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A CRITICAL REVIEW ON THE ANTICANCER ACTIVITY OF A FIRST-IN-CLASS SMALL-MOLECULE TARGETING PCNA

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ABSTRACT

Background: Proliferating cell nuclear antigen (PCNA) is a major controller of DNA replication and repair and is vital in the survival of cancerous cells. Cancer-specific isoform of PCNA (caPCNA) displays structural divergence with normal PCNA, providing a target of treatment. The first-in-class small-molecule inhibitor, AOH1160 is developed to take advantage of this specificity.

Methods: The systematic literature review was performed on the leading scientific databases to find preclinical trials assessing AOH1160. Relevant studies were filtered according to their eligibility criteria. The studies were evaluated based on molecular targeting, anticancer activity, pharmacokinetics, safety, and potential of combination therapy.

Results: The studies that have been included consistently show that AOH1160 selectively binds the L126-Y 133 region of caPCNA, which inhibits the DNA replication and homologous recombination repair of cancer cells. Treatment caused cell-cycle arrest, apoptosis and damage to DNA without damaging normal cells. *In vivo* studies justified tumour suppression, oral bioavailability, desirable pharmacokinetics and low toxicity. The cisplatin synergistic effect was also reported.

Conclusion: The preclinical evidence of AOH1160 is good as a selective anticancer agent against caPCNA. To ensure safety and therapeutic efficacy, its clinical validation is necessary.

KEYWORDS

PCNA, caPCNA, AOH1160, Systematic review, Targeted cancer therapy and DNA repair inhibition.

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INTRODUCTION

Oncology research always aims to find new therapies capable of influencing cancer cells, not healthy ones. In this context, the study titled “The anticancer activity of a first-in-class small molecule targeting PCNA” by Long Gu, Robert Lingeman, Fumiko Yakushijin and colleagues gives a novel understanding of the cancer-specific molecular
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targets. This paper focuses on the Progress Report of AOH1160. This newly synthesized small molecule targets PCNA, a protein critical in DNA replication and repair in eukaryotic organisms, published in October 2018 in Clinical Cancer Research. Castrillon *et al*, working in the Beckman Research Institute of the City of Hope, offer a review on molecular oncology and single out one isoform of PCNA, caPCNA, which is highly specific to cancer cells in terms of expression and structure (Manzari-Tavakoli A, *et al*, 2024)¹.

Based on this study, the authors proposed that targeting PCNA is a rational approach since it plays a central choreographic role during DNA replication and repair cycles. It is a crucial factor for cancer cell survival and proliferation. The authors continue earlier work to recognize caPCNA and establish that peptides can interfere with it selectively at the protein-protein level. Building upon this, the current study assesses the therapeutic application of AOH1160, a first-in-line inhibitor that targets the L126–Y133 domain in caPCNA and triggers apoptotic cell death and chemosensitization of cancer chemotherapy agents such as cisplatin.

This work has very high clinical relevance. It responds to profound questions that have always been issues in oncology, for example, the toxicity of conventional treatments and the search for broad-spectrum but selective drugs. They found that AOH1160 exhibits excellent selectivity and is less toxic to normal cells and tissues. It can be orally administered since it is bioavailability-a key characteristic when considering an agent for clinical application. In addition to proving the compound's effectiveness, the existing *in vitro* and *in vivo* tests complement the analysis of concrete application perspectives of AOH1160 as a multifunctional drug. However, in the paper, weak points also listed the future directions that need to be investigated, such as long-term toxicity, resistance mechanisms, and human clinical trials. In light of the findings made in this study, there is substantial hope in creating new cancer therapies and improving the specificity and reduced toxicity of anticancer drugs based on the knowledge gained on the function of PCNA in cancer-related biology (Manzari-Tavakoli A, *et al*, 2024)¹.

BODY

OVERVIEW OF THE ARTICLE

Key Findings and Methodology

Then, the study starts with the significance of PCNA in cancer cell proliferation and survival, particularly regarding the isotype called caPCNA. While normal cPCNA remains structurally intact, caPCNA undergoes structural alteration, making it a prime candidate for drug-directed intervention. In fine-tuning computational modeling and medicinal chemistry approaches, the authors found AOH1160, which selectively targets the caPCNA L126-Y133 site. The methodology includes:

Selective Cytotoxicity

AOH1160 exhibits reasonable selectivity towards cancer cells irrespective of the origin across multiple cancer lines, including neuroblastoma, breast cancer and small-cell lung cancer, and it does not harm normal cells, including human mammary epithelial cells and neural stem cells. Such selectivity is explained by the correct interaction with the PCNA (caPCNA) cancer-associated isoform, as evidenced by molecular modeling and pharmacokinetic studies. Small molecule AOH1160 selectively triggers apoptosis in cancer cells at concentration ranges of micromolar without impacting non-cancerous cells. It thus holds promise for utilization as a nontoxic approach to cancer treatment. Since the compound targets the structural area relevant to the changes that occur with caPCNA, it decouples critical cellular functions that are indispensable for cancer cells. Such specificity is beneficial in reducing damage to healthy tissues. It makes AOH1160 unique in terms of potential therapeutic effects in searching for more selective and less toxic cancer therapeutics.

Mechanism of Action

AOH1160 blocks cell replication and impairs homologous recombination repair by binding selectively to the cancer-specific isoform of PCNA (caPCNA). This disruption leads to robust cell-cycle dynamics that are especially notable for the S phase and G2/M and involve DNA synthesis and repair. Here, the writers demonstrate that its action causes DNA damage compared to the control as measured by increased levels of the DNA damage marker γ H2A.X and the subsequent build-up of irreparable DNA lesions. These effects induce

apoptosis in cancer cells, as evidenced by the enhanced cleavage of caspase 7. Also interesting is that AOH1160 increases the activity of drugs such as cisplatin by making cancer cells more responsive to chemotherapy treatment and increasing the rate of DNA damage combined with cell death. With this multiple-pronged mechanism, the authors also indicate that AOH1160 can be a monotherapy targeted at resistant cancers but could be equally valuable as an adjuvant in combination therapies.

In vivo therapeutic efficacy

AOH1160 shows considerable anticancer activity, as proven in vitro. It can inhibit cancer cell proliferation in mice without harming typical cells. The compound has good oral bioavailability, further contributing to its clinical utility because it is pretty easy to administer.

In vivo pharmacokinetics and safety

In animal models at the rate of 3.5 hrs half-life, AOH1160 sustains therapeutic plasma level, and no adverse effects were observed even at a 2.5-fold higher dose compared to an effective dose. This is complemented by a few toxicities manifested during the repeated dosing regimens in mice. Besides its direct anti-cancer activity, AOH1160 showed a synergistic effect on cisplatin, a DNA-damaging agent, by improving cancer cell radiosensitivity. This combination has led to the idea of using it for chemo-combination therapies, which may enable cancer patients to receive lower doses of standard chemotherapy drugs, thus the side effects. More importantly, its impressive in vivo activity profile, lack of severe toxicity, and ability to combine with other agents indicate a high clinical relevancy as an anticancer drug (Manzari-Tavakoli A, *et al*, 2024)¹.

Strengths and usefulness

The article showcases several prominent strengths:

Innovative targeting approach

Targeting the cancer-associated isoform of PCNA (caPCNA) is a groundbreaking approach in oncology. Focusing on caPCNA's unique structural features, this method addresses a key challenge of conventional therapies: differentiating between healthy and malignant cells, often resulting in side effects. For instance, AOH1160 targets the L126-Y133 region of caPCNA, which is absent in non-malignant PCNA. This specificity allows for precise interference with tumour cell proliferation

mechanisms like DNA replication and repair, minimizing harm to normal cells while boosting treatment effectiveness. The successful targeting of caPCNA highlights its potential as a model for creating other selective cancer therapies, representing a significant step forward in developing safer cancer treatments.

Comprehensive experimental design

The study systematically utilizes three approaches—computational models, cell culture dishes, and animal testing—to thoroughly evaluate the effectiveness and safety of AOH1160. Molecular modeling helped define the compound's interaction with an isolated isoform, which may inform caPCNA therapeutic applications. Further characterization involved cellular assays of replication forks, DNA combing analysis, and TUNEL assays to quantify apoptosis, providing crucial insights into how AOH1160 targets cancer cell DNA replication and induces cell death. *In vitro* studies in preclinical models showed its ability to reduce tumour volume with minimal side effects. This comprehensive approach underscores the uniqueness of the investigation.

Potential for broad-spectrum application

The results show that AOH1160 is a promising broad-spectrum anticancer compound capable of inhibiting the growth of various tumour cell lines. It selectively targets the cancer-associated isoform of PCNA (caPCNA), disrupting processes in neuroblastoma, breast tumours, and small-cell lung tumours. Additionally, AOH1160 enhances the sensitivity of drug-resistant cancer cells to traditional treatments like cisplatin. This positions AOH1160 as a potential stand-alone therapy and a valuable adjuvant in combination therapies, effectively addressing the complex nature of cancer while reducing the drawbacks of high-dose chemotherapy.

Clinical Relevance

AOH1160 is, therefore, of particular clinical significance; it has the defined specificity and characteristics that allow its progression to clinical trial status. AOH1160 offers excellent therapeutic value by selectively promoting cancer cells' susceptibility to cisplatin, a standard DNA-alkylating chemotherapeutic compound. That might enable a lower cisplatin dose, which should lower

the drug's toxicity and side effects' impact. Furthermore, AOH1160 has been confirmed to have good oral availability and desired safety effects in related measured animal experiments, which suggests that AOH1160 may be very convenient for patients. It specifically binds to the cancer-associated isoform of PCNA (caPCNA); thus, it conforms to the concept of precision medicine, which seeks to leverage unique aspects of cancers while leaving the rest of the cells undisturbed. This study adds importance to the expanding area of targeted anticancer agents, collectively suggesting a promising approach to base future therapy improvements for multifarious neoplasms with minimal toxicity.

Weaknesses and Limitations

Preclinical Limitations

A notable limitation of this study is its narrow focus on translational aspects, as the experiments were exclusively conducted on animal models and cancer cell lines. While the findings are encouraging, further research is essential to assess safety, efficacy and pharmacokinetics through human clinical trials.

Focus on short-term outcomes

The research primarily investigates the short-term outcomes associated with AOH1160, particularly its capacity to suppress tumours and induce programmed cell death. Long-term effects, including the potential for antimicrobial resistance and toxic impacts on human tissue morphology, remain unexamined.

Lack of comparative analysis

This study does not include a comparison of AOH1160 with other established PCNA inhibitors or targeted therapies. Such comparative analyses could enhance the understanding of its therapeutic advantages.

Unexplored combination strategies

While evidence supports the synergistic effect of AOH1160 in combination with cisplatin, the study does not explore other combinations with immunotherapies or radiation therapies. This limitation may impede its clinical application in future investigations.

Evaluation of Methodology

The authors utilize advanced methodologies to assess the characteristics of the new compound, AOH1160. For example:

Virtual screening and molecular modeling

These techniques ensure the precise development of AOH1160 for selective binding to caPCNA. Incorporating crystallographic data and docking studies enhances the compound's selectivity and efficacy.

Pharmacokinetic studies

Significant progress has been made in developing an oral formulation compatible with clinical applications. Nevertheless, further research is required to elucidate drug metabolism and excretion details.

Cellular assays

Data obtained from flow cytometry and Western blotting substantiate the action of AOH1160 on cell cycle regulation and DNA repair mechanisms, showing strong durability.

Despite these strengths, the study would benefit from more extensive sections that conduct additional experiments to identify potential off-target effects and establish optimal dosages.

CONCLUSION

In support of this hypothesis, Gu *et al*, put forth a compelling rationale for the role of AOH1160 as a broad-spectrum anticancer agent targeting caPCNA. This research exhibits several strengths, including a well-defined target audience, high methodological rigor and meaningful real-world implications. By culturally differentiating caPCNA, the findings suggest that AOH1160 may be a viable alternative to conventional therapies, with the added advantage of being non-toxic to non-malignant cells.

Nonetheless, the study has several limitations: it was conducted preclinically and the observed outcomes were assessed over a short period. Future studies should prioritize the following:

Clinical trials

To verify the efficacy, safety and pharmacokinetics of AOH1160 in human subjects.

Combination therapies

To explore interactions with other immunotherapies, radiation, or targeted treatments.

Long-term evaluation

To investigate resistance mechanisms and potential toxicities in various patient populations.

Comparative studies

To provide a clearer understanding of the therapeutic potential of AOH1160 in comparison to other drugs.

In conclusion, this article contributes to cancer research and can inform the development of new, selective and less harmful treatment options. Despite its limitations, the study underscores the potential of targeting PCNA to enhance existing cancer therapies and ultimately improve patient outcomes.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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