Targeting DNA Repair to Drive Immune Responses: It’s Time to Reconsider the Strategy for Clinical Translation

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ABSTRACT

PARP inhibition induces robust local and systemic antitumor immune responses and curative responses when combined with immune checkpoint blockade in many preclinical studies. However, the combination has not markedly improved antitumor effect compared with individual agents in clinical trials to date. We propose that the data from these trials indicate a lack of synergistic interaction of PARP inhibition and immune checkpoint blockade, with implications for reexamining our current strategies for clinical translation. As current mouse models do not recapitulate the genomic heterogeneity or tumor microenvironment of human cancers, better models are urgently needed. Tumor-extrinsic factors modulate immune checkpoint blockade response and they may be better assessed in early-phase clinical trials with frequent tissue and blood sampling. Further work is also needed to uncover the dose and schedule dependency of DNA repair modulation on the immune system. In homologous recombination repair–deficient tumors, randomized trials should be prioritized to address whether the benefit is superior to that of PARP inhibitor monotherapy. In tumors that are not homologous recombination repair deficient, research biopsies should be integrated to early-phase clinical trials to discover biomarkers that can predict clinical benefit. These considerations are relevant to the variety of adjunctive therapeutics being combined with immune checkpoint blockade to improve probability, duration, and potency of antitumor activity.

Introduction

Therapies targeting immune checkpoints have a major impact on outcomes of patients with a wide range of cancers. However, the proportion of patients who benefit from immune checkpoint inhibitor alone is modest at approximately 20%. The ability of the tumors to repair DNA damage plays an important role in immune response to checkpoint blockade. In agreement with this notion, genomically unstable and highly mutated tumors present more tumor neoantigens and are generally more likely to respond to immune checkpoint blockade. This raises the question of whether DNA repair mechanisms can be targeted using drugs to exacerbate genomic instability and drive cancer immunogenicity to improve immune checkpoint blockade responses. Inhibition of PARP, enzymes that are essential for DNA single-strand break repair increased tumor immunogenicity, enhanced the effects of immune checkpoint blockade, and produced curative responses in several preclinical models (1–4). These studies have provided the rationale to therapeutically exploit DNA repair mechanisms to sensitize tumor to immune checkpoint blockade. However, in groundbreaking trials the promise of the combination has not translated to benefit for patients. Here, we propose that the data from these trials indicate that there is a lack of synergistic interaction of PARP inhibitors and immune checkpoint inhibitors in clinic (Fig. 1; Supplementary Table S1), with implications for re-examining our current strategies for therapeutic application of this combination. These considerations are also relevant to the variety of adjunctive therapeutics that are being combined with immune checkpoint inhibitors to improve probability, duration, and potency of immune checkpoint blockade activity.

Rationale for Combining PARP Inhibitors and Immune Checkpoint Inhibitors

PARP inhibitors modulate the base excision repair machinery and trap inactivated PARP onto single-strand DNA breaks, preventing repair and generating DNA replication blocks leading to DNA double-strand breaks. Besides this well-characterized direct cytotoxic effect, which in homologous recombination (HR)-deficient cells can be synthetically lethal, two main mechanisms underlying the antitumor immune effects of PARP inhibitors have been characterized in preclinical models. First, double-strand breaks induced by PARP inhibition generate cyclic GMP-AMP synthase (cGAS) binding, stimulator of interferon genes (STING) activation, and a type 1 IFN response (1, 3). cGAS- or STING-knockout abolished the antitumor effect of PARP inhibitors and the combination with immune checkpoint inhibitors, confirming that the pathway is required for antitumor efficacy. Second, PARP inhibition upregulates programmed cell death-ligand 1 (PD-L1) expression via glycogen synthase kinase-3β inactivation. Blockade of PD-L1 in this setting sensitized the PARP inhibitor–treated cells to T-cell–mediated cell death (2). Together, these coordinated effects on type 1 IFN response and PD-L1 expression significantly increase the therapeutic efficacy when PARP inhibitors were combined with immune checkpoint inhibitors by inducing robust local and systemic antitumor immune responses and formed the basis of more than 30 clinical trials—both ongoing and completed (5).

Clinical Data of Combination with PARP Inhibitors and Immune Checkpoint Inhibitors

Of the notable completed clinical trials of PARP inhibitors and immune checkpoint inhibitors, the TOPACIO study included patients

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Translational Relevance

Several levels of experimental evidence in preclinical models point toward a striking synergy and curative tumor response with PARP inhibition and immune checkpoint blockade. However, the promise of this combination has not been borne out in patients in groundbreaking clinical trials across many cancers. In this article, we propose that the data from these trials indicate that there is a lack of synergistic interaction of PARP inhibition and immune checkpoint blockade, with implications for re-examining our current strategies for clinical translation. We highlight the key challenge of understanding what is happening with such combinations in patients at cellular and mechanistic levels. These considerations are also relevant to the variety of adjunctive combination therapeutics that are being examined to improve the probability, duration, and potency of responses to immune checkpoint blockade.

with platinum-resistant recurrent ovarian cancer and advanced hormone receptors and HER2-negative breast cancer (triple-negative breast cancer, TNBC) irrespective of BRCA mutation status. On the other hand, the MEDIOLA study enrolled patients with BRCA-mutated platinum-sensitive ovarian cancer and HER2-negative advanced breast cancer. In the ovarian cohort of the TOPACIO study, where patients were treated with niraparib and pembrolizumab, the objective response rate (ORR) and median progression-free survival (PFS; the number of patients; 95% confidence interval, CI) were 18% (11/59; 3.5–13.7) and 8.3 months (2.1–not estimable) vs. 2.1 months (1.4–2.5), respectively; ref. 11.

Approximately 20%–25% of patients with metastatic castration-resistant prostate cancer (mCRPC) harbor mutations of the HR pathway (12). As single-agents, PARP inhibitor yields radiographical ORR of 19%–38% irrespective of HR status and 37%–87% in HR-deficient tumors (13). Immune checkpoint inhibitor alone has modest antitumor effect with ORR of 4%–25% (14). In a phase II trial of olaparib and durvalumab, 9 (52.9%) and 4 (23.5%) of 17 patients had ≥50% PSA decline and radiographical responses, respectively (15). Of the nine biochemically responders, four had germline alterations of the HR pathway including deleterious mutations in NBN and BRCA2. The 12-month PFS probability was significantly higher in patients with HR pathway mutation compared with those without (83.3% vs. 36.4%; P = 0.031). In another phase Ib/II study (KEYNOTE-365) of olaparib and pembrolizumab, 5 of 39 patients (13%) with docetaxel-treated mCRPC achieved responses with ≥50% PSA decline and 2 of 28 measurable patients (7%) had radiographical response (16).

PARP inhibitor–immune checkpoint inhibitor combination has been tested in non-BRCA–associated tumors including small-cell lung cancers (SCLC) which are thought to require HR and PARP for unchecked proliferation (17). Among 19 evaluable patients with recurrent SCLC treated with olaparib and durvalumab in a phase II study, 2 patients had confirmed responses yielding an ORR of 10.5% (1.3–33.1) and median PFS of 1.8 months (0.9–2.4; ref. 18). One patient who achieved complete response harbored deleterious

On the contrary, the ORR with olaparib and durvalumab in the MEDIOLA study were relatively high at 71.9% (23/32) and 63.3% (19/30) in patients with BRCA-mutated platinum-sensitive ovarian cancer and HER2-negative advanced breast cancer, respectively (9, 10). In the TNBC cohort of the TOPACIO study also, the antitumor effect was numerically higher in patients with BRCA1/2 mutation than those without [ORR (95% CI) of 47% (24–70) vs. 11% (3–26) and median PFS of 8.3 months (2.1–not estimable) vs. 2.1 months (1.4–2.5), respectively; ref. 11].

Figure 1.
Comparison of ORR with PARPi, ICB, and the combination. Each bar and error bar represent the integrated median and 95% CI of ORR in prospective trials of indicated tumors. The right panel shows the comparison of ORR among tumors with BRCA mutation or other HR deficiency. The trials included in this figure are listed in Supplementary Table S1. PARPi: PARP inhibition; ICB: immune checkpoint blockade; HR: homologous recombination repair.
somatic BRCA1 mutation. Responding tumors harbored high tumor-infiltrating lymphocytes. However, tumor-infiltrating lymphocytes were not improved by the combination treatment. Similar results were reported in the MEDIOLA study of patients with recurrent SCLC with an ORR of 10.5% (4/38 patients had responses) and median PFS of 3.0 months (2.4–4.6; ref. 19). These results are similar to previous studies with immune checkpoint inhibitor alone (ORR of 2%–18% and median PFS of 1–2 months; refs. 20, 21) or with PARP inhibitor monotherapy (ORR ~10%; ref. 22). Patients with relapsed gastric cancer, another non-BRCA-associated tumor, had an ORR of 10% (4/39) with olaparib and durvalumab (23), similar to the efficacy of pembrolizumab alone [ORR (95% CI): 11.6% (8.0–16.1); ref. 24].

**Toward More Rational Clinical Application**

Taken together, data from multiple tumor types point toward the combination of PARP inhibition and immune checkpoint blockade being well-tolerated, but not having markedly improved antitumor effect compared with the individual agents alone. The efficacy of the combination is clearly higher in HR-deficient tumors (Fig. 1; Supplementary Table S1). Consequently, these data raise two overriding questions regarding PARP inhibition and immune checkpoint blockade combinations: (i) what can we learn from the unexpectedly modest outcome in patients despite promising preclinical data? (ii) Is there an opportunity to refine the clinical application of this combination?

It is evident from the clinical data that the current mouse models do not predict response to the combination of PARP inhibitors and immune checkpoint inhibitors in patients, probably because they do not recapitulate the genomic heterogeneity or tumor microenvironment of human cancers. For example, durable complete responses were observed with olaparib and anti PD-L1 antibody in genetically engineered Trp53/Rb1- and Trp53/Rb12/Rbi1-knockout SCLC models (1). In contrast to human SCLC that are characterized by high-tumor mutational burden, the mouse models are driven by deletion of selected genes. As such, the models do not replicate the tumor mutational burden and neoepitope generation, which are critical determinants of immune checkpoint blockade responses in human cancers. The availability of immunocompetent preclinical mouse models that recapitulate human disease is a major challenge and better models are urgently needed across cancers.

In addition to tumor mutational load and other tumor cell intrinsic factors, immune checkpoint blockade response is also modulated by host factors, for example, through the contributions of regulatory T cells, myeloid-derived suppressor cells (MDSC), and environmental factors including intestinal microbiota. PARP enzymes increase the gene expression of IL2 and Th type 2 cytokines, promote T-cell proliferation, and negatively control the expression of forkhead box P3, a key regulator of regulatory T-cell lineage and function (25). PARP inhibition using drugs or gene knockout dampens these inflammatory pathways (25). Because the current preclinical systems are not ideal to interrogate these tumor extrinsic factors, they may be better assessed in early-stage clinical trials with frequent sampling of blood and body fluids to identify predictive biomarkers and biological resistance mechanisms.

Further work is needed to uncover the dose and schedule dependency of DNA repair modulation on the immune system. PARP inhibitors and immune checkpoint inhibitors are concurrently administered in most of the clinical trials to date (6, 11, 15, 16, 18), except in the MEDIOLA study, where olaparib alone is administered for the first 4 weeks before the combination (9, 10, 19, 23). Most combination studies also use the maximum tolerated doses (MTDs) of PARP inhibitors. Immune cells, including T cells, respond to stimuli in a dose-dependent manner. While the appropriate dose can lead to T-cell activation, too strong a signal can cause their anergy or exhaustion (26). Ghonim and colleagues have suggested that low doses of PARP inhibitors may selectively inhibit MDSC and not affect T-cell function (27). Moreover, the potency in trapping PARP, which creates more cytotoxic lesions than catalytic inhibition of PARP enzyme, differs markedly among PARP inhibitors (28) and it is not known whether differential trapping has an impact on immune response. Finally, drugs that induce more DNA damage by similarly trapping protein–DNA complex (e.g., topoisomerase inhibitors) should be considered for their effects on cGAS/STING activation in relation to PARP inhibitors (29).

In clinical studies to date, the combination of PARP inhibitors and immune checkpoint inhibitors has been most effective in BRCA-associated tumors, with antitumor activity demonstrated in terms of ORR. It would seem reasonable to examine the long-term benefits (e.g., duration of response and overall survival) of the combination versus single agents in this population. Supporting this notion are preliminary data from the MEDIOLA study showing complete responses and durable antitumor efficacy among patients with BRCA-mutated platinum-sensitive ovarian cancer and HER2-negative advanced breast cancer (9, 10). Furthermore, BRCA1/2-mutated tumors have higher predicted neoantigens and higher expression of immune genes compared with tumors without HR gene alterations (30). The ongoing clinical trials of PARP inhibitors and immune checkpoint inhibitors with predefined HR-deficient cohorts (NCT02571725, NCT02953457, NCT03334065, NCT03824704, NCT03834519, and NCT04034927) should partly address this question. However, randomized trials are needed to clarify whether the combinations are indeed superior to PARP inhibitor or immune checkpoint inhibitor alone. To the best of our knowledge, no such trials are underway.

In BRCA-lineage tumors, such as ovarian, breast, and prostate cancers, BRCA mutation has tumorigenic effects associated with somatic biallelic or haploinsufficiency, contributes to HR deficiency, and exhibits increased therapeutic sensitivity to PARP inhibitors. The functional relevance of BRCA1/2 mutation is less clear in non-BRCA lineage tumors (31). To date, the combination of PARP inhibitors and immune checkpoint inhibitors has not shown meaningful antitumor efficacy in non-BRCA lineage tumors such as SCLC and gastric cancers (18, 19, 23). In these tumors, research biopsies should be integrated to early-phase clinical trials to discover subgroups of patients who may potentially benefit.

Research biopsies can also address whether PARP inhibition generates cGAS/STING activation and a type 1 IFN response, and the magnitude of these responses. Intriguingly, a recent study suggested that the chronic IFN signaling in the tumor cells opposed the effects of IFN signaling in adaptive and innate immune cells to limit immune response (32). Recent studies also point to a potential role of chronic activation of cytosolic DNA sensing pathways in promoting metastases (33) and suppressing HR-mediated DNA repair (34). Tissue requirements are likely to add to the complexity of the protocol and increase the trial burden on patients and research staff. However, the tradeoff would be improved understanding of mechanisms of
sensitivity and resistance as well as informing the scheduling and sequencing of the agents.

Conclusion

Clinical trials built on a robust synergistic interaction between PARP inhibition and immune checkpoint blockade in mouse models do not demonstrate the expected improvement in outcomes compared with historical cohorts treated with PARP inhibitor or immune checkpoint inhibitor monotherapy. The combination appears effective in HR-deficient tumors. Therefore, randomized trials should be prioritized to address whether the benefit is superior to that of PARP inhibitor monotherapy in these tumors. Clinical utility of the combination among the non-BRCA lineage tumors would be enhanced by identification of predictive biomarkers and to this end collection of tumor and liquid biopsies as part of ongoing trials should be prioritized. Finally, the discrepant outcomes of the preclinical modeling and clinical outcomes underscore the need to characterize models that better recapitulate the human tumor microenvironment and more importantly for heightened efforts to understand the effects of these agents on the tumor and host microenvironment in early-phase clinical trials.

References

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