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The expression of programmed cell death ligand 1 (PD-L1) involves in the clinicopathologic characteristics and prognostic implications of testicular germ cell tumor (TGCT): a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - Not applicable.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 December 2023 and was last updated on 28 December 2023.

INTRODUCTION

Review question / Objective Testicular germ cell tumor (TGCT) is a type of tumor with lower incidence but more prevalent in young men. The expression of programmed cell death ligand 1 (PD-L1) serves as a potential biomarker for predicting the survival outcomes of other tumors. However, the relationship between PD-L1 expression and clinicopathological characteristics of TGCT, as well as their prognostic implications, is not clear. The efficacy of anti-PD-1/ PD-L1 immunotherapy in TGCT still remains controversial. Therefore, the limited knowledge regarding the expression of PD-L1 in TGCT, along with the absence of a published meta-analysis exploring the correlation between PD-L1 expression and TGCT, motivated us to conduct this study.

Condition being studied Testicular germ cell tumor (TGCT) is sensitive to radiotherapy and chemotherapy. However, despite radical orchiectomy and/or the combined treatment with radiotherapy or chemotherapy, approximately 10%–15% of TGCT patients experience relapse, and salvage treatment fails to provide optimal outcomes for 50% of these individuals. Considering both the limited efficacy and the short- or long-term side effects associated with second-line and salvage therapies, alternative novel and effective treatment strategies are being investigated. Recently, immunotherapy targeting immune checkpoint inhibitors, such as PD-L1 or PD-1, has been explored in the context of TGCT treatment. Currently, the use of anti-PD-L1/ PD-1, either alone or in combination with conventional radiotherapy or chemotherapy, has demonstrated promising results in the treatment of various tumors. Experimental studies have revealed a high

prevalence of PD-L1 in TGCT specimens compared to normal testicular tissues, supporting the potential of immunotherapy targeting the PD-L1/ PD-1 pathway in TGCT treatment. Several case reports have shown stable conditions or positive responses, such as decreased serum biomarkers and tumor volumes, in patients with relapsed/ refractory TGCT following the administration of anti-PD-1 antibodies. Conversely, other evidence has observed the absence of PD-L1 expression in TGCT cells, and the inhibition of PD-L1 has failed to elicit anti-tumor effects in relapsed/ refractory TGCT patients. Therefore, the limited knowledge regarding the expression of PD-L1 in TGCT, along with the absence of a published meta-analysis exploring the correlation between PD-L1 expression and TGCT, motivated us to conduct this study.

METHODS

Search strategy A comprehensive literature search was independently conducted by two reviewers in the following databases: PubMed, Embase, Web of Science, and Cochrane Library, until July 23rd, 2023. The search terms utilized included “testis”, “testicle”, “testicular”, “cancer”, “carcinoma”, “tumor”, “neoplasm”, “programmed cell death ligand 1”, “programmed death ligand 1”, “PD-L1”, “PDL1”, “B7 homolog 1”, “B7-H1”, “B7H1” and “CD274”. For the studies included that required full-text retrieval, their references were scrutinized to identify additional relevant publications.

Participant or population Patients were diagnosed with testicular germ cell tumor (TGCT).

Intervention The specimens of TGCT patients were used for the evaluation of PD-L1 expression.

Comparator The expression of PD-L1 in TGCT patients was divided into two groups: high/ positive expression and low/ negative expression. The comparator was the population of TGCT patients with low/ negative expression of PD-L1.

Study designs to be included This meta-analysis adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

Eligibility criteria (1) the study involved patients diagnosed with TGCT; (2) PD-L1 expression in TGCT patients was assessed using immunohistochemistry and categorized as positive (high) or negative (low); (3) the study provided adequate information regarding the pathology or prognosis of TGCT patients; (4) the study was published in English.

Information sources A comprehensive literature search was independently conducted by two reviewers in the following databases: PubMed, Embase, Web of Science, and Cochrane Library, until July 23rd, 2023.

Main outcome(s) A total of seven eligible studies compromising 1556 patients diagnosed with TGCT were finally included in this study. PD-L1 positivity was detected on 24% and 51% of TGCT patients’ tumor cells and TIICs, respectively. The pooled data demonstrated a significant association between elevated PD-L1 expression levels on TIICs and a favorable prognosis characterized by reduced disease progression and relapse events (HR = 0.21, 95% CI = 0.13 to 0.33). Furthermore, PD-L1+ TIICs exhibited higher prevalence rates among seminoma (OR = 2.11, 95% CI = 1.57 to 2.84) and embryonal carcinoma (OR = 6.23, 95% CI = 2.42 to 16.02) patients. Notably, PD-L1 expression on TIICs displayed a tendency to increase in TGCT patients with lower stages or without lymph node metastasis.

Quality assessment / Risk of bias analysis All the included studies were either cohort or case-control studies and obtained a NOS score between 6 and 7, indicating good methodological quality. Furthermore, publication bias was assessed using Egger's test for the aforementioned studies. Results indicated no evidence of publication bias in either of these two studies, as the P-values were both greater than 0.05 (P-value = 0.38 and 0.37, respectively).

Strategy of data synthesis The characteristics of the included studies was extracted independently by two reviewers and checked by another reviewer. Patients were divided into different subgroups depending on their specific situation. The useful data include (1) study information: authors’ name, publication year and country; (2) patient information: age, tumor type and stage, metastasis situation, international germ cell cancer collaborative group (IGCCCG) risk classification, follow-up time and outcomes; (3) experiment information: staining method, PD-L1 antibody and cut-off value for PD-L1 positive; (4) outcome information: total number of included patients and number of PD-L1 positive patients in each subpopulation. We collected and tabulated these data.

Subgroup analysis Patients were divided into different subgroups depending on their specific

situation. (1) histology: the patient group was divided into seminoma and nonseminomatous germ cell tumor (NSGCT), and NSGCT subgroup was divided into embryonal carcinoma, choriocarcinoma, yolk sac tumor and teratoma; (2) stages: the patient group was divided into stage I and stage II/III subgroups, pT1 and pT2-4 subgroups, N0 and N+ subgroups, lymphovascular invasion (LVI) 0 and LVI+ subgroups; (3) IGCCCG risk classification: the patient group was divided into good, intermediate and poor outcome subgroups.

Sensitivity analysis Sensitivity analysis was conducted to evaluate two comparisons: (1) the overall proportion of positive PD-L1 expression on TIICs in TGCT, and (2) the correlation between positive PD-L1 expression on TIICs and seminoma. Both comparisons included five studies. Upon excluding each individual study from the overall analysis, no significant differences were observed.

Country(ies) involved China.

Keywords PD-L1, TGCT, clinicopathology, prognosis, meta-analysis.

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