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Assessment of objective responses in thymic epithelial tumors using ITMIG modified criteria

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ABSTRACT

Objectives: Pleural metastases of thymic epithelial tumors (TETs) are relatively common, and this unique growth pattern makes the use of RECIST (response evaluation criteria in solid tumors) response criteria difficult. To standardize tumor measurement in TETs, the International Thymic Malignancy Interest Group (ITMIG) has proposed newly developed criteria. We compared evaluation of objective response between ITMIG modified criteria and RECIST 1.1 in patients with TET treated with systemic chemotherapy.
Patients and methods: We retrospectively evaluated the tumor response of 40 patients with unresectable TET who were enrolled in a phase II clinical trial using ITMIG modified criteria, and compared the findings with prospectively evaluated tumor response assessed by RECIST 1.1. Agreement analyses for the response at each time point, including overall response and declaring progression, were performed and the time to progression (TTP) was also assessed using the two different measurements.
Results: The overall response rate assessed by the two methods did not differ significantly, with kappa value of 0.897. Agreement analysis for declaring progression of disease (PD) at the date of RECIST 1.1-designated PD showed 95% concordance rate with ITMIG modified criteria ($p = 1.000$, kappa index = 0.875). The median TTP according to RECIST 1.1 and ITMIG modified criteria was 8.4 and 7.9 months ($p = 0.983$), respectively. Validation with another cohort of 27 TET patients treated with neoadjuvant chemotherapy also showed a 96% concordance rate in overall response between the two different criteria.
Conclusions: ITMIG modified criteria showed a high concordance rate with RECIST 1.1 criteria in response assessment of TETs. Given the rarity of TETs, further evaluation of ITMIG modified criteria in a larger number of patients will be required before their implementation in clinical trials.

1. Introduction

Although thymic epithelial tumors (TETs) are rare, with an overall incidence of 1.3–3.2 per million, they are the most common tumors of the anterior mediastinum in adults [1]. Patients with unresectable TETs are usually treated with platinum doublet chemotherapy as palliative treatment [2]. In patients with unresectable TETs, objective assessment of tumor response to therapy is a key component of therapeutic decisions in clinical oncology. In addition, given that TETs are relatively indolent compared with other solid tumors, the overall response rate or time to disease progression (or progression-free survival) is usually used as a primary endpoint rather than overall survival.

To simplify and standardize response assessment of anatomical lesions, the Response Evaluation Criteria in Solid Tumors (RECIST) have been developed, in which unidimensional tumor measurements are used instead of bidimensional measurements from the WHO criteria [3]. RECIST 1.1, an updated version of the original RECIST, has been widely accepted as a standard measure for response and progression assessment. However, RECIST criteria have limitations, especially in the measurement of pleural lesions. Since pleural lesions usually present as curvilinear plaques they are difficult to measure using RECIST 1.1, in which only one CT slice of the lesion along the longest diameter is taken. In addition, long-axis measurement of pleural metastases is not as reproducible as short-axis measurement of these lesions [4]. To overcome these

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Table 1
Baseline characteristics of patients.

Characteristics	Number of Patients (n = 40)
Age (year), median	59 (25–77)
Sex	
Male	29 (72.5%)
Female	11 (27.5%)
Thymoma	
B1	1 (2.5%)
B2	4 (10.0%)
B3	8 (20.0%)
Thymic carcinoma	
Well differentiated, squamous	17 (42.5%)
Poorly differentiated, squamous	6 (15.0%)
Undifferentiated	4 (10.0%)
Stage	
III	4 (10.0%)
IVa	24 (60.0%)
IVb	12 (30.0%)
Metastasis site	
Pleura	27 (67.5%)
Lung	12 (30.0%)
Lymph node	17 (42.5%)
Bone	7 (17.5%)
Prior therapy	
Surgery	16 (40.0%)
Radiotherapy	9 (22.5%)
Chemotherapy	8 (20.0%)
Recurrence	16 (40.0%)

Table 2
Comparison of response at predetermined time points between RECIST 1.1 criteria and ITMIG modified criteria.

RECIST 1.1	ITMIG modified criteria			Total
	PR	SD	PD	
PR	73	12	5	90
SD	10	49	4	63
PD	3	3	23	29
Total	86	64	32	182

Table 3
Comparison of best overall response rates for RECIST 1.1 *versus* ITMIG modified criteria (P = 1.000, Kappa value = 0.897).

RECIST 1.1	ITMIG modified criteria			Total
	PR	SD	PD	
PR	25	1	0	26
SD	1	11	0	12
PD	0	0	2	2
Total	26	12	2	40

There were no cases of complete response.

limitations, modified RECIST criteria have been developed for pleural mesothelioma [4].

In terms of tumor measurement, TETs differ from other solid tumors. First, the primary masses of TETs are often large, contacting the heart and sternum, insinuate around vessels, and have vague borders. Second, pleural metastases are relatively common, and tend to spread along the pleura [5,6]. To standardize tumor measurement in TETs, the International Thymic Malignancy Interest Group (ITMIG) recommended newly developed criteria based on RECIST 1.1 and modified RECIST criteria [4,5].

Compared with RECIST 1.1, the major changes in ITMIG modified criteria include an increased number of pleural lesions as target lesions and methods for assessment of the size of pleural lesions. We investigated differences in evaluation of objective response between ITMIG modified criteria and RECIST 1.1 in patients with TET who were enrolled in a phase II clinical trial and treated with cisplatin plus Genexol-PM [7].

2. Patients and methods

2.1. Major changes in ITMIG modified criteria compared with RECIST 1.1

The ITMIG modified criteria for measuring TETs are fundamentally based on RECIST 1.1, although the method of measurement of pleural lesions is modified. According to RECIST 1.1, all measurable lesions up to a maximum of two lesions per organ and five lesions in total should be identified and measured. RECIST 1.1 suggests measuring only up to two lesions of pleura, whereas ITMIG modified criteria recommend that measurements should be obtained from two sites at three levels, resulting in six separate measurements. If pleural lesions are present, the summation of the pleural measurements (maximum of six) constitutes the total pleural measurement, which is then added to a maximum of four other target lesions. More importantly, the pleural lesion to be measured should have a short axis diameter of at least 10 mm, and unidimensional measurements of pleural tumor thickness perpendicular to the chest wall or mediastinum should be performed.

2.2. Patients and study design

The original cohort included 42 patients with unresectable TET who were enrolled in a prospective phase II trial and were treated with cisplatin and Genexol-PM every three weeks for a maximum of six cycles at Samsung Medical Center between March 2012 and January 2015 [7]. Because two patients discontinued chemotherapy after one cycle without response assessment, we analyzed 40 consecutive patients. Tumor measurement was prospectively evaluated using RECIST 1.1 by independent intramural review. We retrospectively analyzed tumor measurements for these patients using ITMIG modified criteria. Initially, we collected a total of 182 computed tomography (CT) scans and reassessed them for response status at each time point according to the ITMIG modified criteria. Next, we performed agreement analysis for overall response rate between the two different methods. We also performed an agreement analysis for progression at the time of RECIST 1.1-designated PD. If disagreement was observed between RECIST 1.1 and ITMIG modified criteria, we determined which set of criteria revealed progression earlier. In addition, time to progression (TTP), defined as time from the on-study date to date of radiologic progression, with censoring at the date of the final CT if the patient had not progressed, was assessed using the two measurement criteria.

2.3. CT examination and response assessment

Disease assessment was accomplished by thoracic CT after two cycles of chemotherapy, and CT was repeated after every two cycles during chemotherapy. After six cycles of chemotherapy, CT was repeated every three months until disease progression. All CT images were obtained in the full inspiratory state and CT scans were performed with various scanners. Images of the whole thorax were acquired with section thickness of 2.5 mm or less. Axial CT images were displayed in mediastinal window setting (width, 400HU; level, 20HU) and lung window setting (width, 1500HU; level, −700HU) on monitors with a picture archiving and communication system workstation (Centricity 2.0, General Electric Medical Systems Integrated Imaging Solutions, Mt Prospect, IL, USA).

2.4. Statistical methods

McNemar's test for paired categorical data was used to determine the degree of agreement between RECIST 1.1 and ITMIG modified criteria. Wilcoxon signed rank test was used to determine whether one method detected disease progression earlier than the