WT1 peptide-based immunotherapy for refractory thymic epithelial malignancies

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Comment on: Oji Y, Inoue M, Takeda Y, et al. WT1 peptide-based immunotherapy for advanced thymic epithelial malignancies. Int J Cancer 2018;142:2375-82.

Received: 17 March 2019; Accepted: 08 April 2019; Published: 15 April 2019.
doi: 10.21037/med.2019.04.01

View this article at: http://dx.doi.org/10.21037/med.2019.04.01

Thymic epithelial tumors (TETs), including thymomas, thymic carcinomas, and thymic neuroendocrine tumors, are rare malignant tumors arising in the thymus. For resectable disease, the recommended treatment is surgical resection. On the other hand, TETs are often diagnosed in advanced form. If resection is deemed to be difficult, systemic chemotherapy with or without radiotherapy is administered. For thymomas, platinum- and anthracycline-based regimens including ADOC (cisplatin, doxorubicin, vincristine, and cyclophosphamide) and non-anthracycline regimens such as cisplatin/etoposide, carboplatin/paclitaxel, and carboplatin/amrubicin have been used as first-line regimens with a reported response rate of 35–56% (1,2). For thymic carcinomas, carboplatin/amrubicin and carboplatin/paclitaxel have been reported to give response rates of 30–36% (3,4). However, no effective regimens have been established for TETs that either do not respond or are refractory to these chemotherapeutic regimens. Recent small studies have investigated the potential benefit of targeted therapies including imatinib, sunitinib, and everolimus for thymic carcinomas, but they did not provide any conclusive results (5-7).

Recently, the use of immunotherapy including immune-checkpoint inhibitors has been applied in the treatment of advanced TETs. A phase II trial of the anti-PD-1 antibody pembrolizumab showed a response rate of 22.5% in 40 patients with recurrent thymic carcinoma who progressed after at least one-line chemotherapy. However, 6 (15%) patients developed new-onset severe immune-related adverse events (irAEs) including myocarditis and polymyositis (8). Another phase II study of pembrolizumab showed a similar response rate of 24.2% in 33 patients with TETs (26 thymic carcinomas and 7 invasive thymomas) that progressed after platinum-based chemotherapy. Although patients with a past history of autoimmune disease were excluded, 3 (9%) of 33 patients developed grade 4 myocarditis (9). Thus, novel effective treatments with acceptable toxicity are eagerly awaited for the optimal treatment of refractory TETs.

The article “WT1 peptide-based immunotherapy for advanced thymic epithelial malignancies,” which was recently published in the International Journal of Cancer by Oji and associates, reported the results of an investigational phase II study of novel WT1 peptide-based immunotherapy for refractory TETs (10). The WT1 gene was originally isolated from Wilms’ tumor and has been considered to be a tumor suppressor (11). Previous studies have described the clinical response to this WT1 peptide-based immunotherapy, including a reduction of myeloblasts in acute myelogenous leukemia patients and a regression of tumors in cancers of the breast, lung, and pancreas (11,12). In this study, 18 patients with advanced TETs who were resistant to, or could not tolerate, prior conventional chemotherapy were initially screened for WT1 expression status. Positive WT1 expression was found in 11 (84.6%) of 13 thymic carcinomas and in 4 (80%) of 5 thymomas, and these 15 patients were subsequently enrolled in this trial. More than half (8 of 15) of the patients had previously received 2 or more chemotherapy regimens, and most of the patients (11 of 15) had metastatic stage IVb disease at study.
enrollment. Patients were intradermally injected with WT1 peptide vaccine once a week for 3 months as a protocol treatment, and then this immunotherapy was continued at intervals of usually 2–4 weeks until disease progression or intolerable adverse events. Unfortunately, none of the patients had a complete or partial response. However, more than half of the patients experienced disease control. Three (75%) of the 4 thymoma patients had stable disease for a median of 683 days (range, 112–1,015). Remarkably, among the 8 evaluable patients with aggressive thymic carcinomas, a similar proportion (75%, 6/8) had stable disease which was maintained for a median of 133 days (range, 20–1,204). In one thymic carcinoma patient, a metastatic lung lesion that had increased in size during a 4.5-month course of second-line docetaxel monotherapy remained stable for the subsequent 4.5 months under WT1 peptide-based immunotherapy. After ≥2-year administration of the vaccine, 2 (50%) of the 4 thymoma patients developed thymoma-related autoimmune disease, myasthenia gravis and pure red cell aplasia. One thymic carcinoma patient experienced grade 4 cerebellar hemorrhage, but this was possibly related to concomitant von Willebrand disease. Unlike immune checkpoint inhibitors, this WT1 peptide-based immunotherapy was not associated with any irAEs in thymic carcinoma patients (8). Although this study population is small and a further confirmative study is needed using a larger sample, WT1 peptide vaccine immunotherapy may offer disease control without an increased risk of irAEs, especially for previously treated refractory thymic carcinomas. The mild toxicity profile of WT1-based vaccine may encourage its use even for compromised patients who are older and have comorbidities and a poor performance status.

The major concern regarding the present results is that the current protocol therapy did not shrink either primary tumor or metastatic lesions. In this study, the production of WT1 peptide IgG antibody was induced in only 46.2% of candidates. These results indicate that the induction of WT1-specific immune responses was unsatisfactory with the current form of WT1 peptide. As the authors pointed out, the development of a more potent form of WT1 peptide should be considered. Further prospective studies are expected to evaluate the survival benefit of a novel form of WT1 peptide-based immunotherapy for refractory thymic carcinomas with a large sample size.

On the other hand, physicians should be cautious of the administration of this vaccine therapy for thymoma patients due to the possible new onset of thymoma-related autoimmune disease. Progression or new onset of autoimmune disorders has also been reported after other systemic therapy (13). While the precise mechanism is unknown, pre-existing undetectable autoimmune disease might be enhanced by the absence of treatment-related immunosuppression. For thymoma patients, careful patient selection and serial monitoring of immunological findings should be conducted to minimize the risk of auto irAEs.

Currently, there are few efficacious regimens for refractory TETs that have progressed after conventional systemic therapy. This WT1-based immunotherapy may have clinical benefit, especially for refractory thymic carcinomas, by contributing to disease control and prolonged survival without increasing irAEs. Future prospective studies are needed to clarify the potential antitumor effects using a large sample size.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by Section Editor Dr. Zhuoqi Jia (Thoracic Department, The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/med.2019.04.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Suzuki M, Hishida T, Asakura K, Asamura H. WT1 peptide-based immunotherapy for refractory thymic epithelial malignancies. Mediastinum 2019;3:12.