Editorial



# Expression patterns and prognostic value of programmed death ligand-1 and programmed death 1 in thymoma and thymic carcinoma

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Thymic epithelial tumors (TETs) arising in the anterior mediastinum are rare malignancies that account for less than 1% of all adult cancers (1). The incidence of TETs is 1.5 to 3.2 per 1,000,000 person-years (2,3). The International Thymic Malignancy Interest Group database including more than 6,000 patients showed that thymoma and thymic carcinoma accounted for 81% and 14%, respectively, of all TETs (4). Of these, 63%, 23%, and 13% of patients had local (stage I–II), locally advanced (stage III), and disseminated or distant metastatic (stage IV) disease, respectively (4). These figures are consistent with those from population-based studies (2,5).

Complete resection is the curative treatment that assures long-term survival in patients with resectable disease, whereas for patients with disseminated disease or distant metastases systemic chemotherapy is the mainstay of treatment. A combination of carboplatin plus paclitaxel has been used widely, but the response rate and median progression-free survival (PFS) are 43% and 16.7 months, respectively, in patients with advanced thymoma and 22% to 36% and 5 to 7.5 months, respectively, in patients with thymic carcinoma (6,7).

The limitation of conventional chemotherapy has prompted medical oncologists to develop molecular targeted therapies in patients with advanced TET. Recently, early results of phase II trials of antibody therapies that target programmed death 1 (PD-1) were reported. Phase II trials of pembrolizumab in patients with recurrent thymic carcinoma who had progressed after at least one line of chemotherapy showed an objective response in about 20% of patients and stable disease in more than half of patients with a median PFS of 4 to 6 months (8,9). In contrast, a phase II trial of nivolumab in patients with unresectable or recurrent thymic carcinoma with progression after at least one previous platinum-based chemotherapy found no objective response in 15 patients for the first stage with a median PFS of 3.8 [95% confidence interval (CI), 1.9–5.6] months, resulting in early termination of accrual to this study (10). This discrepancy among the trials, as well as among patients, can be explained by the heterogeneity of thymic carcinoma among patients, which should be assessed by adequate biomarkers. Programmed death ligand-1 (PD-L1) expression on tumor cells and PD-1 expression on tumor-infiltrating lymphocytes (TILs) are candidates for such a biomarker, because an association between these markers and survival has been observed in some tumor types (11).

Owen *et al.* investigated the expression patterns of PD-L1 and PD-1 and their association with clinical and pathological parameters in thymoma and thymic carcinoma (12). They assessed PD-L1 and PD-1 expression by immunohistochemistry using anti-PD-L1 antibody (22C3) and anti-PD-1 antibody (NAT105) and graded the expression in a semi quantitative 0–5 scoring system (0= no expression; 1= rare; 2= low; 3= moderate; 4= high; and 5= very high). PD-L1 expression (score ≥1) was detected in 81% (26/32) of thymoma and 100% (3/3) of thymic carcinoma samples. PD-1 expression was noted in

**Table 1** PD-L1 expression in thymoma and thymic cancer

| Study No. | Authors, year | Anti-PD-L1 antibody | Definition of PD-L1 positivity | No. of patients | | Tumor stage | PD-L1 positivity in tumor cells, n (%) | | Association of PD-L1 expression with | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Thymoma | Thymic cancer | | Thymoma | Thymic cancer | Tumor stage | EFS | OS |
| 1 | Brown *et al.*, 2003 | 29E.2A3; 29E.5A9 | Not defined | 26 | 8 | NA | 21 [81] | 7 [88] | NA | NA | NA |
| 2 | Katsuya *et al.*, 2015 | E1L3N | H-score ≥1 | 102 | 37 | I–II: 70%; III: 19%; IV: 11% | 22 [23] | 26 [70] | No | NA | No |
| 3 | Padda *et al.*, 2015 | Sino biological clone 15 | A semiquantitative scoring system (0–3) =3 | 65 | 4 | I–II: 68%; III: 17%; IV: 6 (9%); NA: 4 (6%) | 44 [68] | 3 [75] | A trend for early stage (P=0.056) | A trend for poor EFS (P=0.064) | Poor OS (P=0.035) |
| 4 | Yokoyama *et al.*, 2016 | EPR1161 | PD-L1–positive rate ≥38% | 82 | 0 | I–II: 82%; III: 15%; IV: 4% | 44 [54] | NA | Advanced stage (P=0.019) | Poor DFS (P=0.021) | No |
| 5 | Yokoyama *et al.*, 2016 | EPR1161 | H-score >20 | 0 | 25 | I–II: 28%; III: 36%; IV: 36% | NA | 20 [80] | No | Better DFS (P=0.004) | Better OS (P=0.010) |
| 6 | Katsuya *et al.*, 2016 | E1L3N | H-score ≥1 | 9 | 17 | III: 6%; IV: 77%; relapse: 17% | 6 [67] | 7 [41] | NA | NA | No |
| 7 | Marchevsky and Walts, 2017 | SP142 | % of positive tumor cells ≥1% | 38 | 8 | NA | 35 [92] | 4 [50] | NA | NA | NA |
| 8 | Weissferdt *et al.*, 2017 | EPR4877 | % of positive tumor cells ≥5% | 74 | 26 | I–II: 51%; III: 28%; IV: 22% | 16 [22] | 13 [50] | No | NA | No |
| 9 | Tiseo *et al.*, 2017 | E1L3N | H-score ≥1 | 87 | 20 | I–II: 69%; III: 18%; IV: 13% | 16 [18] | 13 [65] | Advanced stage (P=0.010) | NA | No |
| 10 | Arbour *et al.*, 2017 | E1L3N | % of positive tumor cells >25% | 12 | 11 | I–II: 26%; III: 26%; IV: 48% | 11 [92] | 4 [36] | No | NA | Better OS (P=0.02) |
| 11 | Chen *et al.*, 2017 | SP142 | H-score >3 | 50 | 20 | I–II: 51%; III: 29%; IV: 20% | 24 [48] | 14 [70] | Advanced stage (P=0.004) | NA | NA |
| 12 | Marchevsky *et al.*, 2017 | SP142 | % of positive tumor cells ≥1% | 38 | 8 | NA | 35 [92] | 4 [50] | NA | NA | NA |
| 13 | Guleria *et al.*, 2018 | SP263 | % of positive tumor cells ≥25% | 84 | 0 | I–II: 90%; III: 8%; IV: 2% | 69 [82] | NA | No | NA | NA |
| 14 | Bagir *et al.*, 2018 | AM26531AF-N | % of positive tumor cells >5% | 38 | 6 | I–II: 55%; III: 7%; IV: 16% | 31 [82] | 5 [83] | No | NA | No |
| 15 | Sakane *et al.*, 2018 | SP142, SP263, 22C3, and 28-8 | % of positive tumor cells >50% | 0 | 53 | I–II: 25%; III: 21%; IV: 55% | NA | [41–54] | No | NA | Better OS (P=0.025) by 22C3 |
| 16 | Owen *et al.*, 2018 | 22C3 | A semiquantitative scoring system (0–5) ≥1 | 32 | 3 | I–II: 57%; III: 20%; IV: 20%; NA: 3% | 26 [81] | 3 [100] | No | NA | No |

NA, not available; OS, overall survival; PD-1, programmed death 1; PDL-1, programmed death ligand-1; EFS, event-free survival; DFS, disease-free survival.

**Table 2** PD-1 expression in thymoma and thymic cancer

| Study No. | Authors, year | Anti-PD-1 antibody | Definition of PD-1 positivity | No. of patients | | Tumor stage | PD-1 positivity in TILs, n (%) | | Association of PD-1 expression with | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Thymoma | Thymic cancer | | Thymoma | Thymic cancer | Tumor stage | OS |
| 5 | Yokoyama *et al.*, 2016 | NAT105 | The mean number of TILs with positive staining | 0 | 25 | I–II: 28%; III: 36%; IV: 36% | NA | NA | NA | Poor survival (P=0.034) |
| 6 | Katsuya *et al.*, 2016 | NAT105 | A semiquantitative scoring system (0–3) ≥1 in TIICs | 9 | 17 | III: 6%; IV: 77%; relapse: 17% | 4 [44] | 8 [47] | NA | No |
| 8 | Weissferdt *et al.*, 2017 | EPR4877 | % of positive cells ≥5% in TILs | 74 | 26 | I–II: 51%; III: 28%; IV: 22% | 46 [62] | 6 [23] | Higher stage in thymic carcinoma (P=0.01) | No |
| 10 | Arbour *et al.*, 2017 | NAT105 | A semiquantitative scoring system (0–3) ≥1 in TILs | 12 | 11 | I–II: 26%; III: 26%; IV: 48% | 10 [83] | 6 [55] | NA | NA |
| 11 | Chen *et al.*, 2017 | NAT | % of positive cells ≥5% in interstitial lymphocytes | 50 | 20 | I–II: 51%; III: 29%; IV: 20% | NA | 13 [65] | NA | NA |
| 14 | Bagir *et al.*, 2018 | MRQ-22 | % of positive cells >5% in microenvironment | 38 | 6 | I–II: 55%; III: 7%; IV: 16% | 4 [11] | 2 [33] | No | No |
| 16 | Owen *et al.*, 2018 | NAT105 | A semiquantitative scoring system (0–5) ≥1 in TIICs | 32 | 3 | I–II: 57%; III: 20%; IV: 20%; NA: 3% | 26 [81] | 1 [33] | No | No |

TIICs, tumor infiltrating immune cells; TILs, tumor infiltrating lymphocytes; NA, not available; OS, overall survival; PD-1, programmed death 1.

81% of thymoma and 33% of thymic carcinoma samples. Multiple slides prepared from the same tumor specimen in three patients with thymoma demonstrated intra-tumoral heterogeneity in terms of PD-L1 and PD-1 expression. Inconsistent with results from previous papers, neither the PD-L1 expression nor the PD-1 expression was associated with the pathological WHO grade, tumor stage, or overall survival.

PD-L1 expression in tumor cells varies in the literature with studies showing expression from 23% to 92% in thymoma and 36% to 100% in thymic carcinoma (*Table 1*). When comparing the PD-L1 expression between thymoma and thymic carcinoma within a single study, some studies showed that PD-L1 expression was higher in thymoma than in thymic carcinoma, but others showed that PD-L1 expression was higher in thymic carcinoma than in thymoma. Its association with tumor stage was also inconsistent between studies; PD-L1 expression was associated with advanced stage or early stage in some studies, but most studies showed no association with tumor stage.

How can we explain these discrepant results? They may be attributable to the different PD-L1 immunohistochemical assays used in each study (*Table 1*). In a comparison of four PD-L1 assays with different antibodies (SP142, SP263, 22C3, and 28-8), as high as 47% of cases showed discordance between PD-L1 expression levels (13). The assessment method of PD-L1 expression and definition of PD-L1 positivity also varies among studies. A semiquantitative scoring system was used in two studies, a percentage of positive tumor cells in six studies, a percentage of the PD-L1—positive area/cytokeratin-positive area in one study, and H-score in five studies. Considering the intratumoral heterogeneity of PD-L1 expression, H-score may be better than the other methods, but it was used in less than one-third of studies. The cutoff value of PD-L1 positivity is also not uniform. The threshold for PD-L1 positivity ranged from 1% to 50% when examining the percentage of positive tumor cells and from 1 to 20 when using the H-score.

Interpretation of PD-1 expression in TILs is more complicated, because identification of TILs is difficult. No studies used multiplex immunohistochemistry with antibodies for T-lymphocyte identification. In addition, methods for evaluating the PD-1 expression also vary between studies, as with PD-L1 expression (*Table 2*).

The association of PD-L1 and PD-1 expression with survival is also conflicting (*Tables 1*,*2*). It is difficult to assess the prognostic value of PD-L1 and PD-1 expression in these studies, because established prognostic factors, including the pathological WHO grade and tumor staging system of TETs, were not controlled. Small sample size was also an issue.

In conclusion, establishing biomarkers to select eligible patients for PD-1/PD-L1 pathway inhibitors is an immediate need in the treatment of advanced TETs. PD-L1 expression on tumor cells and PD-1 expression on TILs are clearly candidates for this purpose, but recently obtained clinical data are not sufficient to support their use as biomarkers. A PD-1/PD-L1 immunohistochemical assay with an optimal antibody, an assessment method of staining, and definition of positivity should be standardized in future clinical studies.

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