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Original Research

Phase II trial of veliparib in patients with previously treated BRCA-mutated pancreas ductal adenocarcinoma☆

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Abstract ***Purpose:*** BRCA-associated cancers have increased sensitivity to poly(ADP-ribose) polymerase inhibitors (PARPis). This single arm, non-randomised, multicentre phase II trial evaluated the response rate of veliparib in patients with previously treated BRCA1/2- or PALB2-mutant pancreatic adenocarcinoma (PDAC).
Methods: Patients with stage III/IV PDAC and known germline BRCA1/2 or PALB2 mutation, 1–2 lines of treatment, Eastern Cooperative Oncology Group 0–2, were enrolled. Veliparib was dosed at a volume of 300 mg twice-daily (N = 3), then 400 mg twice-daily (N = 15) days 1–28. The primary end-point was to determine the response rate of veliparib; secondary end-points included progression-free survival (PFS), duration of response, overall survival (OS) and safety.

☆ Data from this trial has been presented at the Gastrointestinal Cancers Symposium 2015

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Results: Sixteen patients were enrolled; male N = 8 (50%). Median age was 52 years (range 43–77). Five (31%) had a BRCA1 and 11 (69%) had a BRCA2 mutation. Fourteen (88%) patients had received prior platinum-based therapy. No confirmed partial responses (PRs) were seen: one (6%) unconfirmed PR was observed at 4 months with disease progression (PD) at 6 months; four (25%) had stable disease (SD), whereas 11 (69%) had PD as best response including one with clinical PD. Median PFS was 1.7 months (95% confidence interval [CI] 1.57–1.83) and median OS was 3.1 months (95% CI 1.9–4.1). Six (38%) patients had grade III toxicity, including fatigue (N = 3), haematology (N = 2) and nausea (N = 1).
Conclusions: Veliparib was well tolerated, but no confirmed response was observed although four (25%) patients remained on study with SD for ≥ 4 months. Additional strategies in this population are needed, and ongoing trials are evaluating PARPis combined with chemotherapy (NCT01585805) and as a maintenance strategy (NCT02184195).

1. Introduction

Patients with germline BRCA1/2 mutations (BRCA+) are at an increased lifetime risk for the development of pancreatic adenocarcinoma (PDAC), estimated at 2–3.5 times that of the general population [1]. Up to 1 in 10 cases occur in the setting of a hereditary cancer predisposition syndrome, of which BRCA+ are the most common mutation [2,3]. In a series of patients of Ashkenazi ancestry unselected for family history with resected PDAC, 5.5% were found to be BRCA+; whereas, in a subsequent series evaluating 211 Ashkenazi Jewish (AJ) patients with a personal history of breast cancer and a family history of pancreatic adenocarcinoma, 30 (14.2%) were BRCA+ [4,5]. Among 159 patients with PDAC and a family history of malignancy who pursued genetic testing at the Memorial Sloan Kettering Cancer Center, BRCA+ prevalence was 13.7% in AJ patients (N = 95) and 7.1% in non-AJ patients (N = 56) [6,7]. More recently, germline mutations in the gene *PALB2*, which encodes a protein critical for the initiation of homologous recombination (HR), have also been identified in patients with PDAC and a personal or family history of breast cancer [8].

Overall, BRCA+ population represents a small but significant number of patients with PDAC, in which the identification of an inherited cancer predisposition syndrome may be potentially exploited for therapeutic benefit. Superior overall survival (OS) has been observed for BRCA+ patients with advanced PDAC treated with platinum versus those treated with non-platinum chemotherapies (22 vs 9 months; p = 0.039), making platinum-based therapy a preferred choice for these patients [9,10]. Poly (ADP-ribose) polymerase inhibitors (PARPis) target defective DNA repair by blocking PARP-mediated repair of single-strand breaks, leading to DSBs which are repaired by the error prone NHEJ pathway in BRCA1/2-mutant cells. These cells are thus unable to maintain genomic integrity, resulting in cell death via a synthetic lethal effect [11]. A prospective phase II study of the PARPi, olaparib, in patients with BRCA+ malignancies enrolled 23 patients with PDAC, of whom 22% had either a complete (CR) or partial response (PR) to treatment with single-agent olaparib [12]. In addition, 35% of PDAC patients demonstrated stable disease (SD) for ≥8 weeks. OS at 1 year was 41% for patients with BRCA + PDAC on this trial [13]. Olaparib has recently obtained the US Food and Drug Administration's approval for the treatment of recurrent BRCA + ovarian cancer, following three lines of chemo and is FDA and EMEA approved for a maintenance indication in second remission in the same population.

Despite initial sensitivity to platinum agents however, resistance to platinum drugs emerges as a result of several potential mechanisms, including the development of secondary mutations in BRCA1/2, which restore the ability to repair DNA by HR [14]; the ability to exploit HR deficiency for therapeutic effect in BRCA+ patients who have progressed on prior chemotherapy therefore remains unclear.

Veliparib is an oral potent inhibitor of PARP1/2, which has demonstrated single-agent preclinical and clinical activity in several germline BRCA+ cancers including breast and prostate cancer [15]. This phase II study evaluated the safety and efficacy of the PARPi, veliparib, in patients with BRCA + PDAC, with progressive disease on 1–2 prior chemotherapy regimens. This study was designed in conjunction with the Cancer Therapeutics and Evaluation Program (NCI CTEP) and the Lustgarten Foundation.

2. Patients and methods

2.1. Study design and treatment

This was a prospective, multicentre, non-randomised phase II study. The primary end-point of the study was to evaluate the response rate according to the Response Evaluation Criteria in Solid Tumours (RECIST),