ATL, ranging from 46% to 86% of patients in each study. The second most common subtype was lymphoma type, ranging from 7% to 39% of patients. The median age of r/r ATL patients ranged from 51 to 75 years old, and the proportion of male patients ranged from 42% to 60% (unweighted average: 50%).

Time to salvage therapy from diagnosis of r/r disease was not explicitly reported in any study. Two studies reported the study regimen as the first salvage therapy after r/r diagnosis,[31,35] and another two studies reported the proportion of patients with only one prior regimen (60–82%).[30,36] However, four studies reported the median time to study regimen initiation from initial diagnosis, which ranged from 6.0 to 25.2 months.[26,33,37,38] Two other studies reported the median time to study regimen initiation from patients' first recorded therapy, which ranged from 2.8 to 6.9 months.[35,39]

3.3 | Overall response rate

ORR ranged from 34% to 64% in the seven mogamulizumab studies that reported ORR, whereas the ORR was 0% to 23% among the three studies that included chemotherapy without mogamulizumab arm. Only one study reported efficacy outcomes by site of disease for mogamulizumab treatment and found that the ORR was 85% (CR 75% and PR 10%) in the peripheral blood, 58% (CR 29% and PR 29%) in skin lesions, 45% (CR 20% and PR 10%) in lymph nodes, and 45% (CR 30% and PR 15%) in other extranodal lesions.[39]

3.4 | Overall survival

OS was defined as the period from the date of the first dose of the study regimen to the date of death or the last follow-up for most (6/8, 75%) mogamulizumab, lenalidomide, and EPOCH studies, whereas OS was defined from the date of relapse for most (3/5, 60%) of the allo-HSCT studies. The median OS varied across studies that included mogamulizumab treatment arms (2.2–17.6 months), mogamulizumab treatment prior to allo-HSCT arms (4.5–7.4 months), allo-HSCT arms (3.8–6.2 months), and other chemotherapy arms (4.1–20.3 months) (Figure 2). One study reported in their subgroup analysis that the median OS for patients who received mogamulizumab treatment prior to allo-HSCT was longer than patients who received mogamulizumab treatment without transplant (7.4 months [95% CI: 5.2–9.9] vs. 5.5 months [95% CI: 4.8–6.4]).[30] In another study, the OS for mogamulizumab treatment prior to transplantation and the OS for patients who did not receive mogamulizumab treatment prior to their transplantation were similar (4.5 months [95% CI: 1.3-NA] vs. 4.9 months [95% CI: 3.7–6.7]).[31]

Out of 21 treatment arms, 13 treatment arms reached 30% OS during their study period. The exploratory 30% OS calculated for mogamulizumab treatment arms ranged from 8.7 to 27.1 months (Figure 3). Excluding estimates for the single mogamulizumab treatment prior to allo-HSCT (12.3 months), estimates were less varied for allo-HSCT arms (7.5–19.8 months) and other chemotherapy arms (7.1–17.0 months). Among the studies with available 30% OS, three mogamulizumab treatment studies, representing over half of patients (n = 169, 56.6%), had noticeably better survival relative to other studies (30% OS time between 24.2 to 27.1 months vs. 7.1 to 19.8 months).[36,38,40]

Two studies evaluated OS by ATL subtype, one mogamulizumab treatment study and one allo-HSCT treatment study. In the mogamulizumab treatment study, patients with acute type were found to have shorter OS than patients with lymphoma type from mogamulizumab treatment initiation (9.7 months vs. 10.7 months).[36] A similar relationship was found in the allo-HSCT treatment study, where the OS was 3.7 months in patients with acute type and 18.2 months from relapse in patients with lymphoma type.[32]

3.5 | Adverse events

Cutaneous adverse reaction was the most common complication/ adverse event reported from patients receiving mogamulizumab, while hematological events were prevalent among patients treated receiving the EPOCH regimen or lenalidomide (Table 2). The proportion of patients reporting cutaneous adverse reactions varied between 14% and 65%. In the two studies examining the EPOCH regimen and lenalidomide treatment, between 50% and 100% of patients reported hematological events (eg, neutropenia, thrombocytopenia, or anemia).[26] Three mogamulizumab single-arm studies found that patients who did not develop skin problems had shorter OS than those who developed skin problems.[36,37,39]

4 | DISCUSSION

The largest number of studies in this review assessed mogamulizumab, followed by allo-HSCT and other chemotherapy. Although studies from all countries were eligible in this review in order to investigate the overall treatment landscape, all but one study included in final data extraction focused on treatment in Japan.[38] This may be due to the high prevalence of ATL in parts of Japan and the first availability of mogamulizumab indicated for ATL in Japan.

The use of mogamulizumab as salvage therapy for r/r ATL showed heterogeneous survival outcomes. Although median OS was similar across all treatment arms, some mogamulizumab studies showed relatively better survival at 30% OS (8.7–27.1 months).[32,38,40] Unlike median OS outcomes, allo-HSCT demonstrated worse 30% OS compared with mogamulizumab, although 30% OS estimate ranges were

TABLE 1 Summary of characteristics for studies of r/r ATL treatment and survival

First author (year) [reference]	Study design	Treatment arm(s)	Total number of patients for efficacy	ATL subtype
Ishitsuka (2019)[30]	Prospective post-marketing survey	Moga	500	–
Tokunaga (2018)[37]	Retrospective cohort	Moga	72	Acute: 50 (69%) Lymphoma: 17 (24%)
Nakashima (2018)[39]	Retrospective cohort	Moga	45	Acute: 32 (71%) Lymphoma: 7 (16%)
Ishida (2017)[36]	Phase II	Moga	26	Acute: 14 (54%) Lymphoma: 6 (23%)
Kawano (2016)[46]	Retrospective cohort	Moga	14	Acute: 10 (71%) Lymphoma: 4 (29%)
Fuji (2018)[31]	Retrospective cohort	1) Moga vs Chemo w/o Moga 2) Allo-HSCT vs w/o Allo-HSCT	723	Acute: 500 (69%) Lymphoma: 223 (31%)
Sekine (2017)[40]	Retrospective cohort	Moga vs Chemo w/o Moga	164	Acute: 106 (65%) Lymphoma: 56 (34%)
Phillips (2019)[38]	Phase II; randomized trial	Moga vs Chemo (GemOx, pralatrexate, DHAP)	71	Acute: 33 (46%) Lymphoma: 28 (39%)
Toriyama (2018)[35]	Retrospective cohort	EPOCH regimen	14	Acute: 12 (86%) Lymphoma: 1 (7%)
Ishida (2016)[26]	Phase II	Lenalidomide	26	Acute: 15 (58%) Lymphoma: 7 (27%)
Kato (2019)[34]	Retrospective cohort	Allo-HSCT + DLI vs allo-HSCT w/o DLI	252	Acute: 150 (60%) Lymphoma: 65 (26%)
Fujiwara (2017)[33]	Retrospective cohort	Allo-HSCT	131	Acute: 62 (47%) Lymphoma: 46 (35%)
Inoue (2018)[32]	Retrospective cohort	Allo-HSCT	26	Acute: 55 (72%) Lymphoma: 21 (28%)
Itonaga (2013)[15]	Retrospective cohort	Allo-HSCT + DLI vs allo-HSCT + cytoreductive	35	Acute: 29 (83%) Lymphoma: 6 (17%)

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATL, adult T-cell leukemia-lymphoma; Chemo, chemotherapy; CR, completed response; DLI, donor lymphocyte infusion; MAC, myeloablative; Moga, mogamulizumab; ORR, overall response rate; PR, partial response; RIC, reduced intensity; and w/o, without.

Proportion for male patients	Age, median (years)	Location	Line of therapy	Time to treatment, Median	Response
54%	67	Japan	59.8% (342/572) had 1 regimen of chemotherapy prior to moga	–	ORR: 42% (n = 523)
58%	65	Japan	Median 2 regimens [range:1–7] prior to moga	6.0 months [range: 0.1–92.9 months] from diagnosis to moga	ORR: 36% CR: 24% (n = 72)
60%	69	Japan	Median 1 regimen [range:1–5] prior to moga	6.9 months [range: 1.0–127.0 months] from initial treatment to moga	ORR: 44% CR: 18% PR: 27% (n = 45)
42%	65	Japan	82% (22/27) received 1 prior regimen	–	–
43%	63	Japan	Average 2 regimens [range: 1–4] of chemotherapy prior to moga	–	ORR: 64% CR: 43% PR: 21% (n = 14)
56%	61	Japan	1st salvage therapy after r/r	–	ORR: Moga: 48% Chemo: 23% (n = 638)
46%	68; 75	Japan	Average 2 regimens overall prior to moga	–	ORR: Moga: 36% CR: Moga: 17% (n = 87)
42%	55; 51	USA, EU, Latin America	Median 2 regimens [range:1–6] prior to moga Median 1.5 regimens [range:1–5] prior to chemo	9.1 months [range: 1.3–116.7 months] from diagnosis to moga 6.6 months [range: 1.3–150.6 months] from diagnosis to chemo	ORR: Moga: 15%; Chemo: 0% CR: Moga: 2%; Chemo: 0% PR: Moga: 28%; Chemo: 0% (Moga, n = 47; Chemo (n = 24)
50%	58	Japan	1st salvage therapy after r/r	2.8 months [range: 1.0–36.9 months] from initial therapy to EPOCH	ORR: 57% CR: 7% PR: 50% (n = 14)
54%	69	Japan	Median 2 regimens [range: 1–4] prior to lenalidomide	2.1 years [range: 0.3–17.5 years] from ATL diagnosis to lenalidomide	ORR: 42% CR: 19% PR: 23% (n = 26)
46%	54	Japan	–	–	CR: 37% (n = 252)
–	54	Japan	–	286 days [range: 53–3753 days] from diagnosis to transplant	–
46%	56	Japan	–	–	–
51%	54; 51	Japan	–	–	–

Overall survival estimates (95%CI)

Mogamulizumab arm

Nakashima et al. (2018) [n=45] — 17.6 (0.1-51.2)

Ishida et al. (2017) [n=26] — 14.4 (7.4-24.3)

Sekine et al. (2017)*♯ [n=96] — 13 (11.2-19.9)

Fuji et al. (2018)¶ [n=55] — 7.4 (5.1-10.6)

Ishitsuka et al. (2019)‡ [n=500] — 5.5 (4.8-6.4)

Tokunaga et al. (2017) [n=72] — 5.4 (4.5-8.3)

Phillips et al. (2019)‡♯ [n=47] — 4.9 (2.8-18)

Sekine et al. (2017)♯ [n=96] — 4 (3-5.4)

Kawano et al. (2016)♯ [n=14] — 2.2 (1.6-NA)

Mogamulizumab prior to allo-HSCT subgroup

Ishitsuka et al. (2019) [n=49] — 7.4 (5.2-9.9)

Fuji et al. (2018)¶ [n=25] — 4.5 (1.3-NA)

Allo-HSCT arm

Itonaga et al. (2013)† [n=35] — 6.2 (NA-NA)

Inoue et al. (2018)†¶ [n=26] — 5.5 (3.8-18.2)

Fuji et al. (2018)§¶ [n=107] — 4.9 (3.7-6.7)

Fujiwara et al. (2017)¶ [n=131] — 4.7 (3.7-5.9)

Kato et al. (2019)† [n=252] — 3.8 (NA-NA)

Other chemotherapy arm

Ishida et al. (2016)♯ [n=26] — 20.3 (15.3-NA)

Toriyama et al. (2018)♯ [n=14] — 12.3 (5.2-NA)

Sekine et al. (2017)*♯ [n=68] — 7.9 (6.2-11.4)

Phillips et al. (2019)‡♯ [n=24] — 6.9 (4-21.6)

Fuji et al. (2018)¶ [n=668] — 4.1 (3.7-4.3)
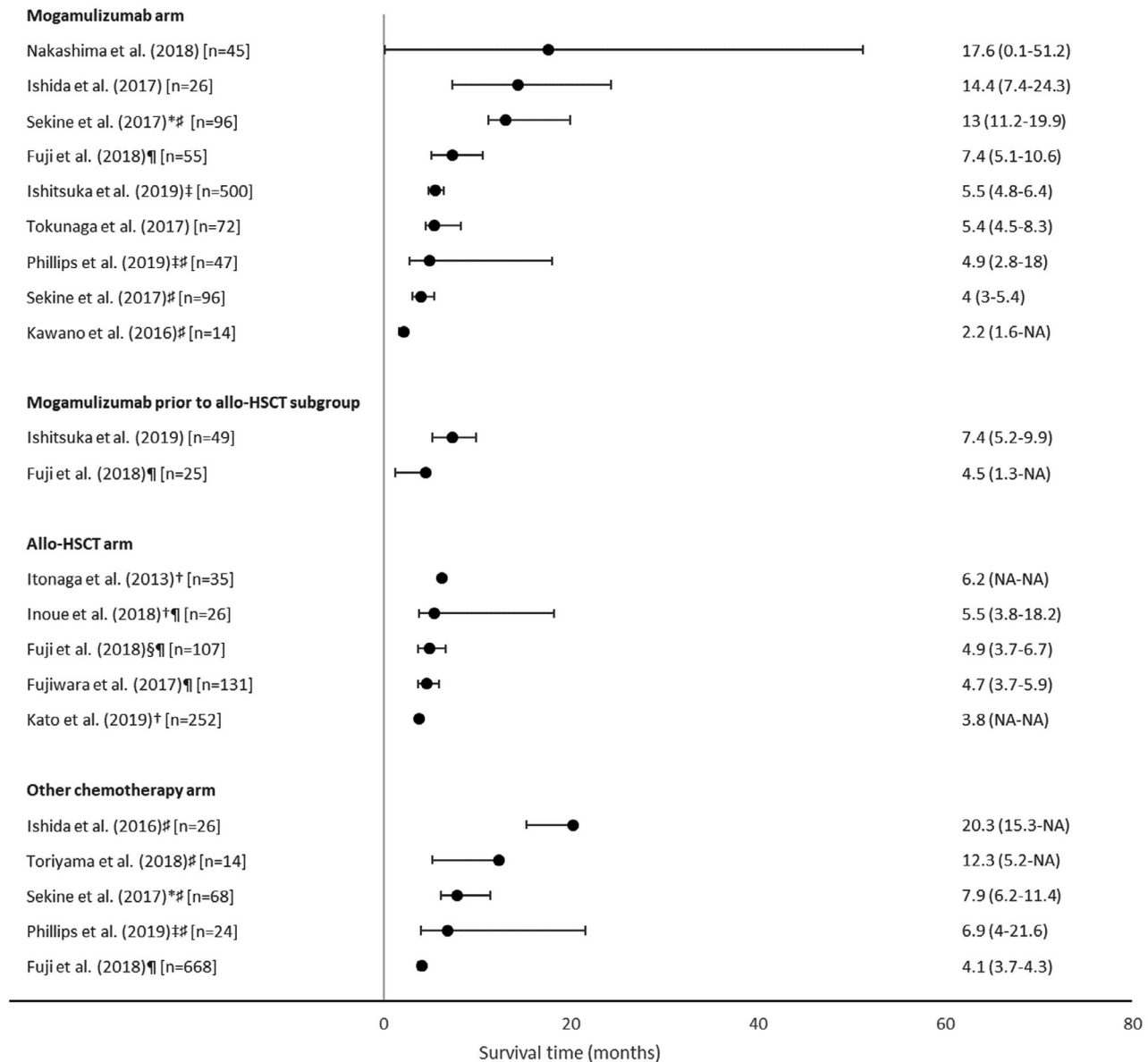
0   20   40   60   80

Survival time (months)

FIGURE 2 Median overall survival of r/r ATL patients by treatment arm. *Studies that reported overall survival from diagnosis; †studies that reported overall survival from relapse; ‡studies did not report the timing of overall survival initiation; studies without those markings reported overall survival from the treatment initiation. §Studies reported without mogamulizumab. # Studies from which KM curves were reconstructed to calculate 95% CI; and ¶studies from which KM curves were reconstructed to calculate median OS and 95% CI

similar between allo-HSCT (7.5–19.8 months) and other chemotherapy arms (7.1–17.0 months) for patients with r/r ATL. Due to the long tail observed at 30% survival probability in several published survival curves, 30% OS may serve as novel reference point for potential survival benefits of mogamulizumab that cannot observed with traditional median OS. However, as this analysis was conducted in an exploratory manner and only studies with survival probability below 30% were included, this outcome should be interpreted with caution. Additionally, mogamulizumab had an ORR nearly double that of chemotherapy without mogamulizumab in patients with r/r ATL, further supporting the use of this targeted therapy.

Overall, positive clinical outcomes of allo-HSCT treatment and mogamulizumab have been reported for r/r ATL patients. For example, Fuji et al. reported that 1-year OS for patients who received allo-HSCT compared with those who did not (37.9% vs. 13.1%, $p < 0.001$).[31] In another study at a single center in Japan not captured in this systematic review, high median OS and 1-year OS rate were demonstrated with mogamulizumab treatment (7.7 months and 42.0%, respectively).[24] These studies highlight the survival benefits of allo-HSCT and mogamulizumab for r/r ATL patients compared with other treatments. In contrast, Fujiwara et al. described poor 3-year outcomes for allo-HSCT patients including
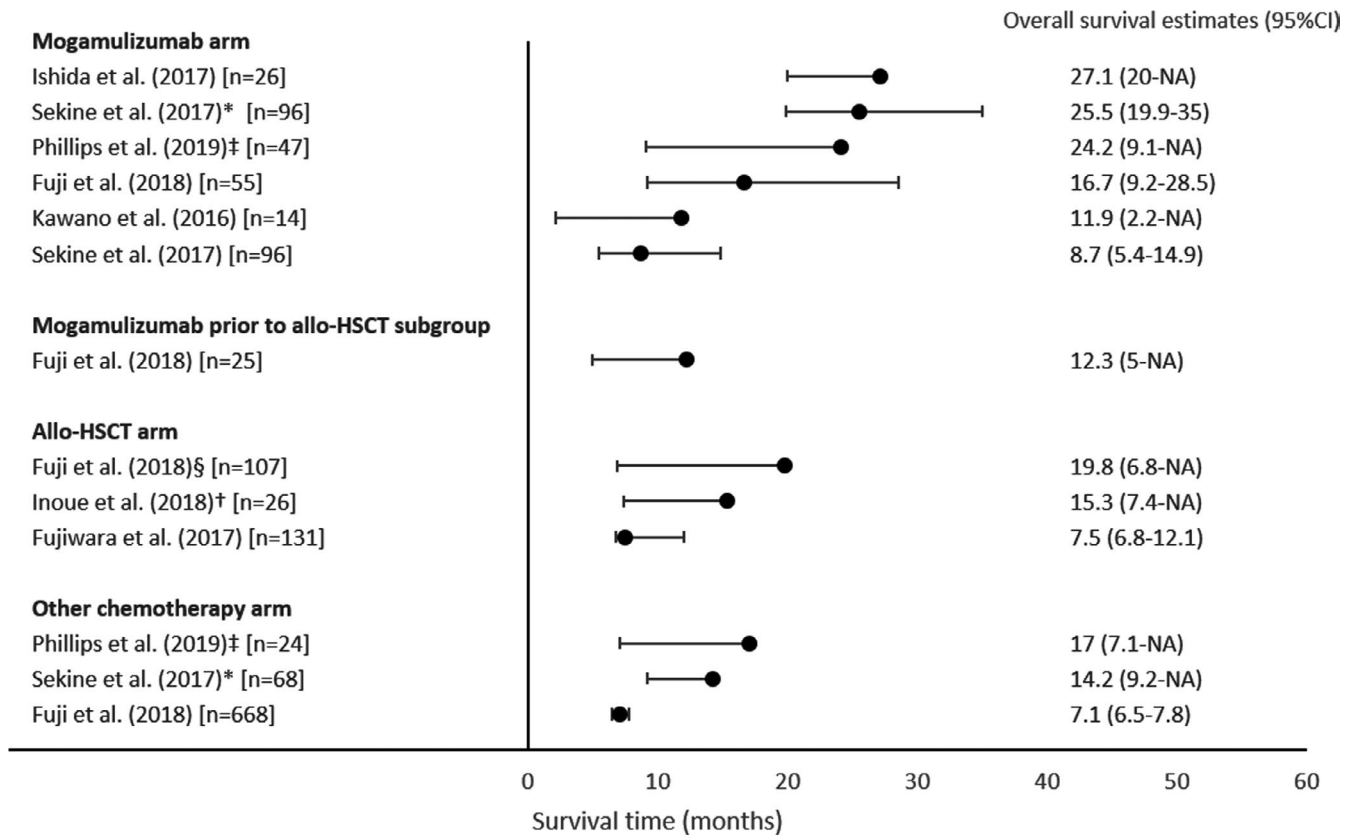
FIGURE 3 Exploratory 30% overall survival of r/r ATL patients by treatment arm (estimated from reconstructed KM curves). * Studies that reported overall survival from diagnosis; [†]studies that reported overall survival from relapse; [‡]studies did not report the timing of overall survival initiation; studies without those markings reported overall survival from the treatment initiation; and §studies reported without mogamulizumab

13% OS and a 50.5% incidence of relapse.[33] While several studies reported positive treatment outcomes, the results of this review were mixed.

Similar heterogeneity was found among survival outcomes for allo-HSCT following mogamulizumab. Ishitsuka et al. described slightly longer survival among patients receiving allo-HSCT following mogamulizumab compared with mogamulizumab alone, although the groups were not directly compared.[30] Another small Japanese study suggested that mogamulizumab may be good as a second-line salvage therapy in cases of relapse after allo-HSCT.[41] In contrast, a retrospective analysis in this systematic review by Fuji et al. demonstrated similar reconstructed median OS, as median was not reported directly in their manuscript, for patients who received mogamulizumab treatment prior to allo-HSCT compared with patients who did not receive mogamulizumab (4.5 months [95% CI: 1.3-NA] vs 4.9 months [95% CI: 3.7–6.7]).[31] However, the cumulative incidence of non-relapsed mortality and the risk of evaluable grade 3 to 4 acute graft-versus-host disease (GvHD) for the same cohorts were higher in patients who received mogamulizumab prior to allo-HSCT than in those who did not. Another study by Fuji et al. indicated that pre-transplantation mogamulizumab was significantly associated with an increased risk of GvHD-related mortality.[42] Establishing evidence for the role and benefits of mogamulizumab

used in combination with allo-HCST for r/r ATL calls for further research and careful consideration of the risks of GvHD.

The wide range of OS outcomes with mogamulizumab in this review may reflect clinical indicators associated with positive outcomes in the patient population. For example, two studies have concluded that cutaneous adverse reactions may reflect mogamulizumab treatment efficacy.[24,43] In addition, Yonekura et al. reported that patient immunological status before mogamulizumab administration was significantly associated with OS.[44] However, more direct evidence is needed to support these possible relationships. According to Yonekura et al., although time to treatment and number of prior therapies may play a role in OS, no significant difference in OS was found between previously treated and untreated patients before mogamulizumab treatment.[44] Only two studies in this SLR reported OS by acute vs. other subtype, and only one showed the comparison among patients treated with mogamulizumab, where acute subtype had slightly worse survival,[36] although statistical testing was not specified and the difference is unlikely to be statistically significant. However, it is important to note that acute subtype itself is heterogeneous in clinical presentation; the Shimoyama classification defined acute subtype as patients who did not otherwise have smoldering, chronic, and lymphoma types.[10] In general, there are some cases with both leukemia and tumor lesions, such

TABLE 2 Major adverse events reported in the identified studies

First author (year) [reference]	Treatment	Cutaneous adverse reaction	CMV infection	Lymphopenia	Leukocytopenia	Neutropenia	Anemia	Thrombocytopenia
Nakashima (2018)[39]	Moga (single arm)	15 (33%)	–	–	–	–	–	–
Ishitsuka (2019)[30]	Moga (single arm)	190 (33%)	47 (8.2%)	–	–	–	–	–
Kawano (2016)[46]	Moga (single arm)	2 (14%)	2 (14%)	6 (43%)	1 (7%)	–	–	–
Tokunaga (2018)[37]	Moga (single arm)	22 (31%)	–	–	–	–	–	–
Ishida (2017)[36]	Moga (single arm)	17 (65%)	–	–	–	–	–	–
Sekine (2017)[40]	Moga arm + Chemo arm	21 (24%)	–	–	–	–	–	–
Toriyama (2018)[35]	EPOCH (single arm)	–	–	–	–	14 (100%)	14 (100%)	12 (86%)
Ishida (2016)[26]	Lenalidomide (single arm)	–	–	18 (69%)	13 (50%)	19 (73%)	14 (54%)	20 (77%)

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; and Moga, mogamulizumab; ATL, adult T-cell leukemia-lymphoma; Chemo, chemotherapy.

as lymphadenopathy and extranodal lesions. There is compelling evidence that mogamulizumab yields a higher response rate against peripheral blood ATL tumors compared with skin, nodal, and extranodal lesions.[10,22,45] As a result, mogamulizumab is used to treat blood tumors regardless of the subtype, although ATL patients with peripheral blood tumors are generally classified into acute subtype according to Shimoyama classification. In this SLR, where all but one study was conducted in Japan, the results showed that most patients (46 to 86%) also presented with acute subtype, consistent with the high proportion of leukemia subtypes in Japan. Given that mogamulizumab is known to be more effective in leukemia compared with lymphoma subtypes, yet survival outcomes within the acute subtype are generally worse than other subtypes in the current literature,[10,38] it may be meaningful for future studies to examine the efficacy of mogamulizumab within acute subtypes[46] and refine classification to better understand survival benefits within the broad classification. The heterogeneous finding with respect to treatment selection, relative timing of treatment, and clinical subtypes may reflect real-world practice of treatment of r/r ATL patients. Yet, the findings may also suggest a need for better diagnostics to segment and identify the patient population who may better benefit from treatment with mogamulizumab at relapse.

A key limitation of this review is the limited number of articles reporting survival outcomes for r/r ATL patients and the small sample size in most articles. Most studies in this review only focus on descriptive characteristics and do not make any statistical comparisons, with only half of all patients included across all studies summarized from a comparative study. Similar to other rare disease areas, the lack of robust research in the literature is also a limitation. The lack of evidence identified by this review suggests a serious need for further research, especially RCTs, in order to make meaningful systematic conclusions. In addition, the OS for each treatment regimen is markedly heterogeneous. This is the only study known to date to attempt to synthesize the data within this rare disease area. Since this study does not make direct statistical comparisons nor present any statistical inference, but rather identifies potential heterogeneous population attributes, the results may provide supportive data for future research where quality statistical integration can be done within each specific area of unmet need.

There is no standard treatment for r/r ATL therapy and clinical decision-making regarding therapeutic options varies[6]; thus, this literature review provides insight into current treatment routes and their outcomes. Mogamulizumab was the most commonly studied treatment regimen and demonstrated a similar median OS range compared with allo-HSCT and chemotherapy, but had better response rates and longer exploratory 30% survival time. However, OS-related outcomes across treatment regimens may have been impacted by considerable heterogeneity among individual study characteristics. These findings underscore the need for more robust comparative data to better inform clinical decision-making for r/r ATL treatment. Given the severity of r/r ATL and higher prevalence in parts of Japan, treatment of relapsed disease remains a key unmet medical need. Future studies may benefit from using external data,

such as synthetic or historical control arms to expand comparisons of treatment efficacy in r/r ATL.

CONFLICT OF INTEREST

KN has received honoraria from Kyowa Kirin, Chugai Pharma, Novartis, Celgene, Eisai, Merck Sharp & Dohme, and Bristol-Myers Squibb and consultant fees from Kyowa Kirin; TT is a full-time employee of Kyowa Kirin Co., Ltd; BC, JY, WK, and TM were employees of Syneos Health at the time of this study and have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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