ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2021 October 21; 27(39): 6515-6736

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 27 Number 39 October 21, 2021

World Journal of Gastroenterology

Weekly Volume 27 Number 39 October 21, 2021

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

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http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
October 21, 2021

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World J Gastroenterol 2021 October 21; 27(39): 6515-6521

DOI: 10.3748/wjg.v27.i39.6515

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Importance of *BRCA* mutation for the current treatment of pancreatic cancer beyond maintenance

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Author contributions: Martinez-Galan J designed the overall concept and outline of the manuscript; Caba O contributed to the discussion, and carried out the design of the manuscript; Martinez-Galan J and Rodriguez I contributed to the writing and editing of the manuscript and review of the literature.

Supported by Junta de Andalucía, No. PC-0498-2017 and No. PC-0549-2017.

Conflict-of-interest statement: Joaquina Martinez-Galan, Isabel Rodriguez, and Octavio Caba have nothing to disclose.

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Abstract

In this editorial, we comment on pancreatic cancer (PC), one of the most aggressive and lethal cancers. Only minimal improvements in survival rates have been achieved over recent years. Available chemotherapeutic regimens have little impact, and surgical resection remains the only reliable curative approach. We address current treatment options for these patients, focusing on the usefulness of *breast cancer (BRCA)* gene mutation as a prognostic biomarker and predictor of response to chemotherapy. Superior survival outcomes have been reported in patients with PC and mutant *BRCA* gene treated with first-line platinum-based chemotherapy. Therefore, it appears appropriate to include *BRCA* gene status among clinical criteria used to select the chemotherapy regimen. In addition, maintenance treatment with poly(ADP-ribose) polymerase inhibitors has been found to improve progression-free survival in patients with PC and mutated *BRCA* whose disease does not progress after first-line platinum-based chemotherapy. This combination has therefore been proposed as the optimal treatment regimen for these patients.

Key Words: Pancreatic cancer; Treatment; *BRCA*; Mutation; Poly(ADP-ribose) polymerase inhibitor; Maintenance

Core Tip: Pancreatic cancer remains one of the most lethal malignant neoplasms, and available treatments have several limitations. Genetic studies are not currently recommended to support treatment selection. However, *breast cancer (BRCA)* gene

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 16, 2021
Peer-review started: March 16, 2021
First decision: May 1, 2021
Revised: May 10, 2021
Accepted: September 3, 2021
Article in press: September 3, 2021
Published online: October 21, 2021

P-Reviewer: Nemunaitis J, Shimada S, Wang WQ
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Xing YX

mutation has been associated with superior survival outcomes in patients treated with platinum-based chemotherapy. Hence, it appears appropriate to consider the *BRCA* gene status of patients with this cancer among clinical criteria for the selection of first-line chemotherapy regimen.

Citation: Martínez-Galán J, Rodriguez I, Caba O. Importance of *BRCA* mutation for the current treatment of pancreatic cancer beyond maintenance. *World J Gastroenterol* 2021; 27(39): 6515-6521
URL: https://www.wjgnet.com/1007-9327/full/v27/i39/6515.htm
DOI: https://dx.doi.org/10.3748/wjg.v27.i39.6515

INTRODUCTION

Pancreatic cancer (PC) continues to be one of the most lethal malignant neoplasms, with a 5-year survival rate of only 5%[1]. It currently represents the third cause of cancer-related mortality and is expected to be the second by 2030[2]. Surgery is considered the sole potentially curative treatment; however, only 20% of patients diagnosed with PC are candidates for surgery at the time of diagnosis, and surgical resection is frequently followed by recurrence and therapeutic resistance[3].

There have been only limited advances in PC treatment over the past few decades. However, progress in basic research has recently generated increased molecular information on PC, improving knowledge of its biology and helping to explain the poor effectiveness of current therapies and the therapeutic resistance observed[4]. For instance, *KRAS*[5], *breast cancer* (*BRCA)*[6], and *ataxia-telangiectasia mutated*[7] genes play a major role in the prognosis and response to treatment of patients with advanced PC. Hence, the identification of patients with mutations in these genes can support the design of individualized therapies that may improve survival outcomes.

In this article, we evaluate the usefulness of *BRCA* gene mutation as a prognostic and predictive biomarker of the response to chemotherapy in PC patients, beyond their maintenance treatment.

CURRENT ADVANCED PC TREATMENT

Two first-line chemotherapy options are currently available for advanced PC, FOLFIRINOX and gemcitabine+nab-paclitaxel (GEM+Nab-P)[8]. These have both demonstrated superior overall survival (OS), progression-free survival (PFS), and response rates (RRs) compared to patients receiving monotherapy with gemcitabine. Specifically, the PRODIGE4/ACCORD11 study reported improved OS (11.1 *vs* 6.8 mo, respectively), PFS (6.4 *vs* 3.3 mo), and RR (31.6% *vs* 9.4%) in the FOLFIRINOX *vs* gemcitabine arm[9]. The MPACT study also reported improved OS (8.7 *vs* 6.6 mo), PFS (5.5 *vs* 3.7 mo), and RR (23% *vs* 7%) with GEM+Nab-P *vs* gemcitabine alone[10]. The higher percentage improvements obtained in the PRODIGE4/ACCORD11 study may be explained by the more favorable prognosis of the participants, who were less representative of the real-life clinical setting compared to those in the MPACT study. Specifically, the functional Eastern Cooperative Oncology Group score was 0 in 37% of PRODIGE4/ACCORD11 study participants *vs* 16% of MPACT study participants, the pancreatic head was tumor site in < 40% of the former *vs* 44% of the latter (60%-65% in clinical practice), the mean number of metastatic sites was two in the former *vs* three in the latter, the carbohydrate antigen 19-9 marker was elevated in 42% of the former *vs* 52% of the latter, and no patient over the age of 76 years participated in the former study. It should be noted that the higher survival and RRs in the PRODIGE4/ACCORD11 study were accompanied by a significant increase in hematologic and non-hematologic toxicity. This explains why FOLFIRINOX is frequently administered at a reduced dose or in modified form in the clinical setting. Finally, no randomized trials have been undertaken to compare these options, hampering evaluation of the optimal first-line treatment of PC. The only published studies have a retrospective or non-randomized prospective design, and the results have been contradictory[11-13]. Consequently, the choice of chemotherapy regimen largely depends on clinical variables, such as the performance status and previous comorbidities of patients[14,

15].

There are currently no recommendations for genetic studies to support the selection of PC treatments. One promising approach is the identification of mutations in genes involved in response mechanisms to DNA damage, such as *BRCA*, whose mutation has been associated with superior OS outcomes in PC patients treated with platinum-based chemotherapy[16]. This evidence is based on multiple *in vitro* studies and is supported by the longer OS observed in patients with advanced PC treated with platinum-based regimens who were *BRCA* mutation carriers than in those who were not (14 mo *vs* 5 mo; hazard ratio [HR] = 0.58; P = 0.08); however, this clinical trial was retrospective and only included 12 patients[17].

ROLE OF POLY(ADP-RIBOSE) POLYMERASE AND ITS IMPORTANCE IN MUTATED *BRCA*

Mutations in the genetic code must be detected and repaired to preserve genome integrity, avoiding the uncontrolled proliferation of healthy cells and possible development of cancer[18]. One DNA repair pathway detects single-strand DNA breaks. If defective, another pathway is involved in the detection of double-strand DNA breaks followed by their homologous recombination repair (HRR), using sister chromatids to restore the original DNA sequence in a high-fidelity mechanism[19]. Nuclear enzyme poly(ADP-ribose) polymerase (PARP) is responsible for detecting DNA damage and facilitating its repair. Specifically, PARP1, the main member of the PARP family, binds to and repairs both single- and double-strand DNA breaks[20]. Conversely, PARP1 inhibition results in persistent single-strand DNA breaks that lead to replication bifurcations and double-strand DNA breaks[21].

About 7% of PC patients possess *BRCA* mutations[22]. In these patients, the inhibition of PARP and resulting loss by the tumor of functional DNA repair pathways can synergically interact and produce the specific death of tumor cells. Studies in patients with ovarian, prostate, or breast cancer found that PARP inhibition enhances the activity of cytotoxic DNA agents including alkylating agents, topoisomerase inhibitors, and radiotherapeutic agents[23]. Hence, it appears plausible to assume distinct biological behaviors and responses to therapy in patients with advanced PC who have *BRCA* mutations, especially germline mutations. This has implications for the treatment selection and suggests that *BRCA* mutations may be a useful biomarker to predict the response to first-line treatment with platinum.

PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH PC AND MUTATED *BRCA* GENE

Tumors with *BRCA* mutations are phenotypically characterized by their susceptibility to platinum-based chemotherapy, as noted above. *BRCA*-deficient cells accumulate double-strand DNA breaks, generating genomic instability and a greater predisposition to malignant transformation and progression. This is because the loss of HRR and PARP1 pathways leads to so-called synthetic lethality during DNA replication [24].

Patients with ovarian cancer who had mutated *BRCA*, either of somatic or germline origin, respond better to platinum-based chemotherapy regimens, with a superior prognosis and survival rate compared to those without this mutation[25]. In a study of 549 patients with metastatic PC, 78% of whom had at least one family member with a history of cancer, a median OS (mOS) of 8.1 mo (95% confidence interval [CI]: 7.5-9.0) was achieved by platinum-based chemotherapy, and 31% remained alive at 1 year. The mOS was higher in the patients with a family history of breast or ovarian cancer (8.5 mo; HR = 0.76; P = 0.042) and even higher in those with a family history of pancreatic and breast or ovarian cancer (14.8 mo; HR = 0. 43; P = 0.0003)[17]. According to these findings, a substantial subpopulation of patients with PC could benefit from platinum-based regimens. However, the underlying molecular mechanisms have not yet been elucidated, and further research is warranted in patients with *BRCA* mutant/deficient profiles. Other studies of PC patients receiving platinum-based chemotherapy have described a longer OS in those with a family history of breast, ovarian, or PC than in those with no family history of these cancers [26].

Cells with mutated *BRCA* are more susceptible to platinum and anthracyclines, which are selectively lethal in cells with HRR defects[27]. In a retrospective study of 36 PC patients treated with FOLFIRINOX, multivariate analyses confirmed a significantly longer mOS in patients with *vs* without homologous repair gene mutations (odds ratio [OR] = 1.47; 95%CI: 1.04-2.06; P = 0.04)[17]. In a study by Lowery *et al*[28] of 15 patients with advanced PC and germline *BRCA* mutation (*BRCA1* in 4 [27%] and *BRCA2* in 11 [73%]), 6 received platinum chemotherapy as first-line treatment, and 5 of these had a radiological partial response according to RECIST criteria, while the remaining patient had a complete response to the infusion of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan[28]. A study by Golan *et al*[26] of 71 patients with PC and a mutation in *BRCA1* (n = 21), *BRCA2* (n = 49), or both (n = 1) reported a longer mOS in patients treated with platinum than in those receiving other agents (22 *vs* 4.4 mo, respectively); the authors concluded that outcomes are more favorable in patients with PC who have *BRCA1* or *BRCA2* mutations than in those who do not[26].

USEFULNESS OF IPARP IN PC WITH MUTATED *BRCA*

In the highly influential POLO study[29], 154 patients with PC and germline *BRCA* mutation who showed no disease progression after at least 16 wk with FOLFIRINOX were randomly assigned to a group receiving maintenance therapy with olaparib, a PARP inhibitor (iPARP), or to a group receiving no maintenance treatment. Patients in the olaparib group showed a statistically significant improvement in PFS (7.4 mo *vs* 3.8 mo; HR = 0.53; 95%CI: 0.35-0.82), and 22% of them remained progression-free at 2 years compared to 9.6% in the untreated group, although there was no between-group difference in OS (18.9 *vs* 18.1 mo, respectively). Accordingly, the United States Food and Drug Administration approved olaparib as maintenance therapy for patients with advanced PC and germline *BRCA* mutation who show no disease progression after at least 16 wk of first-line treatment with platinum-based chemotherapy. In this regard, it has been reported that the iPARP-associated response does not depend on the germline or somatic origin of the *BRCA* mutation. Thus, one meta-analysis[22] describes eight studies that reported a response to PARPi in 24/43 (55.8%) patients with somatic *BRCA* mutation *vs* 69/157 (43.9%) patients with germline *BCRA* mutation, a non-significant difference (P = 0.399). In addition, five studies in the meta-analysis found no difference in PFS between patients with somatic *vs* germline *BCRA* mutations. The authors concluded that the response to iPARP therapy is similar between these types of patient.

Platinum-based chemotherapy has been combined with the administration of iPARP. An open-label, randomized, multicenter phase II trial was conducted on the efficacy of cisplatin plus gemcitabine with *vs* without veliparib in 50 patients with PC and germline-mutated *BRCA*. The RR was 74.1% for cisplatin plus gemcitabine with veliparib *vs* 65.2% for cisplatin plus gemcitabine alone (P = 0.55), obtaining a disease control rate of 100% with the former regimen *vs* 78.3% with the latter (P = 0.02). According to the authors, cisplatin plus gemcitabine is effective in advanced germline-mutated *BRCA* PC, and the addition of veliparib offers no improvement in therapeutic response[30-32]. These results support the selection of platinum-based chemotherapy as first-line treatment for patients with PC and germline *BRCA* mutation.

Various clinical trials are currently exploring the combination of iPARP with different chemotherapy and immunotherapy regimens (Table 1). It has been proposed that PARP inhibition induces tumor immunogenicity by increasing the tumor antigen load and the expression of programmed death-ligand 1 in tumor tissue, thereby increasing the susceptibility of patients with *BRCA* mutations to immunotherapy, as already demonstrated in breast cancer[33], small cell lung cancer[34], and ovarian cancer[35].

In summary, current studies suggest that *BRCA* mutation status may be a useful prognostic and predictive biomarker of the response to platinum in patients with PC, identifying those who may benefit from platinum-based chemotherapy as standard first-line treatment.

CLINICAL IMPLICATIONS

PC is associated with a poor prognosis and high resistance to chemotherapy. Few cytotoxic agents have demonstrated activity against this tumor, including platinum-based (FOLFIRINOX) and gemcitabine-based (GEM+Nab-P) regimens, and they

Table 1 Clinical trials on the combination of poly(ADP-ribose) polymerase inhibitor with chemotherapy and immunotherapy

Identifier	Phase	iPARP	Title	Status
NCT04548752	II	Olaparib	Randomized Phase II Clinical Trial of Olaparib + Pembrolizumab *vs* Olaparib Alone as Maintenance Therapy in Metastatic Pancreatic Cancer Patients with Germline BRCA1 or BRCA2 Mutations	Recruiting
NCT02890355	II	Veliparib	Randomized Phase II Study of 2nd Line FOLFIRI *vs* Modified FOLFIRI With PARP Inhibitor ABT-888 (Veliparib) (NSC-737664) in Metastatic Pancreatic Cancer	Active, not recruiting
NCT01585805	II	Veliparib	A Randomized Phase II Study of Gemcitabine, Cisplatin +/- Veliparib in Patients with Pancreas Adenocarcinoma and known BRCA/ PALB2 Mutation (Part I) and a Phase II Single Arm Study of Single-Agent Veliparib in Previously Treated Pancreas Adenocarcinoma (Part II)	Active, not recruiting
NCT01489865	I/II	ABT-888	A Phase I/II Study of ABT-888 in combination with 5-fluorouracil and Oxaliplatin (Modified FOLFOX-6) in Patients with Metastatic Pancreatic Cancer	Active, not recruiting
NCT03404960	I/II	Niraparib + Nivolumab Niraparib + Ipilimumab	PARPVAX: A Phase 1b/2, Open Label Study of Niraparib Plus either Ipilimumab or Nivolumab in Patients with Advanced Pancreatic Cancer whose disease has not progressed on Platinum-based Therapy	Recruiting
NCT03553004	II	Niraparib	Niraparib in Metastatic Pancreatic Cancer after previous Chemotherapy (NIRA-PANC)	Recruiting

iPARP: Poly(ADP-ribose) polymerase inhibitor.

deliver very modest benefits to the patient. There has been no comparative study of these agents to determine which is more appropriate as a first-line treatment, and this decision relies on the clinical characteristics and comorbidities of the patients. Two important issues must still be resolved: the best regimen for the personalization and optimization of first-line chemotherapy in patients with PC; and the ideal sequencing of chemotherapy lines, taking into account the accumulated toxicity and the molecular profile of the cancer.

As noted above, the *BRCA* gene encodes proteins essential for repairing double-strand DNA damage *via* the HRR pathway, and its mutation has been found to predict the response to first-line chemotherapy with platinum plus iPARP in patients with PC [26]. Thus, patients with advanced PC and germline *BRCA* mutation lived significantly longer when treated with platinum *vs* other cytotoxic agents[17]. In addition, maintenance treatment with iPARP has been found to improve the PFS of patients with PC and mutated *BRCA* whose disease does not progress after first-line platinum-based chemotherapy. Taken together, these findings support the selection of platinum-based regimens as first-line treatment of patients with PC and germline *BRCA* mutation[30-32].

Given the lack of evidence on the optimal treatment of patients with PC, it appears appropriate to consider the presence/absence of *BRCA* mutation among clinical criteria for the selection of first-line chemotherapy regimen.

CONCLUSION

An appreciable number of patients with PC have a mutated *BRCA* gene, and the ongoing development of drugs that target DNA repair pathways may offer relevant therapeutic benefits to this little-studied but clinically important sub-population. This defect in DNA repair pathways has the potential to improve outcomes in patients undergoing platinum-based chemotherapy, assisting individualized selection of the optimal first-line regimen.

ACKNOWLEDGEMENTS

The authors are grateful to Richard Davies for assistance with the English version.

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