



# A narrative review of Safety management of 1 L platinum-based chemotherapy and maintenance olaparib in BRCA mutated advanced pancreatic cancer

Jiayu Yao<sup>1,2</sup>, Yongchao Wang<sup>1,2</sup>, Tiebo Mao<sup>1,2</sup>, Yiyi Liang<sup>1,2</sup>, Xiao Zhang<sup>1,2</sup>, Haiyan Yang<sup>1,2</sup>, Jiong Hu<sup>1,2</sup>, Feng Jiao<sup>1,2</sup>, Jiujiu Cui<sup>1,2</sup>, Liwei Wang<sup>1,2</sup>

<sup>1</sup>Department of Oncology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; <sup>2</sup>State Key Laboratory of Oncogene and Related Genes, Shanghai Cancer Institute, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

*Contributions:* (I) Conception and design: L Wang, J Cui; (II) Administrative support: H Yang, J Hu, F Jiao, J Cui, L Wang; (III) Provision of study materials or patients: J Yao; (IV) Collection and assembly of data: J Yao; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Liwei Wang, Department of Oncology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; State Key Laboratory of Oncogene and Related Genes, Shanghai Cancer Institute, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China. Email: lwwang2013@163.com.

**Objective:** We aimed to review the safety management and efficacy of a modified FOLFIRINOX regimen to help clinicians improve first-line platinum-based chemotherapy and maintenance olaparib to treat patients with advanced PC with BRCA mutations.

**Background:** FOLFIRINOX has relatively high efficacy among all the chemotherapy regimens for advanced pancreatic carcinoma (PC) patients. However, the combination of drugs is often associated with a high incidence of adverse reactions, and safety concerns are the primary reasons limiting its clinical use. In recent years, through the adjustment of drug dosage and administration route, the toxicity of FOLFIRINOX has been reduced while its clinical effect has been maintained. Also, the empirical use of prophylactics in the chemotherapy cycle can reduce chemotherapy-related serious adverse reactions. All these methods have established a good foundation for the maintenance of olaparib.

**Methods:** Pubmed, Embase, and the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) were searched using the terms 'pancreatic cancer', 'folfirinox', 'parp inhibitor', 'chemotherapy', and 'adverse reaction' from 2005 through to March 2021.

**Conclusions:** The historical evidence suggested that modified FOLFIRINOX and maintenance olaparib could significantly improve the therapeutic effect and reduce the toxicity. It also provides some insights for clinicians to choose the most suitable regimen for each patient.

**Keywords:** Pancreatic cancer; FOLFIRINOX; adverse reactions; olaparib

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## Introduction

### Background

Pancreatic carcinoma (PC) is one of the leading causes of death from cancer, with 4.59 million new cases and 4.32 million cancer-related deaths worldwide in 2018 (1). The estimated

5-year survival rate is less than 5% (2). The incidence of PC in China is increasing and is the 10<sup>th</sup> most prevalent of all malignant tumors and the 6<sup>th</sup> leading cause of cancer-related death (3). Although surgical resection is curative, up to 80–85% of patients have unresectable disease at the time of diagnosis due to locally advanced and distant metastases (4).

Therefore, for patients with advanced PC, chemotherapy is the standard treatment to reduce symptoms, prolong survival, and improve life quality. According to the National Comprehensive Cancer Network (NCCN), FOLFIRINOX (or modified FOLFIRINOX) or gemcitabine/nab-paclitaxel (nab-P) chemotherapy is recommended as the first-line treatment for metastatic PC (5,6).

The POLO study in 2019 (7) led first-line maintenance therapy for PC into a new era, with a poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor. For BRCA1/2-mutated metastatic PC that had not progressed during at least 16 weeks of continuous first-line platinum-based chemotherapy, maintenance olaparib 300 mg twice daily significantly prolonged the progression-free survival (PFS) time to 7.4 months, while in the placebo group, the PFS was 3.8 months (HR 0.53,  $P=0.004$ ). This marked improvement was attributed to not only maintenance of olaparib but also to first-line platinum-based chemotherapy. For germline BRCA-mutated advanced PC, platinum-based chemotherapy's superior survival benefits have been reported in many studies compared to non-platinum-based chemotherapy (8-10). As a result, compared with gemcitabine/nab-P therapy, platinum-based chemotherapy, especially the FOLFIRINOX regimen, and gemcitabine plus platinum-based chemotherapy are more suitable for the treatment of advanced PC with BRCA mutation. Specifically, after first-line platinum-based chemotherapy, maintenance therapy with PARP inhibitors has become the most effective treatment for BRCA-mutated advanced PC.

### Objective

Although FOLFIRINOX has demonstrated remarkable clinical benefits in both BRCA-mutated and unscreened advanced PC patients, the combination of drugs has often been associated with toxicity accumulation and safety concerns, limiting the clinical use of this drug regimen. According to a meta-analysis comparing chemotherapies for advanced PC, the FOLFIRINOX regimen had relatively high toxicity in both hematological and non-hematological areas (11). The main reason was the superposition and accumulation of toxicity of the 3 drugs, which makes the side effects of the combined regimen very diverse, and can sometimes lead to serious adverse effects. It is known that the most common side effects of oxaliplatin and irinotecan are gastrointestinal reactions such as nausea, vomiting, and diarrhea. Also, all 3 drugs can cause myelosuppression, leading to coagulation dysfunction, infection, and other

fatal problems. Recent studies on modified FOLFIRINOX found that the toxicity could be reduced, but the clinical effect was maintained by adjusting drug dosage and the administration route. Also, prophylactics' empirical use in the chemotherapy cycle could reduce chemotherapy-related serious adverse events (AEs). Well-controlled AEs with modified FOLFIRINOX would establish a good foundation for maintenance olaparib. This article reviewed the safety management and efficacy of a modified FOLFIRINOX regimen to help clinicians improve first-line platinum-based chemotherapy and maintenance olaparib to treat patients with advanced PC with BRCA mutations. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-3478>).

### Methods

Pubmed, Embase, and the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) were searched using the terms 'pancreatic cancer', 'folfirinox', 'parp inhibitor', 'chemotherapy', and 'adverse reaction' from 2005 through to March 2021. We included literature that discussed FOLFIRINOX and platinum-based chemotherapy as first-line treatment, as well as PARP inhibitors as maintenance therapy. We excluded studies that only focused on mechanisms without clinical data.

#### *First-line platinum-based chemotherapy*

##### **FOLFIRINOX regimen**

Based on the significant efficacy of FOLFIRINOX in the PRODIGE 4/ACCORD 11 study (12) in 2010, FOLFIRINOX has been an option for treating patients with metastatic PC and good performance status. The FOLFIRINOX regimen consisted of oxaliplatin at a dose of  $85 \text{ mg/m}^2$ , leucovorin at  $400 \text{ mg/m}^2$ , irinotecan at  $180 \text{ mg/m}^2$ , and fluorouracil at  $400 \text{ mg/m}^2$  administered by intravenous bolus, followed by a continuous intravenous infusion of  $2,400 \text{ mg/m}^2$  over 46 hours every 2 weeks. The PRODIGE 4/ACCORD 11 study reported a median overall survival (OS) of 11.1 months in the FOLFIRINOX group compared to 6.8 months in the gemcitabine group [hazard ratio (HR) for death 0.57,  $P<0.001$ ], and the difference was statistically significant. However, the survival gain came at a cost. The FOLFIRINOX group was reported to have a higher incidence of serious AEs, including neutropenia (45.7%), vomiting (14.5%), diarrhea (12.7%), thrombocytopenia (9.1%),

sensory neuropathy (9.0%), and febrile neutropenia (5.4%). However, the consensus was reached that FOLFIRINOX should be used in patients <65 years old with a very good performance status (13), the tolerability of the maximum dose remains a concern that limits its clinical use.

### Modified FOLFIRINOX

Although the FOLFIRINOX regimen's efficacy has been proven, the safety and tolerability remain of concern. In 2013, Mahaseth *et al.* first published the result that the elimination of bolus 5-FU and the use of hematopoietic growth factor could improve the safety profile without compromising the activity of FOLFIRINOX (14). In 2018, Conroy *et al.* further demonstrated that adjuvant therapy with a modified FOLFIRINOX regimen led to significantly longer survival than gemcitabine among patients with resected pancreatic cancer (15). Nowadays, an increasing number of studies have modified the FOLFIRINOX regimen to reduce toxicity without compromising efficacy. In this review, a modified FOLFIRINOX regimen was defined as an adjustment of the oxaliplatin, irinotecan, and/or fluorouracil dosage and the administration route. Studies with FOLFIRI or FOLFOX were excluded. As no studies have specifically evaluated modified FOLFIRINOX in BRCA-mutated PC patients, 7 modified FOLFIRINOX regimens as first-line systemic therapy studies in unscreened advanced PC were included in this review (Table 1). The total number of patients that were finally enrolled in all included studies ranged from 18 to 81. Despite the between-group differences, overall conclusions could be readily made.

First, the modified FOLFIRINOX regimen's efficacy in these studies was comparable to full-dose FOLFIRINOX. In the PRODIGE 4/ACCORD 11 study, all patients were metastatic and treatment-naïve. Similarly, most of the patients that were enrolled in the studies mentioned above were metastatic. As discussed above, the median OS of the FOLFIRINOX group in PRODIGE 4 was 11.1 months, and in the modified FOLFIRINOX studies, the median OS was 8–14.9 months. It should be noted that PRODIGE 4 enrolled only ECOG 0–1 patient, but these studies included patients whose ECOG ranged between 0–2. The different trial design suggests that modified FOLFIRINOX may be a better choice for patients with relatively poor general status. Second, decreasing the fluorouracil dose or omitting the intravenous fluorouracil bolus significantly reduced the incidence of grade 3–4 neutropenia and/or thrombocytopenia. At the same time, it also relieved non-

hematological AEs such as fatigue and neuropathy. Stein *et al.* (16) demonstrated that a reduction of irinotecan to 135 mg/m<sup>2</sup> and bolus fluorouracil to 300 mg/m<sup>2</sup> resulted in significantly decreased grade 3–4 neutropenia (from 45.7% to 12.2%), fatigue (nearly half), and sensory neuropathy (from 9.0% to 2.7%). Mahaseth *et al.* (14) reported a reduced incidence of grade 3–4 neutropenia of 3.0% without bolus fluorouracil. Ghorani *et al.* (17) omitted bolus fluorouracil and reduced irinotecan to 130–135 mg/m<sup>2</sup> and found a further reduction in the incidence of serious neutropenia and sensory neuropathy, even reaching zero. Vivaldi *et al.* (18) pointed out that the fluorouracil bolus and higher doses of irinotecan were related to the hematological toxicities of FOLFIRINOX. Third, besides omitting the fluorouracil bolus and decreasing the irinotecan dose, reduction of the oxaliplatin dose was associated with a lower incidence of serious fatigue and neuropathy. Both Li *et al.* (20) and Wang *et al.* (21) omitted bolus fluorouracil, reduced the irinotecan dose, and adjusted the oxaliplatin dose to 72.25 mg/m<sup>2</sup> and 65 mg/m<sup>2</sup>, respectively, and no grade 3–4 fatigue or sensory neuropathy was detected.

On the other hand, the empirical use of prophylactics in the chemotherapy cycle is also an effective method to reduce chemotherapy-related AEs. In the studies of Stein *et al.* (16) and Li *et al.* (20), anti-emetic drugs were used, and the incidence of grade 3–4 vomiting was reduced from 14.5% to 2.7% or even to zero. Granulocyte colony-stimulating factor (G-CSF) can stimulate the proliferation, differentiation, and activation of neutrophils and, therefore, be used to prevent and treat leucopenia hematopoietic dysfunction and myelodysplastic syndrome caused by radiotherapy or chemotherapy. It also plays a role in the prevention of possible infection complications associated with leucopenia. Thus, adding G-CSF to the modified FOLFIRINOX regimen can help prevent the development of severe neutropenia. In the study of Yoshida *et al.* (19), G-CSF was not administered prophylactically, and the incidence of grade 3–4 neutropenia was as high as 83.9%. The significantly low incidence of serious neutropenia in the studies of Mahaseth *et al.* (14) and Ghorani *et al.* (17) (3.0% and 0, respectively) was apparently associated with the use of prophylactic G-CSF.

For some clinicians, gemcitabine/nab-P therapy is considered safer and has been used to treat advanced PC patients who were unable to tolerate FOLFIRINOX. As there is no randomized controlled clinical trial (RCT) that can compare the 2 therapies directly, the efficacy and safety of the 2 therapies have not been unequivocally established.

**Table 1** Summary of FOLFIRINOX and modified FOLFIRINOX studies

Trials	Number of patients	FOLFIRINOX and modified FOLFIRINOX regimens					Grade 3–4 hematologic AEs			Grade 3–4 non-hematologic AEs				Concomitant medication	Efficacy	
		FU IV bolus	FU IV infusion	Irinotecan	Leucovorin	Oxaliplatin	Neutropenia	Thrombocytopenia	Others	Fatigue	Sensory neuropathy	Diarrhea	Others		Median PFS (months)	Median OS (months)
FOLFIRINOX (12)	342 MPC, ECOG 0–2 points	400 mg/m <sup>2</sup>	2,400 mg/m <sup>2</sup> over a 46 h period	180 mg/m <sup>2</sup>	400 mg/m <sup>2</sup>	85 mg/m <sup>2</sup>	45.7%	9.1%	Febrile neutropenia 5.4%; anemia 7.8%	23.6%	9.0%	12.7%	Vomiting 14.5%; elevated level of ALT 7.3%; thrombo-embolism 6.6%	G-CSF (pegfilgrastim) 42.5%	6.4	11.1
Stein <i>et al.</i> (16)	44 MPC, ECOG 0–1 point	300 mg/m <sup>2</sup>	Unchanged	135 mg/m <sup>2</sup>	Unchanged	Unchanged	12.2%	9.5%	Anemia 5.4%; Febrile neutropenia 4.1%	12.2%	2.7%	16.2%	Elevated level of ALT 4.1%; thromboembolism 4.1%; vomiting 2.7%	Prophylactics: anti-emetic agents (palonosetron and aprepitant), dexamethasone, growth factors	6.1	10.2
Mahaseth <i>et al.</i> (14)	36 MPC	Omitted	Unchanged	Unchanged	Unchanged	Unchanged	3.0%	4.0%	None	13.0%	4.0%	13.0%	Nausea/ vomiting 8%; allergic reaction 5%; mucositis 3%; infection 4%	Prophylactics: G-CSF (pegfilgrastim), atropine, anti-diarrheal medications	8.5	8
Ghorani <i>et al.</i> (17)	15 MPC; 3 LAPC	Omitted	Unchanged	130–135 mg/m <sup>2</sup>	Unchanged	Unchanged	0	0	Febrile neutropenia 5.6%	5.6%	0	16.7%	Vomiting 27.8%; nausea 22.2%; fever 16.7%; dysarthria 5.6%	Prophylactics: G-CSF (pegfilgrastim), anti-emetic agents (ondansetron), dexamethasone; treatment: domperidone, ondansetron, aprepitant and loperamide	Stage IV 9.3	Stage IV 7.2
Vivaldi <i>et al.</i> (18)	81 MPC; 56 LAPC, Stage III or IV	Omitted	2,800 mg/m <sup>2</sup> over a 48 h period	150 mg/m <sup>2</sup>	200 mg/m <sup>2</sup>	Unchanged	35.7%	5.8%	Febrile neutropenia 0.7%; anemia 2.9%	1.4%	2.2%	8.0%	Nausea 7.3%; vomiting 3.6%; stomatitis 6.5%; anorexia 2.9%; liver toxicity 4.4%; thromboembolism 2.9%	G-CSF 20.4%	Stage III 11; Stage IV 5.8	LAPC 14.9; MPC 10.8
Yoshida <i>et al.</i> (19)	21 MPC	Omitted	Unchanged	150 mg/m <sup>2</sup>	200 mg/m <sup>2</sup>	Unchanged	83.9%	6.5%	Febrile neutropenia 16.1%	0	9.7%	6.5%	Anorexia 6.5%; vomiting 3.2%; nausea 3.2%	Prophylactics: anti-emetic agents (aprepitant and granisetron), dexamethasone	7.0	14.9
Li <i>et al.</i> (20)	62 MPC, ECOG > 1 point	Omitted	Unchanged	135 mg/m <sup>2</sup>	No change	72.25 mg/m <sup>2</sup>	29.0%	4.8%	Anemia 8.1%	0	0	0	Infection 4.8%; elevated level of ALT 14.5%; no vomiting or thromboembolism	Prophylactics: anti-emetic agents (ondansetron, azasetron and metoclopramide), anti-acid agents (omeprazole), dexamethasone; G-CSF 69.4%; IL-1 8.1%; TPO 3.2%	7.0	10.3
Wang <i>et al.</i> (21)	65 MPC, ECOG 0–2 points	Omitted	Unchanged	150 mg/m <sup>2</sup>	200 mg/m <sup>2</sup>	65 mg/m <sup>2</sup>	12.3%	0	Anemia 1.5%	0	0	6.2%	Vomiting 1.5%; elevated level of ALT 1.5%	G-CSF was used when grade 3–4 neutropenia occurred	5.77	11.6

FU, fluorouracil; IV, intravenous; MPC, metastatic pancreatic cancer; LAPC, locally advanced pancreatic cancer; BRPC, borderline resectable pancreatic cancer; PFS, progression-free survival; OS, overall survival; ALT, alanine aminotransferase; G-CSF, granulocyte-colony stimulating factor; IL-1, interleukin 11; TPO, thrombopoietin.

However, 2 phase III clinical studies by Von Hoff *et al.* (22) and Tehfe *et al.* (23) found that the safety profile of gemcitabine/nab-P therapy was similar to that of modified FOLFIRINOX. In these studies, advanced PC was treated with nab-P 125 mg/m<sup>2</sup> plus gemcitabine 1,000 mg/m<sup>2</sup> on days 1, 8, and 15 every 4 weeks, and common grade 3–4 AEs including neutropenia (38% and 22%, respectively), fatigue (17% and 34%, respectively), and sensory neuropathy (17% and 25%, respectively) were reported. Since modified FOLFIRINOX has greater efficacy in BRCA-mutated advanced PC, reduced toxicity will surely help more patients achieve the best possible clinical benefits.

### Gemcitabine plus platinum-based chemotherapy

Based on its mechanism, patients with BRCA1/2 or PALB2 mutations are more sensitive to platinum-based chemotherapy (24), and in real-world clinical practice, some other platinum-based chemotherapies are available apart from FOLFIRINOX. Among them, gemcitabine plus cisplatin has been recommended by the NCCN guidelines as the first-line chemotherapy for advanced PC with BRCA1/2 or PALB2 mutations. O'Reilly *et al.* (25) treated BRCA/PALB2-mutated stage III to IV PC patients with gemcitabine 600 mg/m<sup>2</sup> plus cisplatin 25 mg/m<sup>2</sup> intravenously in cycles every 3 weeks and reached a median OS of 16.4 months without grade 4 hematological toxicity. Grade 3 hematological AEs included neutropenia (30%), thrombocytopenia (9%), and anemia (35%). Like FOLFIRINOX, gemcitabine plus cisplatin can also improve BRCA1/2 or PALB2-mutated advanced PC, with AEs being more controllable. Hence, this regimen has good prospects for clinical application. Also, another platinum-based chemotherapy—gemcitabine plus oxaliplatin—also exhibited good tolerability (26). Further studies will focus on its clinical benefits in PC patients with BRCA1/2 or PALB2 mutations, which will be a promising research direction in the future.

### Safety profile of maintenance olaparib in BRCA mutated advanced PC

The total dosage of multi-drug chemotherapy for patients with advanced PC is usually limited, and patients often need to receive maintenance therapy (27). Recently, the FDA has approved olaparib for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated metastatic PC. Thus, after first-line platinum-based chemotherapy, maintenance olaparib should

be one of the standard treatments for BRCA-mutated advanced PC in the clinic.

The most commonly reported AEs produced by olaparib were nausea/vomiting, fatigue, and anemia. These AEs were typically mild or moderately severe, and in most cases, were short-term in nature, self-limiting, and did not require discontinuation of treatment (28,29). In the POLO study (7) of maintenance olaparib in patients with BRCA1/2 mutations and metastatic PC, the most common grade 3–4 AE in the olaparib group was anemia (11%), and it did not differ significantly when compared with the placebo group. AEs were usually managed by dose interruption or a reduction in dosage. Similar findings were also reported in the study of Kaufman *et al.* (30), which demonstrated that olaparib monotherapy could be used in BRCA1/2-mutated patients with advanced PC progression during gemcitabine treatment (including 65% platinum-based chemotherapy). The tumor response rate was 21.7%. Anemia was the most common grade  $\geq 3$  AE (17.4%), and only 9.7% of patients required AE-related olaparib dose modifications. All the data indicated that olaparib was reasonably well tolerated.

The management of olaparib-related AEs in advanced PC can be compared to olaparib's treatment experience in other tumors. A meta-analysis of RCTs (31), including 9 studies of advanced ovarian, gastric, prostate, lung, and breast cancer, showed that olaparib treatment was associated with an increased risk of fatigue and anemia. Although the incidence of olaparib-related serious fatigue and anemia was low, it is important to manage these AEs effectively as they have a major impact on patients' quality of life. To control serious fatigue, clinicians should investigate other possible causes of fatigue and provide supportive care, including conservation of energy and exercise. If fatigue cannot be controlled by supportive care, olaparib should be interrupted until the symptoms are  $\leq$  grade 1, then restarted at the same or a lower dose. As for the management of serious anemia, a monthly assessment of complete blood counts is necessary. Dose interruptions can manage toxicities. However, it is noteworthy that blood transfusions can manage treatment-related anemia without interruption of treatment (28).

In general, the majority of olaparib-related AEs were mild and occurred early during treatment. Patient counseling regarding the side effects of olaparib can help them be prepared for the potential AEs and thereby continue with the treatment—as the alternative provides a bleak outlook. Also, clinicians should detect and control serious AEs related to olaparib treatment as early as possible

to maximize the effect of maintenance therapy.

## Discussion

First-line platinum-based chemotherapy followed by maintenance olaparib further improves the clinical benefits for BRCA1/2-mutated advanced PC patients. For platinum-based chemotherapy, the modified FOLFIRINOX regimen maintains the remarkable clinical effects of FOLFIRINOX and reduces the frequency of the occurrence of hematological and non-hematological AEs. Other platinum-based chemotherapies, for example, gemcitabine plus cisplatin/oxaliplatin, have controllable AEs and good tolerability. After first-line platinum-based chemotherapy, maintenance olaparib for treating patients with advanced PC with BRCA mutations is both effective and safe, given that the incidence of serious AEs is low.

However, this review has some limitations. First, the topic was mainly focused on clinical trials and manifestations. The mechanisms that underlie the adverse reactions have not been mentioned. Second, we only listed the efficacy and safety of FOLFIRINOX and gemcitabine plus platinum-based chemotherapy but failed to illustrate which regimen was better or more suitable for a specific population. The major reason is that there is a lack of sufficient clinical trial data to conclude.

Thus, in addition to BRCA mutations, more studies are needed to screen out reliable biomarkers to benefit patients who are sensitive to platinum-based chemotherapy and PARP inhibitors and have fewer side effects. Additionally, more clinical trials are needed to find a more effective and safe regimen as a first-line treatment in pancreatic cancer patients.

With the further study of chemotherapy and targeted therapy for PC, the treatment-related AEs will be better controlled, and greater benefits will be brought to patients with advanced PC and BRCA mutations

## Conclusions

In conclusion, BRCA1/2-mutated advanced PC patients benefited from platinum-based chemotherapy followed by maintenance olaparib. Among all the platinum-based chemotherapies, modified FOLFIRINOX was proven to have clinical efficacy and could reduce adverse reactions. Furthermore, other platinum-based chemotherapies such as gemcitabine combined with cisplatin or oxaliplatin also showed clinical benefits and controllable side effects.

Although this review provides evidence of feasible clinical application regimens, further studies are still needed to help make better clinical decisions. For example, precision medicine requires clinicians to make decisions based on each individual's specific situation, and we still lack evidence regarding the best regimens and dosages in different races and regions. More trials are needed to focus on patient-reported outcomes besides efficacy and toxicity evaluated by the standard clinical guidelines and equipment. Ultimately, our goal is to help patients live longer and help them live better.

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