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Original Research

Response to anti-programmed cell death protein-1 antibodies in men treated for platinum refractory germ cell cancer relapsed after high-dose chemotherapy and stem cell transplantation

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Abstract ***Introduction:*** Treatment options for patients with platinum refractory metastatic germ cell tumours (GCT) relapsing after high-dose chemotherapy and autologous stem cell transplantation are limited and survival is poor. Antibodies directed against programmed cell death protein-1 (PD-1) and programmed cell death ligand-1 (PD-L1) are currently assessed within clinical trials. We present updated data on our experience with checkpoint inhibitors as a compassionate use off-label treatment attempt for highly-pretreated patients with GCT and provide an overview of the current literature on PD-L1 expression in this rare tumour entity.

Patients and methods: We analysed all patients with platinum refractory GCT treated with checkpoint inhibitors at our institutions between 2015 and 2017. Data were retrieved retrospectively from the patient charts.

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Results: Seven patients were treated with nivolumab or pembrolizumab. Four patients received single-dose treatment and died shortly afterwards due to tumour progression; the remaining three patients received treatment for at least 6 months. No significant treatment toxicity was observed. Long-term tumour response was achieved in two of the three patients, both of them highly positive for PD-L1 staining.
Interpretation: We consider checkpoint inhibition to be efficient in carefully selected patients with platinum refractory GCT. However, predictive markers associated with tumour response are not yet known and larger prospective clinical trials are warranted.

1. Introduction

Metastasised germ cell tumours (GCTs) are a highly treatable disease and even in first and potentially second relapse cure can be achieved. However, relapse after two previous platinum containing regimens is considered to be platinum refractory disease. For this group of patients, high-dose chemotherapy (HDCT) with subsequent autologous stem cell transplantation (ASCT) is the standard second salvage treatment that can achieve a 5-year survival rate of 20% [1]. Tumours refractory to or relapsing after HDCT are considered to be not curable and the therapeutic strategy is changed into palliative care [2]. Treatment options for those patients are mainly combination chemotherapies, the most common regimen being gemcitabine, oxaliplatin and paclitaxel (GOP). A 2-year disease free survival has been demonstrated for a proportion of 11% of patients treated with GOP and aggressive salvage surgery [3]. However, those data are from two small phase 2 trials with a limited follow-up, and no 5-year disease free survival rates have been published so far. Very few patients achieved a complete remission, and patients with a partial remission in those trials required additional surgery to maintain a longer disease free survival. Most of the patients in this phase of the disease have already undergone several previous salvage surgery attempts and further salvage surgery is technically difficult or impossible. A number of small trials with new targeted therapies have been conducted in recent years including sunitinib and everolimus with only limited clinical activity [4,5]. Eventually, 3% of all the GCT patients ultimately die due to their malignant disease [6].

A new class of drugs are antibodies that manipulate the immune checkpoint system by blocking either cytotoxic T-lymphocyte–associated protein 4 or programmed cell death protein-1 (PD-1). These checkpoints play a crucial role in maintaining the tumour immunosurveillance. Especially, PD-1 is utilised by cancer cells for immune evasion [7]. A number of antibodies targeting PD-1 or programmed cell death ligand-1 (PD-L1) have been already approved as monotherapy in several tumour entities with differing dependency of the PD-L1 expression status within the tumour [8]. Hence, this therapeutic principle has activity across organ and tissue specificities of cancer warranting clinical investigation in platinum refractory GCT.

We earlier reported on the clinical course of four patients treated with anti-PD-1 antibodies [9]. Beside this data, a published case report of a 32-year-old male patient initially suspected to suffer from malignant melanoma and treated upfront with an anti-PD-1 antibody before the diagnosis was revised to testicular cancer reported also the signs of clinical activity [10]. He was treated with nivolumab and showed partial response (33% disease reduction by RECIST version 1.1 criteria and 49% regression by immune-related response criteria) after single application. Because further histological examinations revealed embryonal cell carcinoma, the patient was then treated with standard chemotherapy.

We present an update of the previously shown four patients with an extended follow-up and three additional patients also treated with anti-PD-1 antibodies.

1.1. Patients and methods

Seven patients with metastatic GCT were treated with anti-PD-1 antibodies at the university hospitals in Heidelberg and Mannheim and two private practices. Each patient was consented by his respective physician to be treated on a compassionate use off-label treatment attempt. Individual approval was obtained for each patient by the respective health agency and reimbursement for a limited time—with the option to prolong treatment in case of activity of the substances—was provided with reference to cross entity basket trials and the lack of conventional curative treatment options. Records were accessed retrospectively through the electronic patients' charts. Compassionate use treatment is covered by the local ethics committees according to Declaration of Helsinki from 2013 § 37.

Clinical parameters assessed included tumour stage, histology, types of prior and subsequent treatment regimens, tumour marker and imaging responses as well as data on toxicity. Evaluation of tumour response was