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Immunotherapy and targeted therapies efficacy in thymic epithelial tumors: a systematic review

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - Mariana Brandão: Travel grant from: Sanofi, Takeda, AstraZeneca, Sanofi. Speaker fee: Janssen, Takeda, Pfizer, BMS. Advisory board from: Sanofi, Janssen, Amgen. Research grants (my Institution): Roche/GNE, AstraZeneca, Merck, Boehringer, Merus, Sanofi, Oxford, and iTeos. PI in clinical trials: Roche/GNE, AstraZeneca, Boehringer, Merus, Sanofi. Thierry Berghmans has the following conflict of interest but none is related to the work under consideration: Consultancy for InhaTarget, participation to Advisory Board for Bayer, Janssen, Merck, BMS, Daiichi-Sankyo, Roche is/was investigator for Pfizer, Merck, Astra Zeneca, Novartis, Peregrine, Amgen, Novocure, Travel grant (Takeda).

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 August 2023 and was last updated on 18 August 2023.

INTRODUCTION

Review question / Objective This systematic review aimed to evaluate the current evidence concerning the efficacy of immunotherapy treatments, and the benefit of targeted therapies against potentially druggable mutations, in thymic epithelial tumors. In addition, the elements of the TME that could be predictive factors of ICI efficacy were assessed.

Condition being studied Thymic epithelial tumors (TET) are rare neoplasms of the anterior mediastinum, and represent 15% of all anterior mediastinal tumors. They originate from thymic epithelial cells and are classified according to the proportion of the non-tumoral lymphocytic component, and resemblance to normal thymic architecture. This heterogeneous group of neoplastic lesions includes thymomas and thymic carcinomas (TC). The 2015 revised World Health Organization (WHO) classification classified TET as A, AB, B1, B2, and B3 thymoma, and TC. Thymomas may present an indolent course and for that reason, they were formerly considered benign neoplasms. However, they are nowadays classified as malignant lesions.

METHODS

Participant or population Patients treated with immune checkpoint inhibitors, studies assessing targeted therapies against an oncogenic driver mutation or translocation.

Intervention n/a.

Comparator n/a.

Study designs to be included Phase II/III clinical trials and retrospective series (> 14 patients according to Simon's design).

Eligibility criteria Phase I trials concerning different types of tumors, even including TET, were not considered.Phase II/III clinical trials and retrospective series (> 14 patients according to Simon's design) [34, 35] assessing ICI in TET and reporting at least one of the following clinical outcomes: a. Progression-free survival (PFS), defined as the time from randomization to disease progression or death from any causeb. Overall survival (OS), defined as the time from randomization until death from any causec. Objective response rate (ORR), defined as the proportion of patients who achieved an objective response (partial or complete according to the Response Evaluation Criteria in Solid Tumors - RECIST)d. all grade or grade ≥3 treatment-related adverse events (2) Phase I/II/III clinical trials and retrospective series (> 14 patients according to Simon's design) assessing targeted therapies against an oncogenic driver mutation or translocation (EGFR, cKIT, KRAS, ALK, BRAF, PDGFR, HER2, MET etc.)(3) Experimental cohort studies investigating any of the following:- TME of TET, % of PD-L1 expression in TET or tumor mutational burden (TMB) AND prediction of ICI efficacy.

Information sources The literature search was conducted in February 2023 using the Ovid Medline and SciVerse Scopus databases and was elaborated by a scientific librarian experienced in medical literature research. The search criteria were translated into MeSH terms and free-text keywords that were searched for in titles, abstracts, keywords, and names of substances (when relevant) in Medline, and in titles, abstracts, and keywords in Scopus. The resulting citations were exported from Medline and Scopus into a reference manager software (EndNote) to remove any duplicates, and then in a dedicated systematic literature reviews system (https://rayyan.ai) for the selection process.

Main outcome(s) Six trials assessed ICI efficacy in TET. Five were phase II trials whereas the last one was a retrospective cohort with 77 patients enrolled. All were recently published, from 2018 to 2023. The median number of patients was 37 (range 15-77). ORR was the primary endpoint of four phase II trials and the PFS rate at 6 months of the fifth one. In half of the studies, only patients with TC were enrolled whereas patients with thymomas and TC were assessed in the remaining studies. The Masaoka-Koga classification was used throughout the trials. All patients presented with stage III (not amenable to curative surgical resection) or IV (IVa and/or IVb). The median follow-up duration was 14.9 months (range 13.3-22.4 months). The ORR varied from 0% to 34%. In trials enrolling exclusively patients with TC, the ORR was 0% to 22.5%. The mPFS ranged from 3.8 to 8.6 months overall, being 3.8 to 4.2 months in TC. The mOS ranged from 14.1 to 35.4 months. Treatment-related AE occurred in 6.6% to 27.3% of patients (Table 2).
Sixteen studies testing targeted therapies were deemed eligible for further analysis. There were thirteen phase II trials, two retrospective studies, and one prospective cohort. Publication years ranged from 2008 to 2023, and the number of enrolled patients varied from 14 to 72. The median follow-up duration ranged from 15.5 to 46 months. The majority of studies (13 out of 16) enrolled patients with both thymomas and TC. In all studies, patients received at least one prior chemotherapy treatment. In seven studies, the ORR was the primary endpoint and ranged from 0% to 38%. The highest ORR (38%) was observed in patients with TC treated with lenvatinib, and mOS was not reached.

Quality assessment / Risk of bias analysis n/a.

Strategy of data synthesis Given the high heterogeneity in the selected studies in terms of inclusion criteria, treatments, and data presentation, a quantitative analysis was not performed.

Subgroup analysis n/a.

Sensitivity analysis n/a.

Country(ies) involved Belgium.

Keywords immunotherapy, targeted therapies, thymoma, thymic carcinoma, tumor microenvironment.

Contributions of each author
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