AUCTORES
Globalize Your research

Journal of Cancer Research and Cellular Therapeutics
Edward J. Kim, J Cancer Research and Cellular Therapeutics

Open Access

Short Review

Strategic Combinations of Aurora Kinase an Inhibiton with Targeted Drugs for Synergistic Anti-Tumor Effect

Jasmine C. Huynh[1], Justin A. Chen[1], Mili Arora[1], May Cho[1], Edward J. Kim[1*]

[1]Department of Internal Medicine, University of California Davis, USA.

***Corresponding Author :** **Edward J. Kim**, UC Davis Comprehensive Cancer Center, Sacramento, CA 95817 USA. **E-mail:** jhkim@ucdavis.edu

Received date: May 25, 2019;**Accepted date :** June 05, 2019; **Published date:** June 06, 2019.

Citation : Jasmine C. Huynh, Justin A. Chen, Mili Arora, May Cho, Edward J. Kim. Strategic Combinations of Aurora Kinase an Inhibiton with Targeted Drugs for Synergistic Anti-Tumor Effect, J. Cancer Research and Cellular Therapeutics. **Doi**: 10.31579/ 2640-1053/051.

Abstract

Inhibition of mitosis is an established therapeutic approach in the treatment of cancer. However, existing drugs that use this mechanism including taxanes cause off-target effects leading to dose-limiting toxicity such as sensory neuropathy. Development of inhibitors of mitosis-specific targets has created the next generation of mitosis inhibitors with the goal of achieving similar anti-tumor efficacy but with less toxicity. Aurora Kinase A is one example of a mitosis-specific target for which multiple drugs have been developed as anti-cancer therapy. Although early preclinical studies have showed on-target effects, clinical development has been slowed by minimal efficacy as monotherapy. However, strategic combinations of Aurora Kinase A inhibition with various targeted drugs has shown promise and led to renewed interest in the potential of inhibiting this mitosis-specific target.

Keywords: aurora kinase A; mitotic inhibitor; cell cycle; tumorigenesis

Introduction

The Aurora Kinase family is comprised of three members; Aurora Kinase A (AKA), Aurora Kinase B (AKB) and Aurora Kinase C (AKC). Aurora Kinases are serine/threonine kinases that regulate chromosomal segregation during mitosis and meiosis. AKA and AKB are expressed in most cell types whereas AKC is only expressed in the testis. AKA controls premetaphase events, AKB is crucial for precise chromosome segregation and cytokinesis, and AKC controls spermatogenesis [1-3]. Though all members of the Aurora Kinase family have oncogenic properties, AKA was the first family member to be identified as one of the main kinases that regulates cell proliferation and for this reason, is an attractive drug target[1]. This review focuses on AKA as a potential target for next-generation mitotic inhibition, especially in combination with other targeted agents.

AKA plays a crucial role in centrosome maturation, mitotic entry, G2/M transition, spindle assembly and cytokinesis [2,4,5]. In normal cells, AKA induces phosphorylation of TACC, leading to complex formation with XMAP215 to promote centrosomal microtubule stabilization [2,6,7]. Prior to M phase, AKA couples with Bora to induce phosphorylation and activation of PLK. Activated PLK1 then activates CDK1/cyclin B via degradation of Wee1, a CDK-inhibitory kinase, and activation of CDK-promoting phosphatase CDC25C. Simultaneously, AKA activates CDC25B, another CDK-activator. This series of events further enhances the G2/M transition[2]. AKA additionally phosphorylates Ajuba which is a LIM protein and this interaction forms a positive feedback loop to initiate mitosis. There is an additional positive feedback loop between AKA and TPX2, and deficiencies in either component leads to defective spindle formation[2].

Role of AKA in tumorigenesis

AKA has several roles in tumorigenesis and has been associated with multiple cancers, including breast cancer, gliomas, lung cancer, head and neck carcinoma, gastric cancer, esophageal cancer, and hematologic malignancies. In general, cancer cells with AKA overexpression have amplified centrosomes and multipolar spindles, genomic instability due to failure to resolve cytokinesis, and aberrant activation of pro-oncogenic signaling pathways, such as the nuclear factor kB and B-catenin/WNT pathway [4,8,9].

AKA's specific role in tumorigenesis has been investigated in multiple tumor types. AKA has been shown to prevent N-myc degradation in neuroblastoma[10], promote epithelial-to-mesenchymal transition (EMT) in breast cancer cells[11], and promote growth of KRAS-mutant lung and GI tumor cells potentially through phosphorylation of RPS6KB1 [8,12].

Targeting AKA for cancer therapy

Given AKA's role in tumorigenesis, inhibition of AKA has been an attractive strategy based on its potential to provide a novel effective way to suppress cancer progression. Multiple AKA inhibitors have been developed, including MLN8237 (alisertib), MK5108 (VX-689), and MLN8054[1]. Alisertib has progressed the furthest in clinical development among the AKA inhibitors and has been tested in multiple Phase I-II trials, with some Phase III trials emerging [13-18]. However, AKA inhibitors as monotherapy have consistently disappointed demonstrating minimal clinically meaningful efficacy. A phase III study of single-agent alisertib in relapsed/refractory peripheral T-cell lymphoma showed no improvement of progression-free survival or response rate compared to investigator's choice, leading to early study termination[18].

Combining inhibition of AKA with targeted drugs

This overall poor response of cancer cells to AKA inhibition alone has led to investigation of combination strategies anchored on AKA inhibition.

Wee1 inhibitor

In TP53-mutant HNSCC cells, the addition of adavosertib, a Wee1 inhibitor, to alisertib resulted in mitotic catastrophe-mediated cell death through highly abnormal mitoses with unaligned, dispersed chromosomes, disorganized multipolar spindles, and distorted and ballooned cellular morphology[4]. Cells treated with combination therapy also showed increased levels of cleaved-PARP, suggesting induction of apoptosis. These findings were confirmed in in vivo models where combination therapy dramatically decreased tumor growth and prolonged survival of mice compared to vehicle or single-agent therapy. Additionally, murine weight remained stable suggesting the combination was minimally toxic. Mechanistically, Wee1 is an inhibitor of CDK1; its addition promotes cell-cycle progression, mitotic entry, and transition through the G2/M-checkpoint in the presence of defective spindle assembly and failed centrosome maturation induced by AKA inhibition, thus resulting in mitotic catastrophe.

MEK inhibitor

MEK is part of the MAPK signaling pathway and affects cellular response to DNA damage [19,20]. This has led to the hypothesis that combining MEK inhibition with AKA inhibition may result in more robust cell death. MEK inhibition disrupts DNA repair and cell cycle progression in G1, thus addition of MEK inhibitors promotes genomic instability induced by AKA inhibition and facilitates sustained cell cycle arrest [19,21,22]. Furthermore, MEK inhibition can induce degradation of c-Myc which upregulates expression of AKA in hepatocellular carcinoma and B-cell lymphomas [19,23,24]. In BRAF-mutant melanoma cell lines, combination trametinib (MEK inhibitor) and MLN8054 had more pronounced anti-proliferative effects as compared to combination trametinib and dabrafenib, the latter of which is a now a first-line regimen in BRAF-mutated advanced melanomas[19,25]. In KRAS- and PIK3CA-mutant colorectal cancer cell models, combining alisertib with MEK inhibition led to a more robust anti-proliferative response[19].

BH3 mimetic

The Bcl2 family of proteins include both pro- and anti-apoptotic members that share Bcl2 homology (BH) domains including BH3. BH3 mimetics such as ABT263 block select anti-apoptotic members of the Bcl2 family of proteins but fail to inhibit all, including MCL-1[26]. This incomplete blockade is thought to be one potential pathway of resistance to BH3 mimetic monotherapy. MLN8237 induces mitotic arrest which leads to MCL-1 degradation, thus introducing a way to overcome this potential resistance mechanism. In four pancreatic cancer cell lines treated with monotherapy MLN8237 or ABT263, there was variable sensitivity to either single agent[26]. However, combination MLN8237 and ABT263 resulted in a synergistic increase of sensitivity in all four cell lines. In vivo testing of this combination on pancreatic cell xenografts and patient-derived pancreatic cancer organoids (PDO) showed greater tumor growth inhibition compared to either agent alone. Both pancreatic cancer cell lines and PDOs showed an increase in Caspase 3/7 activity, suggesting that an increase in apoptosis was responsible for the observed cell growth inhibition. Combining AKA inhibition with Bcl2 inhibition has also been tested in double hit lymphoma and has shown promise through arrest of cell cycle progression and promotion of apoptosis[27].

EGFR inhibitor

EGFR inhibitors have become a standard treatment option for EGFR-mutated non-small cell lung cancers (NSCLC). However, inevitable development of resistance to EGFR inhibitors limits durability of response. One potential mechanism of EGFR inhibitor resistance is through an increase in expression of TPX2 which activates AKA and protects it from degradation[28]. Patient-derived NSCLC xenografts treated with combination rociletinib, a 3rd generation EGFR inhibitor, and MLN8237 led to stronger initial reduction in tumor growth as compared to single-agent rociletinib, which only partially abrogated tumor growth and led to rapid tumor progression. Similarly, the combination of osimertinib, another 3rd generation EGFR inhibitor, and MLN8237 resulted in decreased tumor growth in nine out of ten tested xenografts[28]. Combination treatment caused a decrease in ERK and NF-κB signaling with induction of apoptosis, synergistically leading to greater suppression in the growth cells with acquired resistance and delaying emergence of resistant clones.

Estrogen receptor inhibitor

In endocrine-resistant, estrogen receptor positive (ER+) breast cancer cells, aberrant MAPK signaling promotes phosphorylation and stabilization of AKA. This down-regulates ERα expression via SMAD5 activation, leading to endocrine resistance and tumor progression[29]. Alisertib has been shown to reverse the AKA-mediated restoration of stemness of breast cancer cells, ultimately leading to increased estrogen receptor expression and increased sensitivity to endocrine therapy in in vitro studies [11,29]. Addition of fulvestrant to alisertib induced an even stronger effect on inhibition of cell proliferation[29].

These preclinical findings were the basis of a Phase I clinical trial evaluating the addition of alisertib to fulvestrant in women with endocrine-resistant, ER+ metastatic breast cancer[11]. The combination of alisertib with fulvestrant was well-tolerated with a favorable safety profile and a median PFS of 12.4 months compared to 7.9 months in a similar patient population receiving alisertib monotherapy[11,17].

Discussion & Conclusion

AKA is intricately involved in cell cycle regulation, particularly in centrosome maturation and spindle assembly[8]. Overexpression of AKA has been found in multiple cancer types and has been shown to cause genomic instability and activation of pro-oncogenic signaling pathways [30,31]. Inhibition of AKA is an attractive therapeutic target, but there is insufficient efficacy when an AKA inhibitor is used as monotherapy. There are multiple targeted agents that have been tested in combination with AKA inhibitors, and the resultant synergy have not only shown efficacy in vitro, but have also shown promising efficacy in vivo. Taxanes achieve proven clinical efficacy through mechanism of mitotic inhibition but are ultimately limited by dose-limiting toxicities like neuropathy. AKA inhibitors also attack cancer cells by inhibiting mitosis but do so more specifically by targeting a mitosis-specific kinase and thus have the potential to achieve benefit with less toxicity. Combining targeted therapies with AKA inhibitors to achieve synergy and increased efficacy is a promising therapeutic strategy in a variety of malignancies and further prospective clinical trials examining these combinations are warranted.

Conflict of Interest

Authors report no conflict of interest related to the subject of this short review.

References

1. Damodaran AP, Vaufrey L, Gavard O, Prigent C. Aurora A Kinase Is a Priority Pharmaceutical Target for the Treatment of Cancers. Trends Pharmacol Sci. 2017;38(8):687-700.
2. Yan M, Wang C, He B, Yang M, Tong M, et al. Aurora-A Kinase: A Potent Oncogene and Target for Cancer Therapy. Med Res Rev. 2016;36(6):1036-79.
3. Long L, Wang YH, Zhuo JX, Tu ZC, Wu R, et al. Structure-based drug design: Synthesis and biological evaluation of quinazolin-4-amine derivatives as selective Aurora A kinase inhibitors. Eur J Med Chem. 2018;157:1361-75.
4. Lee JW, Parameswaran J, Sandoval-Schaefer T, Eoh KJ, Yang DH, et al. Combined Aurora Kinase A (AURKA) and WEE1 Inhibition Demonstrates Synergistic Antitumor Effect in Squamous Cell Carcinoma of the Head and Neck. Clin Cancer Res. 2019.
5. Borisa AC, Bhatt HG. A comprehensive review on Aurora kinase: Small molecule inhibitors and clinical trial studies. Eur J Med Chem. 2017;140:1-19.
6. Kinoshita K, Noetzel TL, Pelletier L, Mechtler K, Drechsel DN, et al. Aurora A phosphorylation of TACC3/maskin is required for centrosome-dependent microtubule assembly in mitosis. J Cell Biol. 2005;170(7):1047-55.
7. Barros TP, Kinoshita K, Hyman AA, Raff JW. Aurora A activates D-TACC-Msps complexes exclusively at centrosomes to stabilize centrosomal microtubules. J Cell Biol. 2005;170 (7):1039-46.
8. Wang-Bishop L, Chen Z, Gomaa A, Lockhart AC, Salaria S, et al. Inhibition of AURKA Reduces Proliferation and Survival of Gastrointestinal Cancer Cells With Activated KRAS by Preventing Activation of RPS6KB1. Gastroenterology. 2019;156(3):662-75 e7.
9. Katsha A, Belkhiri A, Goff L, El-Rifai W. Aurora kinase A in gastrointestinal cancers: time to target. Mol Cancer. 2015;14:106.
10. Otto T, Horn S, Brockmann M, Eilers U, Schuttrumpf L, et al. Stabilization of N-Myc is a critical function of Aurora A in human neuroblastoma. Cancer Cell. 2009;15(1):67-78.
11. Haddad TC, D'Assoro A, Suman V, Opyrchal M, Peethambaram P, et al. Phase I trial to evaluate the addition of alisertib to fulvestrant in women with endocrine-resistant, ER+ metastatic breast cancer. Breast Cancer Res Treat. 2018;168(3):639-47.

12. Dos Santos EO, Carneiro-Lobo TC, Aoki MN, Levantini E, Basseres DS. Aurora kinase targeting in lung cancer reduces KRAS-induced transformation. Mol Cancer. 2016;15:12.
13. Barr PM, Li H, Spier C, Mahadevan D, LeBlanc M, Ul Haq M, et al. Phase II Intergroup Trial of Alisertib in Relapsed and Refractory Peripheral T-Cell Lymphoma and Transformed Mycosis Fungoides: SWOG 1108. J Clin Oncol. 2015;33(21):2399-404.
14. Cervantes A, Elez E, Roda D, Ecsedy J, Macarulla T, et al. Phase I pharmacokinetic/pharmacodynamic study of MLN8237, an investigational, oral, selective aurora a kinase inhibitor, in patients with advanced solid tumors. Clin Cancer Res. 2012;18(17):4764-74.
15. Dees EC, Cohen RB, von Mehren M, Stinchcombe TE, Liu H, et al. Phase I study of aurora A kinase inhibitor MLN8237 in advanced solid tumors: safety, pharmacokinetics, pharmacodynamics, and bioavailability of two oral formulations. Clin Cancer Res. 2012;18(17):4775-84.
16. Friedberg JW, Mahadevan D, Cebula E, Persky D, Lossos I, et al. Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphomas. J Clin Oncol. 2014;32(1):44-50.
17. Melichar B, Adenis A, Lockhart AC, Bennouna J, Dees EC, et al. Safety and activity of alisertib, an investigational aurora kinase A inhibitor, in patients with breast cancer, small-cell lung cancer, non-small-cell lung cancer, head and neck squamous-cell carcinoma, and gastro-oesophageal adenocarcinoma: a five-arm phase 2 study. Lancet Oncol. 2015;16(4):395-405.
18. O'Connor OA, Ozcan M, Jacobsen ED, Roncero JM, Trotman J, et al. Randomized Phase III Study of Alisertib or Investigator's Choice (Selected Single Agent) in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma. J Clin Oncol. 2019;37(8):613-23.
19. Davis SL, Robertson KM, Pitts TM, Tentler JJ, Bradshaw-Pierce EL, et al. Combined inhibition of MEK and Aurora A kinase in KRAS/PIK3CA double-mutant colorectal cancer models. Front Pharmacol. 2015;6:120.
20. Wei F, Yan J, Tang D. Extracellular signal-regulated kinases modulate DNA damage response - a contributing factor to using MEK inhibitors in cancer therapy. Curr Med Chem. 2011;18(35):5476-82.
21. Hirota T, Kunitoku N, Sasayama T, Marumoto T, Zhang D, et al. Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells. Cell. 2003;114(5):585-98.
22. Collins S, Blair, D., Zarycki, J., Szynal, C., Mettetal, J., et al. "A rationale for combining the targeted investigational agents TAK-733, a MEK 1/2 inhibitor, with alisertib (MLN8237), an Aurora A kinase inhibitor, in cancer". American Academy of Clinical Research Annual Meeting2012.
23. den Hollander J, Rimpi S, Doherty JR, Rudelius M, Buck A, et al. Aurora kinases A and B are up-regulated by Myc and are essential for maintenance of the malignant state. Blood. 2010;116(9):1498-505.
24. Lu L, Han H, Tian Y, Li W, Zhang J, et al. Aurora kinase A mediates c-Myc's oncogenic effects in hepatocellular carcinoma. Mol Carcinog. 2015;54(11):1467-79.
25. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877-88.
26. Duan Z, Chinn D, Tu MJ, Zhang QY, Huynh J, et al. Novel Synergistic Combination of Mitotic Arrest and Promotion of Apoptosis for Treatment of Pancreatic Adenocarcinoma. Transl Oncol. 2019;12(4):683-92.
27. Kong LZ, Jia XH, Song Z, Qiu LH, Li LF, et al. Co-targeting Aurora kinase A and Bcl-2 synergistically inhibits the viability in double-hit lymphoma cells. Transl Cancer Res. 2017;6(4):746-+.
28. Shah KN, Bhatt R, Rotow J, Rohrberg J, Olivas V, et al. Aurora kinase A drives the evolution of resistance to third-generation EGFR inhibitors in lung cancer. Nat Med. 2019;25(1):111-8.
29. Opyrchal M, Salisbury JL, Zhang S, McCubrey J, Hawse J, et al. Aurora-A mitotic kinase induces endocrine resistance through down-regulation of ERalpha expression in initially ERalpha+ breast cancer cells. PLoS One. 2014;9(5):e96995.
30. Li D, Zhu J, Firozi PF, Abbruzzese JL, Evans DB, et al. Overexpression of oncogenic STK15/BTAK/Aurora A kinase in human pancreatic cancer. Clin Cancer Res. 2003;9(3):991-7.
31. Zhu J, Abbruzzese JL, Izzo J, Hittelman WN, Li D. AURKA amplification, chromosome instability, and centrosome abnormality in human pancreatic carcinoma cells. Cancer Genet Cytogenet. 2005;159(1):10-7