Prognostic Factor in Patients with Advanced, Inoperable Thymic Carcinoma: An Application of the Lung Immune Prognostic Index

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Abstract

Background: The prognostic implications of palliative chemotherapy for advanced or recurrent thymic carcinomas require full elucidation. The lung immune prognostic index (LIPI) is a novel prognostic index whose effectiveness has recently been reported in lung cancer patients. This study aimed to evaluate the LIPI's clinical value in advanced or recurrent thymic carcinoma patients.

Methods: We retrospectively analyzed 41 advanced or recurrent thymic carcinoma patients undergoing palliative chemotherapy between January 2001 and December 2020. Survival-time analysis was conducted using the Kaplan–Meier method and log-rank test. Multivariate analysis using the Cox proportional hazards model was performed to investigate the LIPI's predictive and/or prognostic value.

Results: Median progression-free survival (PFS) for first line chemotherapy and overall survival (OS) were significantly longer in the good-LIPI group (LIPI: 0) than in the intermediate/poor-LIPI group (LIPI: 1 or 2) (PFS: 13.4 vs. 6.8 months, $p=0.0425$; OS: 48.2 vs. 28.9 months, $p=0.00506$). Multivariate analysis revealed that serum albumin <3.5 g/dL and an intermediate/poor LIPI were independent adverse prognostic factors for OS. Moreover, an intermediate/poor LIPI was the only adverse prognostic factor for PFS.

Conclusions: Our study indicates that the LIPI is a potential prognostic marker in patients with advanced or recurrent thymic carcinoma undergoing palliative chemotherapy.

Introduction

Thymic carcinomas are rare neoplasms that arise in the anterior mediastinum, with a reported annual incidence of 0.29 per 100,000 population in Japan^[1]. Thymic carcinoma is a highly progressive disease characterized by a poor survival rate, local invasion, and distant metastases often present at the time of diagnosis^[2,3]. Patients with advanced (stage IVa and IVb according to the Masaoka–Koga stage classification) or recurrent thymic carcinoma are usually treated with palliative intent chemotherapy or radiotherapy. However, due to the rarity of this patient population, the optimal chemotherapeutic strategy and sequence of treatment are debatable. Thus, there are conflicting findings in previous reports regarding the prognostic implications of palliative intent chemotherapy for patients with advanced and/or recurrent thymic carcinoma.

Inflammatory dynamics in the tumor microenvironment play a key role in carcinogenesis^[4]. In recent years, the prognostic utility of hematological and biochemical parameters that can be routinely evaluated in daily clinical practice and that potentially reflect tumor inflammation have been validated. Typically, the neutrophil-to-lymphocyte ratio (NLR) and derived NLR (dNLR), comprising leukocyte fractions, are commonly used parameters^[5,6]. In cancer patients, these parameters have been reported to act as predictive and/or prognostic biomarkers, indicating tumor inflammatory status reflected by alterations in peripheral blood leukocytes^[6]. Furthermore, serum lactate dehydrogenase (LDH) is a well-known

prognostic marker for various types of cancer. Elevated LDH levels have been reported to reflect tumor inflammation^[7] and significant tumor growth potential^[8]. Based on these perspectives, Mezquita et al. proposed the lung immune prognostic index (LIPI), a composite index comprising the dNLR and LDH, and demonstrated its prognostic and predictive value in non-small-cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors (ICIs)^[9]. Since then, numerous reports on the clinical utility of the LIPI, especially in lung cancer, have been published^[10–12]. However, the clinical value of the LIPI in thymic carcinoma remains uncertain, and its prognostic role is unclear. Therefore, we conducted this study to validate the clinical value of the LIPI in patients with advanced or recurrent thymic carcinoma undergoing palliative intent chemotherapy.

Results

Patient characteristics

During the study period, data on 54 patients with thymic carcinomas were collected from their medical records. Ten patients with insufficient clinical data for analysis and three who had been administered curative treatment, including radiotherapy or salvage thoracic surgery, were excluded; therefore, a total of 41 eligible patients were enrolled (Fig. 1). The patient characteristics are presented in Table 1. The median age was 66 years (range: 35–79 years), with 27 (65.9%) men and 14 (34.1%) women. Squamous cell carcinoma was the most common histological type (85.4%). According to the Masaoka–Koga stage classification, 12 (29.3%) and 21 (51.2%) patients were classified as stage IVa and IVb, respectively. Regarding the locations of metastatic sites, serosal metastasis was the most prevalent (46.3%), followed by bone and lung metastases (22% each). Eighteen (43.9%) patients presented multiple metastatic lesions at the time of diagnosis. Regarding laboratory test values, the mean Alb, dNLR, and LDH values were 3.8 ± 0.5 g/dL, 2.8 ± 1.5 , and 266 ± 133 U/mL, respectively. LIPI scores of 0, 1, and 2 were present in 13 (31.7%), 20 (48.8%), and 8 (19.5%) patients, respectively. Comparisons of patient characteristics according to LIPI score are presented in Table 2. The intermediate/poor-LIPI group exhibited a higher prevalence of poor PS scores of 2 or 3 (good LIPI vs. intermediate/poor LIPI: 15.4% vs. 28.6%), bone metastasis (7.7% vs. 28.6%), and presented more metastatic sites (38.5% vs. 46.4%) than the good-LIPI group; however, none of these differences was statistically significant. Data on anticancer agents, treatment response to first line chemotherapy, additional supportive therapy, and survival outcomes are displayed in Table 3. Anthracycline with platinum-based chemotherapy was the most frequently administered first-line chemotherapy both in good and intermediate/poor LIPI group (84.6% vs. 89.1%), followed by platinum doublet chemotherapy (15.4% vs. 7.1%). Objective response rate and disease control rate were slightly higher in the good-LIPI group but not with significant difference. In addition, 30.7% of good-LIPI patients and 28.6% of intermediate/poor-LIPI patients received palliative radiotherapy during their clinical course.

Survival-time analysis

Median PFS and OS were 7.6 months (95% confidence interval [CI]: 6.5–13.8) and 34.9 months (95% CI: 23.9–41.6), respectively (Fig. 2). PFS and OS were both superior in the good-LIPI group (good LIPI vs. intermediate/poor LIPI: PFS, 13.4 vs. 6.8 months, $p = 0.0425$; OS, 48.2 vs. 28.9 months, $p = 0.00506$; Fig. 3).

Prognostic factors for PFS and OS

The results of univariate and multivariate analyses of PFS and OS using the Cox proportional hazards model are presented in Tables 4 and 5, respectively. Univariate analysis revealed an association between an intermediate/poor LIPI and inferior PFS (hazard ratio [HR] = 2.15, $p = 0.0464$); moreover, an intermediate/poor LIPI was also an independent prognostic factor in multivariate analysis (HR = 2.41, 95% CI: 1.09–5.35, $p = 0.0306$). In univariate analysis of OS, two or more metastatic sites (HR = 2.16, $p = 0.043$), Alb < 3.5 g/dL (HR = 2.85, $p = 0.00977$), and an intermediate/poor LIPI (HR = 3.41, $p = 0.008$) were associated with inferior OS. Multivariate analysis also revealed that Alb < 3.5 g/dL [HR = 2.85, 95% CI: 1.24–6.58, $p = 0.0139$] and an intermediate/poor LIPI (HR = 2.85, 95% CI: 1.08–7.54, $p = 0.0347$) were independent prognostic factors for OS.

Discussion

The present study demonstrated that pretreatment LIPI has prognostic potential for patients with thymic carcinoma treated exclusively with palliative intent chemotherapy. Pretreatment LIPI was also associated with PFS for first line chemotherapy. The patients were divided into the following two groups according to LIPI score: the “good-LIPI group” and “intermediate/poor-LIPI group,” based on the study by Mezquita L et al^[9]. In the intermediate/poor-LIPI group, there were higher rates of poor PS, histological types other than squamous cell carcinoma, and multiple metastatic lesions, and these differences were not statistically significant. In the survival-time analysis, PFS and OS were both significantly shorter in the intermediate/poor-LIPI group. In the multivariate analysis, Alb < 3.5 g/dL and an intermediate/poor LIPI were independent adverse prognostic factors for OS. Notably, an intermediate/poor LIPI was also an independent adverse prognostic factor for PFS for the first line treatment. To the best of our knowledge, this is the first study to demonstrate the clinical utility of the LIPI in patients with advanced and metastatic thymic carcinoma.

Recently, a multicenter, retrospective study on advanced thymic carcinoma, involving a comparatively large sample size, was conducted in Japan^[16–18]. The results of the study revealed no significant difference in OS between the first-line chemotherapy regimens, whereas tumor staging (Masaoka–Koga stage IVa) was an independent prognostic factor for OS^[16, 17]. In addition, hypoalbuminemia was identified as an independent prognostic factor^[16]. These findings indicate that in patients with advanced or metastatic thymic carcinoma, clinical characteristics and laboratory findings may have prognostic potential superior to that of chemotherapy regimen. Thus, in the present study, we applied the LIPI and evaluated its clinical utility as a novel prognostic marker in patients with thymic carcinoma.

LDH plays an unfavorable role in various cancers; it is reportedly associated with tumor invasion and proliferation^[19], metastatic potential^[20], and drug resistance^[21]. Elevated dNLR indicates a preference for granulocytes and monocytes over lymphocytes, reflecting the promotion of inflammatory dynamics in the tumor microenvironment^[6]. The LIPI is a novel clinical indicator initially proposed by Mezquita et al., who validated its prognostic value in NSCLC patients treated with ICIs^[9]. In their seminal report, it was suggested that LIPI potentially strengthens the prognostic power of LDH and the dNLR and facilitates better stratification of the patient population. Thereafter, its prognostic value was reported not only in ICIs but also in NSCLC patients treated with epidermal growth factor receptor tyrosine kinase inhibitors^[11] and cytotoxic chemotherapy^[10] as well as in patients with small-cell lung cancer^[22]. In recent years, the LIPI has been applied not only in lung cancer but also in the analysis of other cancer types. In their retrospective analysis of 361 resected esophageal squamous cell carcinomas, Feng et al. reported that a good LIPI was significantly associated with a superior 5-year survival rate, and this was observable at any stage of the disease^[23]. Daniel et al. retrospectively analyzed 578 solid-tumor patients, including 145 renal cell carcinoma patients treated with ICIs, and demonstrated that in the renal cell carcinoma cohort, an intermediate/poor LIPI was significantly associated with shorter PFS and OS^[24]. Chen et al. also analyzed 108 patients with advanced hepatocellular carcinoma treated with ICIs and found that an intermediate/poor LIPI was significantly associated with a poor disease control rate as well as shorter PFS and OS^[25]. To date, the clinical value of the LIPI for advanced thymic carcinoma has not been investigated. Only one observational study suggested that elevated serum LDH is an independent prognostic factor for advanced thymic carcinoma, although, unlike our patient population, it included patients who underwent curative surgical or radiological treatment^[26].

Our data revealed that hypoalbuminemia and an intermediate/poor LIPI were significantly associated with unfavorable survival outcomes. Serum albumin is a well-known prognostic marker for several cancer types^[27]. In addition to being a nutritional indicator, albumin also acts as a parameter representing inflammatory dynamics, and it is affected by several factors, such as extracellular fluid volume, dehydration status, and inflammatory dynamics. Our results corroborate those of a previous study by Okuma et al., in which hypoalbuminemia was found to be an adverse prognostic factor for OS in advanced thymic carcinoma^[16]. Notably, the present study demonstrated that an intermediate/poor LIPI was an independent negative prognostic factor for both PFS and OS. Although there was no significant difference in response rate according to LIPI score, pretreatment LIPI was associated with longer PFS to first line treatment, which might have better stratified subsequent long-term survival. We believe that, in advanced thymic carcinoma, for which the optimal chemotherapeutic strategy is debatable, the LIPI, an easy stratification tool, may be beneficial in clinical practice.

This study had certain limitations. First, the small sample size and retrospective nature of this study might have influenced patient background and selection. Due to the small sample size, it was difficult to make a comparison between three LIPI groups, that is, good (0), intermediate (1), and poor (2), as in the previous studies. Second, in our study, patients who underwent curative radiotherapy or surgical resection during their clinical course were excluded, whereas those who received palliative radiotherapy were

included. As the definition of “palliative radiotherapy” is unclear, there might have been selection bias in the process of patient recruitment. Furthermore, we did not examine treatment beyond second-line chemotherapy; although there is no established strategy for chemotherapy beyond second-line therapy in advanced thymic carcinoma, the course of post-treatment may affect OS.

In conclusion, this is the first study to suggest the clinical benefits of the LIPI in the prognosis of advanced or recurrent thymic carcinoma. The results of the present study suggested that LIPI might be superior to Alb, a universal cancer prognostic marker; the intensity of tumor growth reflected by LDH and the inflammatory dynamics in the tumor microenvironment reflected by dNLR could have better stratified the patients.

Methods

Patients and setting

The present study was conducted retrospectively at a single institution. All methods of this study were performed in accordance with the amended Declaration of Helsinki. The Institutional Review Board of Shinshu University School of Medicine approved the conduct of this study (approval number: 5155) and waived off the patient informed consent because this was a retrospective observational study. Instead, an opt-out document for this study has been posted on the website of Shinshu University School of Medicine. Analysis data were collected from paper-based or electrical medical records. We extracted data on patients diagnosed with thymic carcinoma at our institute between January 2001 and December 2020. Patients meeting the following criteria were included: histopathological diagnosis of thymic carcinoma based on the 2015 World Health Organization classification of thymic tumors^[13], unresectable and advanced-stage (Masaoka–Koga stage Ia or Ib) carcinoma or postoperative recurrence thereof, receiving at least one regimen of systemic chemotherapy with cytotoxic agents, and not receiving curative treatment other than chemotherapy (i.e., curative intent radiotherapy, salvage surgery, etc.).

Data collection

Data on patient characteristics included age, sex, smoking history, histology, and clinical stage according to the Masaoka–Koga stage classification for thymic tumors, metastatic lesions, and performance status (PS) as evaluated by the Eastern Cooperative Oncology Group. The laboratory data measured at the initiation of first-line chemotherapy included serum albumin (Alb); peripheral complete blood count, including absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) to calculate the dNLR; and serum LDH to evaluate the LIPI. The LIPI was evaluated according to the dNLR ($ANC/[WBC-ALC]$) and serum LDH levels, with scores ranging from 0 to 2 and calculated as follows: $dNLR < 3$ and $LDH < 223$ U/L = 0, $dNLR \geq 3$ and $LDH < 223$ U/L or $dNLR < 3$ and $LDH \geq 223$ U/L = 1, and $dNLR \geq 3$ and $LDH \geq 223$ U/L = 2. In this study, the patients were divided into the following two groups according their LIPI scores: the “good-LIPI group,” including patients with an LIPI score of 0, and “intermediate/poor-LIPI group,” including those with LIPI scores of 1 or 2. Regarding clinical course, data on the types of first line chemotherapy regimen, treatment response, palliative intent radiotherapy, and survival time were

collected. The treatment response for first line chemotherapy was evaluated according to the revised Response Evaluation Criteria in Solid Tumors guidelines (v.1.1)^[14]. Overall survival (OS) was defined as the period from initiation of chemotherapy to either a fatal event or censored observation. Progression-free survival (PFS) for first-line chemotherapy was defined as the period from initiation of chemotherapy to death or disease progression.

Statistical analysis

Kaplan–Meier analysis was performed to plot the PFS and OS curves, and the log-rank test was employed for intergroup comparisons of PFS and OS. A Cox proportional hazards model was used to identify the prognostic factors for PFS and OS, with statistically significant variables used for the univariate model and clinically important variables further analyzed using multivariate analysis. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at $P < 0.05$ ^[15].

Declarations

Author contributions

The study was initially conceived by T.K. All authors contributed to the study conception and design. The first draft of the manuscript was written by T.A., and all authors provided recommendations for the improvement of previous versions of the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, K.T., upon reasonable request.

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Tables

Table 1 Patient characteristics		N	%
Variables		41	
Age, years	Median (range)	66 (35–79)	
Sex	Male	27	65.9
	Female	14	34.1
Smoking history	Current or former	22	53.7
	Never	19	46.3
ECOG-PS	0–1	31	75.6
	2–3	10	24.4
Histology	Squamous cell carcinoma	35	85.4
	LCNEC	1	2.4
	Undifferentiated carcinoma	5	12.2
Tumor stage	ⅰa	12	29.3
	ⅰb	21	51.2
	Post-ope.	8	19.5
Metastatic location	Serosal	19	46.3
	Bone	9	22
	Lung	9	22
	Lymph node	6	14.6
	Liver	6	14.6
No. of metastatic sites	1	23	56.1
	≥2	18	43.9
Laboratory parameter	Alb, g/dL	3.8 ± 0.5 [†]	
	dNLR	2.8 ± 1.5 [†]	
	LDH, U/mL	266 ± 133 [†]	

† Mean ± standard deviation

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group Performance Status; LCNEC, large cell neuroendocrine carcinoma; Alb, albumin; dNLR, derived neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; LIPI, lung immune prognostic index

Table 1 Patient characteristics		N	%
LIPI	0	13	31.7
	1	20	48.8
	2	8	19.5
† Mean ± standard deviation			
Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group Performance Status; LCNEC, large cell neuroendocrine carcinoma; Alb, albumin; dNLR, derived neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; LIPI, lung immune prognostic index			

Table 2 Comparison according to LIPI score		Good LIPI LIPI: 0	Intermediate/poor LIPI LIPI: 1–2	P value
No. of patients	N (%)	13 (%)	28 (%)	
Age	Median (range)	65.5 (35–79)	65.5 (36–79)	0.483
Sex	Male	10 (76.9)	17 (60.7)	0.482
	Female	3 (23.1)	11 (39.3)	
ECOG-PS	0–1	11 (84.6)	20 (71.4)	0.458
	2–3	2 (15.4)	8 (28.6)	
Histology	Squamous	12 (92.3)	22 (78.6)	0.399
	Other	1 (7.7)	6 (21.4)	
Tumor stage	Ⅱa	2 (15.4)	10 (35.7)	0.276
	Ⅱb	6 (46.1)	15 (53.6)	0.744
	Post-ope.	5 (38.5)	3 (10.7)	0.084
Metastatic location	Serosal	5 (38.5)	14 (50)	0.524
	Liver	2 (15.4)	4 (14.3)	1.00
	Bone	1 (7.7)	8 (28.6)	0.228
	Lymph node	4 (30.8)	2 (7.1)	0.0685
	Lung	4 (30.8)	5 (17.9)	0.429
No. of metastatic sites	1	8 (61.5)	15 (53.6)	0.742
	≥ 2	5 (38.5)	13 (46.4)	
Abbreviations: LIPI, lung immune prognostic index.				

Table 3 Comparison of clinical course according LIPI score		Good LIPI LIPI: 0	Intermediate/poor LIPI LIPI: 1–2	P value
First line regimens	Platinum with anthracycline	11 (84.6)	25 (89.3)	0.645
	Platinum doublet	2 (15.4)	2 (7.1)	0.58
	Monotherapy	0 (0)	1 (3.6)	1.00
Response to first line treatment	PR	7	14	
	SD	5	9	
	PD	1	2	
	NE	0	3	
ORR	%	53.8 (25.1–80.8) [†]	50 (30.6–69.4) [†]	1.00
DCR	%	92.3 (64–99.8) [†]	82.1 (63.1–93.9) [†]	0.645
Survival time	Median PFS	13.4 (6.3–18.9) [†]	6.8 (5.9–8.4) [†]	
	Median OS	48.2 (25.3–NA) [†]	28.9 (10.4–35.6) [†]	
Additional treatment				
Palliative radiotherapy		4 (30.7)	8 (28.6)	1.00
[†] 95% confidence interval				
Abbreviations: PR, partial response; SD, stable disease; PD; progressive disease; NE, not evaluated; ORR, objective response rate; DCR, disease control rate; PFS, progression free survival; OS, overall survival; NA, not applicable.				

Table 4 Cox proportional hazards model for PFS		Univariate		Multivariate	
Variables		HR, 95% CI	P value	HR, 95% CI	P value
Age <65 vs. ≥65		0.81 (0.41–1.61)	0.548		
Sex Female vs. male		1.13 (0.54–2.37)	0.744		
Smoking Non-smoker vs. smoker		1.33 (0.67–2.65)	0.411		
ECOG-PS 0–1 vs. 2–3		0.81 (0.36–1.83)	0.616		
Histology Other vs. SCC		0.96 (0.37–2.49)	0.927		
Stage (Masaoka–Koga) Ⅰa, post-ope. vs. Ⅰb		1.17 (0.51–2.72)	0.710		
No. of metastatic sites 1 vs. ≥2		1.28 (0.65–2.54)	0.471	1.16 (0.58–2.31)	0.68
Alb ≥3.5 vs. <3.5		0.88 (0.41–1.91)	0.752	0.64 (0.28–1.44)	0.279
LIPI Good (0) vs. Intermediate/poor (1–2)		2.15 (1.01–4.55)	0.0464	2.41 (1.09–5.35)	0.0306
Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; SCC, squamous cell carcinoma; Alb, albumin; LIPI, lung immune prognostic index					

Table 5 Cox proportional hazards model for OS	Univariate	Multivariate		
Variables	HR, 95% CI	P value	HR, 95% CI	P value
Age <65 vs. ≥65	0.96 (0.45–2.01)	0.904		
Sex Female vs. male	0.54 (0.25–1.14)	0.106		
Smoking Non-smoker vs. smoker	1.32 (0.64–2.76)	0.455		
ECOG-PS 0–1 vs. 2–3	1.60 (0.72–3.53)	0.247		
Histology Other vs. SCC	0.89 (0.36–2.21)	0.803		
Stage (Masaoka–Koga) Ⅰa, post-ope. vs. Ⅰb	1.17 (0.56–2.43)	0.682		
No. of metastatic sites 1 vs. ≥2	2.16 (1.03–4.53)	0.043	1.74 (0.78–3.85)	0.174
Alb ≥3.5 vs. <3.5	2.85 (1.29–6.29)	0.00977	2.85 (1.24–6.58)	0.0139
LIPI Good (0) vs. intermediate/poor (1–2)	3.41 (1.38–8.46)	0.008	2.85 (1.08–7.54)	0.0347
Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; SCC, squamous cell carcinoma; Alb, albumin; LIPI, lung immune prognostic index				

Figures

Figure 1 Patient selection

Figure 1

Flowchart showing the process of patient inclusion and exclusion in this study

Figure 2 Kaplan-Meier curve for OS and PFS

Figure 2

Kaplan–Meier curves of (A) overall survival and (B) progression-free survival in all patients

Figure 3 OS/PFS comparison according to LIPI score

Figure 3

Kaplan–Meier curves of (A) overall survival and (B) progression-free survival stratified by LIPI score. The black line represents the good-LIPI group and the red line the intermediate/poor-LIPI group.