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Commentary

CHK1 Inhibitor-Based Checkpoint Abrogation: A Classic, Yet New Therapeutic Approach in Advanced Cancer

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ABSTRACT

Recent advances in small molecule kinase inhibitors have markedly improved patient survival in various types of cancer. Most of these successes can be attributed to the concept of "targeting driver oncogenes," as in the case of tyrosine kinase inhibitors (i.e., EGFR inhibitors), but not in serine/threonine kinase inhibitors including CHK1 inhibitor. Further investigation of the underlying mechanisms is needed to identify synergistic interactions of CHK1 that would help prolong patient survival and improve their quality of life.

Keywords: Checkpoint Abrogation; Advanced Cancer; DNA Repair

INTRODUCTION

With the exception of favorable cases of patients that experience complete tumor regression or an opportunity for curative surgical resection, acquired resistance to these inhibitors against the driver oncogenes will eventually occur resulting in an unfavorable outcome and tumor progression [1]. Therefore, targeting other cellular or molecular machineries is urgently needed to improve the quality of life of patients. From past decade or two, "checkpoint abrogation" has been expected as an efficient therapeutic approach to target common cellular machinery and widely applicable across various cancers [2], suggesting possible application for recurring tumors during the therapy by "targeting driver oncogenes". Mechanistically, when normal and cancer cells are faced with DNA insults, genomic surveillance mechanisms respond at the G1/S, S, and/or G2/M cell cycle checkpoints and subsequently enable DNA repair to sustain genomic integrity.

The rationale for the clinical application of the checkpoint abrogation strategy was originally based on the observation that the majority of cancer cells are supposed to be vulnerable to G2 checkpoint inhibition. Because defects in the G1 checkpoint, attributable to functional deficiency of the tumor suppressors, p53 or Rb, are conventional cancer characteristics, such cancer cells would be largely dependent on the G2 checkpoint for their genomic integrity. UCN-01 is an earlier protein kinase inhibitor is capable of G2 checkpoint abrogation by inhibition of CHK1 and is considered a potential chemo/radio sensitizer [3].

To date, several selective CHK1 inhibitors (henceforth CHK1i) as well as the inhibitors of its upstream DNA damage sensor kinase, the ataxia telangiectasia mutated and Rad3 related (ATR), have been developed; however, the clinical benefit of single agents or combination therapy with conventional cytotoxic drugs, such as gemcitabine, has been considerably limited [4]. Accumulating evidence suggests that in addition to the G2 checkpoint, CHK1 plays multiple roles in the intra-S-phase checkpoint, including replication origin firing and stabilizing stalled replication forks, making it difficult to design proof-of-concept clinical trials of CHK1i. Alternatively, instead of conventional cytotoxic agents, blockade of DNA repair pathways has emerged as a possible combination partner for CHK1i. Several lines of evidence have indicated this possibility.

For instance, synthetic lethal screen has identified that deficiency of the Fanconi anemia DNA repair pathway is critical for CHK1i sensitivity [5]. Neuroblastoma cell lines, in which

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genomic alteration-associated functional defects of DNA damage response-associated molecules, including CHK1, were sensitive to an inhibitor of the polyadenosine-diphosphate-ribose polymerase (PARP) that is responsible for base excision repair [6]. Consistently, we and other investigators have proposed the ataxia telangiectasia mutated serine/threonine kinase (ATM) and the DNA-dependent protein kinase (DNA-PK) as potential candidate targets that potentiated synergistic or additive effects in combination with CHK1i [7]; these kinases are involved in the two core pillars of DNA damage repair pathways, the homologous recombination and non-homologous end-joining pathway, respectively.

Collectively, inhibition of the three prominent DNA damage sensors has arisen as an alternative approach for combination treatment with CHK1i-induced "checkpoint abrogation." Since many studies have reported that CHK1i itself has an ability to induce DNA damage by increasing the phosphorylation of histone H2AX, it seems reasonable to infer that the blockade of DNA repair pathways have a functionally favorable interaction with CHK1 inhibition rather than conventional cytotoxic agents.

DISCUSSION

We presume that this "checkpoint abrogation" approach may improve clinical benefit and the quality of life for patients that would face disease progression during the later stage of targeted therapy or conventional chemotherapies by avoiding the side effects of conventional cytotoxic agents. The second-generation of CHK1i in combination with inhibitors of DNA repair molecules is now being investigated in clinical trials. "Combination Study of Prexasertib and Olaparib in Patients with Advanced Solid Tumors" (NCT03057145) and "Treatment With Oral LY3023414 to Inhibit Homologous Recombination Followed By Prexasertib (ExIST)" for triple-negative breast cancer (NCT04032080) are underway. Apart from curing the disease, delaying disease progression is a primary goal and an urgent clinical need in the treatment of advanced cancer.

CONCLUSION

Further investigation of the underlying mechanisms is needed to identify synergistic interactions of CHK1i that would help prolong patient survival and improve their quality of life.

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