Aurora kinase inhibitors in head and neck cancer

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Abstract

Aurora kinases are a group of serine/threonine kinases responsible for the regulation of mitosis. In recent years, with the increase in Aurora kinase-related research, the important role of Aurora kinases in tumorigenesis has been gradually recognized. Aurora kinases have been regarded as a new target for cancer therapy, resulting in the development of Aurora kinase inhibitors. The study and application of these small-molecule inhibitors, especially in combination with chemotherapy drugs, represents a new direction in cancer treatment. This paper reviews studies on Aurora kinases from recent years, including studies of their biological function, their relationship with tumor progression, and their inhibitors.

1. INTRODUCTION

Mitosis is a precise and orderly process that is strictly regulated. During the process of cell proliferation, to correctly pass the genetic information from the parental cell to the daughter cells, accurate cell division is very important to maintain the body's stability. If regulatory factors encounter a problem, cell division will be abnormal, leading to tumorigenesis. The mitotic process primarily depends on three mechanisms: protein localization, protein hydrolysis, and substrate phosphorylation. These mechanisms are regulated by mitotic kinases [1, 2]. Mitotic kinases are divided into tyrosine kinases and serine/threonine kinases. Mitotic kinases can implement intracellular signal transduction by phosphorylating downstream substrates at specific sites, thereby completing the cell cycle. In recent years, a novel family of serine/threonine protein kinases, Aurora kinases, was discovered. Aurora kinases are involved in the regulation of mitotic checkpoints, centrosome maturation and separation, spindle assembly and maintenance, chromosome segregation and cytokinesis, playing a key role in the cell cycle [3, 4]. Previous studies have shown that Aurora kinases have an important relationship with tumorigenesis and tumor development through chromosomal instability. Aurora kinases can be vital targets in the development of anticancer drugs [5, 6].

2. BIOLOGICAL FUNCTIONS OF AURORA KINASES

Aurora kinases were originally discovered by David Glover in Drosophila [7] and by Bischoff and Zhou in human [8, 9]. To date, three family members, Aurora-A, -B, and -C, have been identified in mammalian genomes. Aurora kinases are all nucleoproteins, with different cellular locations and different functions [10]. Aurora kinase family

members are evolutionarily conserved in structure. Aurora-A, -B, and -C proteins are composed of 403, 344, and 309 amino acids, respectively. Regarding secondary structure, they have a conserved N-terminal regulatory domain and C-terminal catalytic domain. The sequences of the regulatory domains of the Aurora kineases show no similarity, while the sequences of the catalytic domain are highly homologous. In the catalytic domain, the similarity of Aurora-A and -B is 57%, the similarity of Aurora-B and -C is 75%, and the similarity of Aurora-A and -C is 60%. This high conservation is important for the specificity of the substrates and inhibitors [11]. Aurora-A contains a catalytic kinase domain, an activated T-loop, a degradation domain (D-box) and D-box activation domain (DAD). Aurora-B and -C do not contain DAD.

2.1. Aurora-A

Aurora-A was the first member to be discovered and is the most important member, with the encoding gene located on chromosome 20q13.2. During cell cycle progression, Aurora-A is mainly located around the central body in prophase; it is on the microtubules near the spindle pole in metaphase; and it is located on the polar microtubules in anaphase and telophase, where it plays an important role in centrosome maturation, spindle assembly, and mitosis. Aurora-A phosphorylates a large number of substrates, including p53, Polo-like kinase-1 (PLK1), Cell division cycle 25B (CDC25B), Breast cancer 1 (BRCA1), Centrin, Large tumor suppressor kinase 2 (LATS2), Guanine nucleotide exchange factor-H1 (GEF-H1), Transforming acidic coiled-coil containing protein 3 (TACC3), NudE neurodevelopment protein 1 like 1 (NDEL1), Histone deacetylase 6 (HDAC6), SKI proto-oncogene (Ski), Hepatoma up-regulated protein (HURP), Serine/threonine protein phosphatase 1 (PP1), Targeting protein for

Xklp2 (TPX2), Eg5, histone H3, Centromere protein-A (CENP-A), CENP-E, Centrosomal protein 192 (CEP192), Cytoplasmic polyadenylation element binding protein (CPEB), LIM domain kinase 1 (LIMK1), LIMK2, SRC, Ras like proto-oncogene A (RalA), AKT, and polycystin 2 (PC2) [12]. Aurora-A-mediated phosphorylation of substrates contributes to the activation of kinase activity, protein degradation, protein stabilization, targeting of the centrosome, maturation and separation of centrosome, translocation, and negative regulation of protein function [12]. The expression and distribution of Aurora-A during mitosis are strictly regulated under normal circumstances [13-15]. Aurora-A expression starts to increase in late S phase, reaches a peak in G2/M phase, and begins to decrease after G1 phase [13-15]. The protein level of Aurora-A is regulated by the ubiquitin-proteasome system. Indeed, in early G1, Aurora-A protein is degraded via the ubiquitin ligase APC/C (anaphase-promoting complex/cyclosome) and its co-activator Cdh1 is involved [16, 17]. Proposed requirements for Aurora-A ubiquitylation are recognition of the C-terminal D-box by Cdh1 [18] and an additional A-box/DAD motif in *Xenopus* Aurora-A [19, 20]. Furthermore, it has been suggested that Ser53 (equivalent to Ser51 in human Aurora-A) of the A-box is phosphorylated during mitosis and that phosphorylation on Ser53 (or 51 in human) is essential for the mitotic stabilization of *Xenopus* [21] and human Aurora-A [22, 23].

Injection of an anti-Aurora-A antibody or interference with the biological effect of Aurora-A can inhibit centrosome separation at the single stage of the spindle, causes G2-M phase arrest, and induces apoptosis in HeLa cells [24, 25]. In addition, by phosphorylating Geminin at Thr25, Aurora-A can prevent its degradation via ubiquitination, enhances its stability, and ensures the formation of the pre-replication complex and DNA replication [26, 27].

2.2. Aurora-B

The gene encoding Aurora-B is located on chromosome 17p13.1, and its catalytic domain shows 71% similarity with Aurora-A; however, their locations and functions are different. Aurora-B is located on the centromere in prophase and metaphase; once the cell enters anaphase, it is located in the central portion of the spindle on the equatorial plane; and in telophase, it is located in the furrow and the central body [10]. The main functions of Aurora-B are phosphorylating histone H3, recruiting chromatin during prophase, arranging and segregating the chromosomes, regulating mitotic checkpoints, and regulating cytokinesis [24, 28, 29]. Aurora-B can form a tetramer with Survivin, Borealin and inner centromere protein (INCENP); this tetramer, termed the chromosomal passenger complex (CPC), regulates chromosome segregation and cytokinesis [30-32]. Tow groups have shown that protein level of Aurora-B is controlled by APC^{Cdh1}, in similar to Aurora-A [33, 34]. However, in our previous study, Aurora-B expression level did not change after co-transfection with Cdh1 [23]. Moreover, E32A and E32S mutants (Glu32 correspond to Ser51 of Aurora-A) of Aurora-B were degraded by APC^{Cdh1}, strongly suggesting that Aurora-B may not be degraded because of phosphorylation mimicking at Glu32 [23]. To know the detailed mechanism of Aurora-B degradation, further studies will be required.

2.3. Aurora-C

The gene encoding Aurora-C is located on chromosome 19q13 and is highly expressed in testis, with little expression in other normal tissues [35-37]. Aurora-C and -B show 83% similarity in the catalytic domain, with the same location and similar

functions. During mitosis, Aurora-C is located on the chromosome in prophase and on the centromere in metaphase. Aurora-C is transferred to the central portion of the spindle in anaphase and is located in the central body during cytokinesis [38]. Together, Aurora-C and -B regulate chromosome segregation and cytokinesis. In addition, Aurora-C and -B were co-immunoprecipitated [37], and Aurora-C can save polyploid cells with Aurora-B depletion or null induction of Aurora-B [36]. To date, Aurora-C has rarely been investigated, and its functions require further elucidation.

3. THE ROLE OF AURORA KINASES IN THE OCCURRENCE AND DEVELOPMENT OF TUMORS

Aurora kinases are a group of serine/threonine kinases responsible for the regulation of mitosis. If the expression of an Aurora kinase is abnormal, errors may occur in the mitotic signaling pathway, resulting in uncontrolled cell proliferation, an abnormal number of cellular chromosomes, or a change in their order. These phenomena can lead to cell death or can transform. The overexpression of Aurora kinases is frequently observed in a variety of solid tumors and hematological tumors and is associated with poor prognosis [6, 28].

3. 1. The role of Aurora-A in tumors

The gene encoding Aurora-A is located on 20q13.2, a chromosomal segment characterized by translocations, deletions, or active amplification, showing natural instability. Aurora-A is closely related to human malignancies. Nishida et al. found that the overexpression of Aurora-A was associated with chromosomal instability in colon cancer [39]. Other studies reported that in hepatocellular carcinoma and gastric cancer,

the overexpression of Aurora-A could predict an abnormal number of chromosomes and poor prognosis [40, 41]. In addition, the high expression of Aurora-A is related to malignant behaviors in a variety of tumors, including breast, prostate, bladder, ovary, and pancreatic cancer. The overexpression of Aurora-A indicates abnormal cytokinesis and centrosome amplification, resulting in aneuploidy or genomic instability and leading to tumorigenesis [39-43]. These phenomena can regulate the mitogen-activated protein kinase (MAPK) pathway by epithelial-mesenchymal transition and stem cell reprogramming, thereby inducing distant metastasis [44]. Aurora-A can also phosphorylate the *p53* gene *in vivo*, thus breaking the balance between the hydrolysis of ubiquitinated proteins and the transcriptional activity of p53 [45]. Aurora-A kinase is involved in a number of important processes, such as the constituent to RAS/RAF/MEK/ERK/MAP kinase pathway of carcinogenesis [46]. Moreover, Aurora-A influences the growth rate of cancer cells, stimulates telomerase activity, and promotes collagen I-induced cell migration [46].

3. 2. The role of Aurora-B in tumors

Aurora-B is highly expressed in various cancers, including colon cancer, liver cancer, thyroid cancer, head and neck squamous cell carcinoma (HNSCC), and breast cancer, and is related to indicators of malignancy, such as the tumor type and lymph node metastasis [47, 48]. In addition, as a member of the CPC, Aurora-B can jointly regulate chromosome segregation and cytokinesis together with Survivin, Borealin and INCENP [30-32]. Our previous studies demonstrated that i) Aurora-B is highly expressed in colon cancer and oral squamous cell carcinoma (OSCC), and ii) Aurora-B expression is associated with cell proliferation and malignant behaviors. Additionally, cases with high

expression of both Aurora-B and Survivin were more severe in the degree of malignancy [49-52], indicating that components of the CPC may interact with each other to jointly promote the tumorigenesis and tumor development.

3. 3. The role of Aurora-C in tumors

Aurora-C is highly expressed in the tumor cell lines, such as HeLa, HepG2, MDA-MB-453 and HUH7 [53]. Moreover, Aurora-C is highly expressed in colon, breast, and prostate cancer [36]. We speculate that Aurora-C as well as Aurora-A and -B may play a certain role in the tumorigenesis and tumor development. However, its specific mechanism in the molecular pathways in tumorigenesis is not fully elucidated, and further research in this area is required.

In summary, overexpression of Aurora kinases is closely related to a large range of tumors. Therefore, Aurora kinases are excellent targets for cancer therapy. In addition, because Aurora-A and -B are expressed and activated only during mitosis, they are ineffective for non-proliferating cells. Thus, compared to other non-specific cytotoxic drugs, inhibitors targeting Aurora-A and/or -B have the advantage of mild adverse reactions and good tolerance. Therefore, Aurora kinase inhibitor can be an ideal drug for cancer therapy.

4. AURORA KINASE INHIBITORS

To date, a variety of Aurora kinase inhibitors have been developed, and some of them have entered clinical trials, showing good anti-tumor activity [54]. As Aurora

kinases are highly expressed in a variety of tumors, Aurora proteins can serve as anticancer targets to develop a variety of small-molecule inhibitors. The current study showed that the Aurora-A, -B, and -C proteins had amino acid sequences of different lengths and amino-termini with different characteristics; however, their ATP-binding sites were highly homologous [55]. Small-molecule inhibitors that inhibit the activity of Aurora kinases by targeting the ATP-binding site have become the main direction of development for Aurora kinase inhibitors. Aurora kinase inhibitors are divided into pan-Aurora kinase inhibitors and selective Aurora kinase inhibitors, and they are developed for the treatment of various cancers, including myeloid leukemia, non-Hodgkin's lymphoma, melanoma, colon cancer, and HNSCC. Aurora kinase inhibitors are listed in Table 1.

4.1. Pan-Aurora kinase inhibitors

Pan-Aurora kinase inhibitors include AMG 900, PHA-680632, VX-680, VE-465, Reversine, CCT1337690, CCT129202, CHR-3520, SNS-314, AKI-001 and ZM447439. Multikinase inhibitors, including KW-2449, CYC116, R763, XL-228, PHA-739358, JNJ-7706621, SU-6668, AT-9283 and PF-03814735 also inhibit Aurora kinases. These molecules are described in detail below.

4.1.1. AMG 900

AMG 900 is an orally available pan-Aurora kinase inhibitor and inhibits Aurora-A, -B, and -C with half-maximal inhibitory concentration (IC50) values of 5, 4, and 1 nM, respectively [56]. AMG 900 cross-reacts with other kinases, including p38α, TYK2, JNK2, MET, and TIE2. AMG 900 inhibits auto-phosphorylation of Aurora-A at Thr288 and

histone H3 phosphorylation at Ser10 in a dose-dependent manner. Interestingly, AMG 900 inhibits the proliferation of various cancer cells, including cells resistant to the antimitotic drug paclitaxel and to other aurora kinase inhibitors (AZD1152, MK-0457, and PHA-739358), at low concentrations [56]. Moreover, TP53 loss-of-function mutations and low baseline p21 protein levels were significantly associated with increased sensitivity to AMG 900 [57]. As various drug-resistant cancers exhibits TP53 mutations or downregulation, it is interesting to use AMG900 in drug-resistant cancers. Importantly, AMG-900 has great potential to overcome both the tumor multidrug resistance and to show activity in cancers resistant to other Aurora kinase inhibitors due to mutation of the Aurora-B binding site. Currently two Phase I studies are underway in patients with advanced solid tumors and acute myeloid leukemia.

4.1.2. PHA-680632

PHA-680632 identified from the combinatorial expansion of the 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole bi-cycle, a novel and versatile scaffold designed to target the ATP pocket of protein kinases [58]. PHA-680632 inhibits Aurora-A, -B, and -C with IC50 values of 27, 135, and 120 nM, respectively [59]. PHA-680632 cross-reacts with FGFR1 [59]. PHA-680632 is active on a wide range of cancer cell lines and shows significant tumor growth inhibition in different animal tumor models at well-tolerated doses [59].

4.1.3. VX-680/MK-0457/Tozasentib

VX-680 (MK-0457/Tozasentib) was designed during the SAR exploitation of a lead molecule amino pyrazole linked to 2-substituted quinazoline [60]. VX-680 can

specifically bind to the ATP-binding domain, thus inhibiting its activity. VX-680 showed long-lasting inhibition of Aurora-A, -B, and -C with the IC50 values of 0.6, 18 and 4.6 nM, respectively [61]. VX-680 can inhibit the proliferation of multiple tumor cell lines, including breast cancer, cervical cancer, colon cancer, leukemia, melanoma, pancreatic cancer, and prostate cancer [62]. In addition to inhibiting the Aurora kinase family, VX-680 can effectively inhibit the BCR-ABL and JAK-2 kinases, with broad-spectrum pre-clinical anti-tumor activity. In murine xenograft models, VX-680 could inhibit the tumorigenesis of acute myeloblastic leukemia, pancreatic cancer, and colon cancer cells [61]. VX-680 was the first Aurora kinase inhibitor to be used in patients. Open-label Phase I/II clinical trial reveals that this compound is active in leukemia patients with BCR-ABL T315I mutations [63]. This study reveals that 8 of 18 chronic myelogenous leukemia patients with T315I-BCR/ABL mutations had hematologic responses during the treatment. Despite the positive response with the drug, all the clinical trials involving VX680 were discontinued due to QTc prolongation occurred in one patient. The efficacy of VX680 alone and in combination with other chemotherapeutic compounds is still being evaluated in various preclinical models. A recent studies showed that i) VX680 is effective in human hepatoblastoma cells [64], and ii) combination of VX680 with methotrexate and cisplatin induces either additive or synergistic growth inhibition in human osteosarcoma and hepatocellular carcinoma cells [65, 66].

4.1.4. VE-465

VE-465 was designed by SAR optimization of the lead amino pyrazole. The chemical structure is similar to that of VX-680. VE-465 inhibits Aurora-A, -B, and -C with Ki values

of 1, 26, and 8.7 nM, respectively by ATP competitive binding assays [67]. In preclinical studies, VE-465 exhibited anticancer effects on hepatocellular carcinomas. In addition, VE-465 has a significant activity against paclitaxel-resistant ovarian carcinoma at higher doses [68].

4.1.5. Reversine

Reversine (2-(4-morpholinoanilino)-N6-cyclohexyladenine) is a substituted purine analogue and was originally shown to promote the dedifferentiation of myotubes derived from the murine myoblast cell line C2C12 [69]. Reversine inhibits Aurora-A and -B activities by 80% and Aurora-C by 55% at a concentration of 0.5 µM [66]. The crystal structure of the reversine-Aurora-B kinase complex shows that reversine is a novel class of ATP-competitive Aurora kinase inhibitors [70]. Reversine inhibits multiple myeloma cells, to suppress the kinase activity of Aurora-A, -B, JAK2, and SRC [71]. In addition, reversine suppresses the proliferation of human oral squamous cells via cell cycle arrest, polyploidy, and/or apoptosis induction [72].

4.1.6. CCT137690

CCT137690 is a newly synthesized compound, which has been shown to inhibit the activities of Aurora kinases. CCT137690 inhibits Aurora-A, -B, and -C with IC50 values of 15 ± 3 µM, 25 µM, and 19 µM, respectively [73]. CCT137690 has shown promising therapeutic effects on cancer cells, including colon cancer, neuroblastoma, and acute myeloid leukaemia [73-75].

4.1.7. CCT129202

CCT129202 was developed through SAR optimization of an imidazopyridine scaffold and has high activity against Aurora-A and -B. CCT129202 inhibits Aurora-A, -B, and -C with IC50 values of 42, 198, and 27 nM, respectively [76]. CCT129202 cross-reacts with FGFR3, PDGFRβ (platelet-derived growth factor receptor), and GSK3β (glycogen synthase kinase 3 beta) at high concentrations. CCT129202 inhibits the growth of several human cancer cell lines [76].

4.1.8. CHR-3520

After screening many small molecule inhibitors, Chroma selected CHR-3520 for entry into pre-clinical development during 2006. CHR-3520 is a potent inhibitor of Aurora kinases along with several other kinases that are important for the growth and development of tumors. Details of the specificity and cellular potency of CHR-3520 in relation to the AKs have not yet been disclosed [77].

4.1.9. SNS-314

SNS-314 was designed from the lead molecule, 2-aminoethyl phenyl benzamide via structure-activity optimizations. SNS-314 inhibits Aurora-A, -B, and -C with IC50 values of 9, 31, and 3 nM, respectively [78]. In addition, SNS-314 inhibits 24 other kinases with higher IC50 values. SNS-314 inhibits cell proliferation in various human cell lines and induces polyploidy. The antiproliferative activity of SNS-314 was attributed to Aurora kinase inhibition, as observed by the inhibition of auto-phosphorylation of the Aurora kinases and histone H3 phosphorylation [79]. SNS-314 has been subjected to a Phase I

clinical trial involving advanced solid tumor patients [80].

4.1.10. AKI-001

AKI-001 is a potent Aurora kinase inhibitor, which exhibits low nanomolar potency against both Aurora-A and -B (IC50 < 100 nM). AKI-001 was discovered by high-throughput screening against Aurora-A kinase [81]. Further optimization and inclusion of lactam ring and hydrocarbon constraint to pentacyclic scaffold led to the discovery of the highly potent AKI-001, which is orally bioavailable phthalazine derivative with improved enzyme and cellular activity and a high level of kinase selectivity. AKI-001 inhibits the proliferation of various cancer cell lines.

4.1.11. ZM447439

ZM447439 was the first reported Aurora kinase inhibitor [82]. As a quinazoline derivative, ZM447439 can inhibit both Aurora-A and -B with IC50 values of 110 nM and 130 nM, respectively. In HeLa, A549, MCF-7, and DLD1 cells, ZM-447439 can regulate chromosome arrangement, cell division, and mitosis checkpoints as well as kill proliferating cells with no effect on non-proliferating cells currently showing no obvious clinical progression [82, 83].

4.1.12. KW-2449

KW-2449 is a multikinase inhibitor of FLT3, ABL, ABL-T315I, and Aurora kinase. KW-2449 was identified by screening the chemical libraries of Kyowa Hakko Kirin using several leukemia cells, which have several activated mutations in FLT3 or BCR-ABL

translocation [84]. Indeed, KW-2449 has an antiproliferative activity against various types of leukemia. KW-2449 acts by targeting Fms-like tyrosine kinase 3 (FLT3), ABL, ABL-T315I mutant, Aurora-A and -B. KW-2449 inhibited Aurora-A with IC50 of 48 nM and Aurora-B with the equivalent potency [84]. Oral administration of KW-2449 showed dose-dependent inhibition of tumor growth in FLT3-mutated xenograft model 84]. Moreover, KW-2449 in combination with HDAC inhibitors increases lethality in Bcr/Abl^{+} leukemia cells [85]. Two Phase I trial of KW-2449 in leukemia patients were terminated due to suboptimal dosing schedule and failure to identify a tolerable dose that had potential for efficacy.

4.1.13. CYC116

CYC116 is an orally available Aurora kinase inhibitor that which was discontinued from Phase I clinical trials. CYC116 was designed from the subset of lead N-phenyl-4-(thiazol-5-yl) pyrimidin-2-amines via cell-based screening of kinase-directed compound library [86]. CYC116 inhibits Aurora-A, -B, and -C with IC50 values of 44, 19, and 65 nM, respectively [87]. In addition, CYC116 inhibits VEGFR2 (vascular endothelial growth factor receptor 2) with an IC50 of 69 nM [87]. CYC116 is a targeted drug that has antimitotic and anti-angiogenesis properties [86]. Indeed, CYC116 induces failed mitosis, resulting in polyploidy via suppressed autophosphorylation of Aurora-A and -B in lung cancer cells [86]. Further, CYC116 exhibited antitumor activity in various leukemia, solid tumor xenograft and leukemic syngenic models [86]. It recently has been revealed that resistance to CYC-116 treatment is mediated via serine hydroxymethyltransferase by comparing the protein composition of CYC-116-sensitive and -resistant HCT116 colon cancer cell, suggesting that it may be a good target to

overcome resistance in combination therapy [88].

4.1.14, R763/AS703569

R763 (AS703569) is an orally available Aurora kinase inhibitor, currently in Phase I study. R763 was designed and developed based on an image-based phenotypic screen. R763 inhibits Aurora-A, -B, and -C with IC50 values of 4, 4.8, and 6.8 nM, respectively [89]. In addition, R763 inhibits Abl, FLT1 (fms-related tyrosine kinase), and FLT3 kinases. R763 has potent anti-proliferative activity against many cell types accompanying unique phenotypic changes such as enlarged cell size, endoreduplication and apoptosis [89]. Oral administration of R763 markedly inhibits tumor growth in xenograft models of pancreatic, breast, colon, ovarian, and lung tumors and leukemia [89]. Previous studies showed that R763 has significant antitumor activity in single-agent Phase I studies [90, 91]. Several preclinical data indicated that the combination of gemcitabine with R763 showed either additive or synergistic effects both *in vitro* and *in vivo*.

4.1.15. XL-228

XL228 is a protein kinase inhibitor targeting IGF1R, the AURORA kinases, FGFR1-3, ABL and SRC family kinases [92, 93]. Particularly promising in the field of leukemia, XL-228 harbors activity against a mutant form of Abl, T315I, which is largely resistant to imatinib and dasatinib in chronic myelogenous leukemia (CML). It is being evaluated in a phase 1 trial in patients with advanced malignancies [92, 93].

4.1.16. PHA-739358/Danusertib

PHA-739358 is a class of tricyclic tetrahydropyrrolo pyrazole compounds which had previously been identified as an ATP-mimetic pharmacophore suited for kinase binding [94]. The structure activity relationship (SAR) analysis of several pyrrolopyrazole subclasses resulted in the synthesis of PHA-680632, which showed high anti-cancer activity both *in vitro* and *in vivo* [94]. Through combinatorial expansion of a related 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole core and SAR refinements of the 5-amido-pyrrolopyrazole series a potent Aurora kinase inhibitor PHA-739358 was identified [95]. PHA-739358 inhibits Aurora-A, -B, and -C with IC50 values of 13, 79, and 61 nM, respectively [95]. PHA-739358 cross-reacts with ABL, showing inhibitory activity against the T315I mutant with BCR/ABL mutations [96]. Moreover, PHA-739358 cross-reacts with Abl (Abelson), Ret (rearranged during transfection), Trk-A, and FGFR1 (fibroblast growth factor receptor 1) kinases at high concentrations, [97]. Clinical trials of PHA-739358 involving solid tumors and hematological malignancies of chronic myeloid leukemia with imatinib resistance showed good drug tolerance and clinical efficacy [98-100].

4.1.17. JNJ-7706621

JNJ-7706621 was designed by the refinement of a series of acyl-substituted 1,2,4-triazole-3,5-diamine analogues [101]. JNJ-7706621 inhibits Aurora-A and -B with IC50 values of 11 and 15 nM, respectively [102]. In addition, JNJ-7706621 inhibits CDK1 (cyclin dependent kinases), CDK2, CDK3, CDK4, and CDK6. JNJ-7706621 inhibits the proliferation of various cancer cell lines, but showed less potency against normal cell lines. Interestingly, JNJ-7706621 inhibits cell proliferation of both drug-sensitive and

drug-resistant cancer cells. JNJ-7706621 has been subjected to preclinical *in vivo* testing using the human melanoma xenograft model [102].

4.1.18. SU-6668/TSU-68/Orantinib

SU6668 was originally designed as a selective inhibitor of receptor tyrosine kinases involved in tumor vascularization. SU6668 was characterized as an ATP-competitive inhibitor of the PDGFR, VEGFR2, and FGFR1 RTKs *in vitro* [103]. In cell-based assays, low concentrations of SU6668 effectively blocked autophosphorylation of βPDGFR and VEGFR2 [103]. In addition, SU6668 targets Aurora kinases and TANK-binding kinase 1 [104]. SU6668 induced cell cycle arrest via inhibition of Aurora kinase activity and potently suppressed antiviral and inflammatory responses by interfering with TANK-binding kinase 1–mediated signal transmission [104]. Recent reports show that SU6668 is significantly more efficacious, when combined with either tumor irradiation or immune therapy [105, 106].

4.1.19. AT-9283

AT9283 is the first Aurora kinase inhibitor discovered via the company's proprietary fragment-based screening approach. The lead optimization was guided by X-ray crystallography and finally resulted in AT9283 as a clinical candidate [107]. AT9283 is a multi-targeted kinase inhibitor that inhibits tyrosine and serine/threonine kinases such as Aurora A and B, JAK-2 and JAK-3, Tyk2 and RSK2. AT9283 inhibits Aurora-A and -B with IC50 values of 3 nM [107]. The safety, tolerability, and preliminary efficacy of AT9283 were evaluated in Phase I/II clinical studies [108, 109].

4.1.20. PF-03814735

PF-03814735 is orally available dual Aurora-A and Aurora-B inhibitor, which is currently in a Phase I study. PF-03814735 was discovered by SAR exploitation of lead pyrimidine scaffold. PF-03814735 was eventually designed by SAR optimizations at C2 and C4 positions of pyrimidine scaffold [110]. PF-03814735 inhibits Aurora-A and Aurora-B with IC50 values of 5 and 0.8 nM, respectively. In addition, PF-03814735 inhibits FLT1, FAK (focal adhesion kinase), TrkA, MET, and FGFR1 kinases at higher IC50 values [111]. PF-03814735 inhibits the proliferation of various human tumor cell lines. In Phase I initial clinical study, 57 patients with solid tumors were treated [112]. Now Phase I study has completed. In addition, small cell lung cancer (SCLC) is very sensitive to PF-03814735 among a diverse panel of 87 cancer cell lines. Particularly, the status of the Myc gene family significantly correlated with the efficacy of PF-03814735, suggesting that Myc family gene-driven SCLC and other malignancies are suitable indications for the treatment with PF-03814735 [113].

4.2. Selective Aurora-A kinase inhibitors

As mentioned above, both Aurora-A and -B play an important role in the tumorigenesis and tumor development, while Aurora-A and -B kinases are not distinguished as different therapeutic targets frequently, so it has not yet been determined which is the better target [54]. Previous studies have found that potential clinical consequences and the biological outcomes of inhibiting Aurora-A or -B are very dissimilar. They should be distinguished as two distinctive therapeutic targets that can be targeted independently. Therefore, selective Aurora kinase inhibitors are divided

into Aurora-A and -B kinase inhibitors, because of the different effects on cancers [108]. Selective Aurora-A inhibitors are described in detail below.

4.2.1. MLN8054

MLN8054 (Millennium) is an ATP-competitive and selective inhibitor of Aurora-A kinase (with IC50 values for Aurora-A and -B of 4 and 172 nM, respectively) [109]. The conformation change and the difference between the binding pockets for Aurora-A and -B are key factors responsible for the selectivity [110]. MLN8054 is used for the treatment of solid tumors, including lymphomas. In a phase I clinical trial, orally administered MLN8054 was quickly absorbed, with the side effect of drowsiness [62]. Recently, MLN8054 was replaced by the second-generation Aurora kinase inhibitor, MLN8237, and clinical trials of MLN8054 were terminated due to sever somnolence and central nervous system toxicity [62].

4.2.2. MLN8237/Alisertib

MLN8237 (alisertib) is an investigational, orally active, selective small molecule inhibitor of Aurora-A that is being investigated for the treatment of both heme-lymphatic malignancies and solid tumors [111]. MLN8237 was designed through SAR optimization of lead 5- H-pyrimido[5,4-d][2]benzazepine. MLN8237 is approximately 200-fold more selective for Aurora-A (IC50 = 6.7 nM) than Aurora-B (IC50 = 1,534 nM) in cell-based assays [111]. In both preclinical and clinical studies, MLN8237 has shown preliminary antitumor activity in heme-lymphatic malignancies [112-116]. Moreover, MLN8237 research has entered phase I and II clinical trials for the treatment of periodic epithelial ovarian cancer, fallopian tube cancer, early peritoneal cancer, advanced solid

tumors, and advanced types of blood malignancy [54]. MLN8237 can effectively improve the efficacy of chemotherapy to enhance its anti-tumor capacity. Data showed that after treatment, 49% of patients had a stable disease condition, 11% of patients achieved partial remission, and 13% of patients experienced relapse or remained uncured. In a study of chronic myeloid leukemia, MLN8237 could effectively kill T315I mutant cells by an independent BCR-ABL mechanism, although this type of cell can tolerate other targeted therapies [6, 59]. In addition, the combination of MLN8237 and nilotinib significantly enhanced the therapeutic effect [6, 59].

4.2.3. ENMD-2076

ENMD-2076 was designed by SAR optimization of a lead imidazole-vinyl-pyrimidine scaffold. ENMD-2076 is an orally active, vinyl-pyrimidine-based compound. ENMD-2076 selectively inhibits Aurora-A with an IC50 of 14 nM by biochemical assays [117]. Moreover, ENMD-2076 inhibits multiple oncogenic kinases, including FLT3, Src, VEGFR2, and FGFR1, as well as the growth of various cancer cell lines [117]. Recently, ENMD-2076 has been shown to be highly effective against malignant melanoma and colon cancer cells [117-119]. Now Phase 2 studies are currently underway being tested in fibrolamellar carcinomas, triple-negative breast cancer, advanced/metastatic soft tissue sarcoma, and advanced ovarian clear cell carcinomas [120, 121].

4.2.4. VX-689/MK-5108

VX689 (MK-5108) has been studied in a Phase I clinical trial in patients with advanced solid tumors. VX-689 is a highly selective Aurora A inhibitor with IC50 of 0.064 nM in a cell-free assay and is 220- and 190-fold more selective for Aurora A than

Aurora B/C, while it inhibits TrkA with less than 100-fold selectivity [122]. Moreover, VX689 inhibits the proliferation of diverse cancer cell lines and significantly enhanced the efficacy of docetaxel in HeLa-S3 and ES-2 cell lines. It has completed Phase I testing in patients with advanced and/or refractory solid tumors as a single agent and in combination with docetaxel.

4.2.5. TC-A 2317 hydrochloride

TC-A 2317 hydrochloride is a potent Aurora-A inhibitor (K_i = 1.2 nM compared to 101 nM for inhibition of Aurora-B) [123]. In addition, TC-A 2317 hydrochloride is selective over 60 other kinases (IC_{50} values > 1000 nM). TC-A 2317 hydrochloride was created by transforming 4-(5-methyl-3-pyrazoloamino)pyrimidine moiety of VX-680 to 3-cyano-6-(5-methyl-3pyrazoloamino)pyridine. TC-A 2317 hydrochloride exhibited good cell permeability and effective antitumor activity.

4.2.6. MP529

MP-529 was designed to block the action of Aurora-A kinase by CLIMB drug discovery process, which is based on the clustering of representative chemical structures and pharmacophores that embody large virtual library of nearly 50 million compound structures [124]. The MP529 represents a novel scaffold, which improves upon the pharmacological activities of known Aurora kinase inhibitors. MP529 exhibits nanomolar activity or better against the Aurora-A kinase, and have been carried forward into ex vivo and in vivo evaluations.

4.2.7. Aurora-A inhibitor 1

Aurora-A Inhibitor I is a 2,4-dianilinopyrimidine that selectively and potently inhibits Aurora-A kinase. Aurora-A Inhibitor I effectively inhibits the proliferation of various cancer cell lines including HCT116, HT29, HeLa and leukemia cell lines [125, 126]. The Aurora-A selectivity of Aurora-A Inhibitor I against Aurora-B depends on a single amino acid (Thr217) of Aurora-A [127].

4.3. Selective Aurora-B inhibitor

Selective Aurora-B inhibitors are described in detail below.

4.3.1. GSK1070916

GSK1070916 is a reversible Aurora-B and -C inhibitor. GSK1070916 was designed from the various SAR refinements of a lead 7-azaindole series [134]. GSK1070916 inhibits Aurora-B-INCENP and Aurora-C-INCENP with IC50 values of 3.5 and 6.5 nM, respectively. In addition, GSK1070916 cross-reacts with FLT1, TIE2 (tyrosine kinase with immunoglobulin-like and EGF-like domains 1), SIK (salt inducible kinase), FLT4, and FGFR1 at higher concentrations [135]. GSK1070916 inhibits the proliferation of various cancer cell lines [136]. Interestingly, GSK1070916 showed no effects on non-proliferating HUVEC cells. Phase I clinical study is currently completed in patients with advanced solid tumors.

4.3.2. BI 811283

BI 811283 is an Aurora-B inhibitor that is currently in a Phase II clinical study. BI

811283 inhibits Aurora-B with IC50 value of 9 nM and inhibits the proliferation of various cancer cell lines with an IC50 value <14 nM [137]. In Phase I dose escalation study, BI 811283 has been tested in advanced and metastatic solid tumors [138]. A Phase II clinical study in combination with cytarabine has completed in previously untreated AML ineligible for intensive treatment.

4.3.3. Hesperadin

Hesperadin is the first generation Aurora kinase inhibitor. Treatment of cancer cell lines with hesperadin resulted in Aurora-B inhibition phenotype. The specificity of hesperadin towards Aurora-A and -C is unknown. Most of the basic functions of Aurora-B in mitosis and its role in cancer cell proliferation were discovered by inhibiting it with Hesperadin [139].

4.3.4. AZD-1152

AZD-1152 is a pyrazole quinazoline-dihydrogen phosphate derivative. AZD-1152 was designed and developed from the lead pyrazole-acetanilide-substituted quinazoline by SAR exploitation [140]. As a selective inhibitor of Aurora-B (with IC50 values in the inhibition of Aurora-A, -B, and -C of 687, 3.7 and 17 nM, respectively), AZD-1152 can be quickly converted into the active drug AZD1152-hydroxyquinazoline pyrazole anilides (HQPA) in plasma [141], showing activity against a number of solid tumors (colon, breast, and lung cancer as well as myelogenous leukemia in xenograft models) [142]. Non-clinical studies showed that AZD1152 could weaken the phosphorylation of histone H3 and cell cycle progression with abnormal mitosis [143], suggesting that phosphorylated histone H3 can be used as a biomarker of the inhibition of Aurora-B

kinase. Studies have also shown that combination therapy of AZD-1152 with dexamethasone could significantly increase the activity of myeloma inhibition [143]. Additionally, AZD-1152 can be synergistically used with vincristine, daunorubicin, and other commonly used conventional anticancer drugs to enhance their anti-proliferative activity [140]. Initial clinical study was conducted on 13 patients having colon cancer, melanoma or some other solid tumors [144]. AZD1152 recently entered Phase I/II clinical trials focusing on its safety, tolerability, pharmacokinetics, and efficacy profiles in AML patients [145]. Currently, Phase I testing of AZD1152 in patients with diffuse large B-cell lymphoma and advanced solid malignancies is in progress.

5. EXPRESSION AND TREATMENT WITH AURORA KINASES IN HNSCC

The overexpression of Aurora-A mRNA and protein in HNSCC is closely related to tumor type, lymph node metastasis, and prognosis (5). Studies have shown that the overexpression of Aurora-A was not due to the overexpression of its mRNA; instead, it was due to protein phosphorylation inhibiting the ubiquitin-mediated degradation of Aurora-A protein. In HNSCC, the phosphorylation of Ser51 in Aurora-A can inhibit protein degradation mediated by APC[Cdh1], leading to protein accumulation in cancer cells, reflected as overexpression [23]. Furthermore, the overexpression of Aurora-A results in genomic instability and formation of aneuploidy, eventually leading to cancer. The elevated expression of Aurora-A is closely related to a poor disease outcome and a high risk of metastasis. Moreover, Aurora-A polymorphism has also been regarded as a genetic risk factor for the occurrence and development of esophageal tumors [146].

Aurora-B has been rarely investigated in HNSCC. It has been reported that the overexpression of Aurora-B in OSCC is related to cell proliferative activity, lymph node

metastasis and poor prognosis [49, 52]. The nuclear expression levels of Aurora-B and Survivin are closely related in OSCC, and cases with high expression levels of both are associated with cell proliferation and malignancy, suggesting that the co-expression of both promotes the occurrence and development of HNSCC [49].

In HNSCC, high expression of both Aurora-A and EGFR are shown [146]. Owning to Aurora-A/-B polymorphism, the efficiency of treatment with the EGFR inhibitory antibody, cetuximab varies significantly. Aurora-A/-B genotypically homozygous HNSCC cells react to cetuximab treatment, whereas heterozygous cells do not. It has been described that Aurora-A/-B knockdown or treatment with Aurora kinase inhibitor can abolish cetuximab resistance [146]. The combination of anti-Aurora-A/-B targeting and cetuximab in HNSCC cells improves the efficiency of treatment, compared to an individual therapy [67]. Then, a new and efficient therapeutic strategy comes: the combination of Aurora kinase inhibitor, the monoclonal antibody cetuximab and chemo-radiotherapy [54, 146].

Moreover, in consideration of close interactions between Aurora-B and Survivin in cancer, and the premise that Survivin inhibitor YM155 has been used in clinical trials currently (e.g., in solid tumors (phase I) and advanced NSCLC (phase II)), the combination of YM155 with Aurora kinase inhibitor may become a potential therapeutic strategy [147].

CONCLUSION

The Aurora kinase family plays an important role in the cell cycle, and abnormal expression of Aurora kinases is a key factor in tumorigenesis. Researchers consider Aurora kinases as excellent targets for anticancer drugs. Therefore, targeted drugs with

high efficiency and low toxicity have been developed. To date, a variety of Aurora kinase inhibitors have entered clinical studies, with some success. Aurora kinase inhibitors also show some disadvantages. For example, their efficacy against solid tumors is not satisfactory. With in-depth research on the Aurora kinase family, the prospect of Aurora inhibitors in the future is expected in the field of cancer research. As the effective anticancer drugs were not developed for HNSCC treatment, the development of target therapy drugs including Aurora kinase inhibitors are expected.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Inhibitor		Inhibitor	Target	Cross-reaction	Formula	Company	Clinical Trial	Oncological applications
Pan-Aurora kinase inhibitor	Aurora kinase inhibitor	AMG 900	Aurora-A/-B/-C	p38α, TYK2, JNK2, MET, TIE2	C28H21N7OS	Amgen	Phase 1	advanced solid tumors and acute leukemia
		PHA-680632	Aurora-A/-B/-C	FGFR1	C28H35N7O2	Nerviano/Pfizer Italia	Phase 2	Chronic myelocytic leukemia, Hormone refractory prostate cancer, Multiple myeloma
		VX-680/MK-0457/Tozasentib	Aurora-A/-B/-C	BCR-ABL, JAK2	C23H28N8OS	Vertex/Merck	Phase 1, Phase 2 (Terminated)	Non-small cell lung carcinoma, Solid cancer, Hematological malignancies
		VE-465	Aurora-A/-B/-C	-	structure analog of MK-0457	Merck	Preclinical	Hepatocellular carcinoma cell lines, Paclitaxel-resistant ovarian carcinoma
		Reversine	Aurora-A/-B/-C	JAK2, SRC	C21H27N7O	The Scripps Research Institute	Phase 2	Acute myeloid leukemia
		CCT137690	Aurora-A/-B/-C	-	C26H31BrN8O	Cambridge Research Institute	Preclinical	Colorectal cancer, Neuroblastoma , Acute myeloid leukemia
		CCT129202	Aurora-A/-B/-C	FGFR3, PDGFRβ, GSK3β	C23H25ClN8OS	Chroma	Preclinical	Solid tumors
		CHR-3520	Aurora-A/-B/-C	-	-	Chroma	Preclinical	-
		SNS-314	Aurora-A/-B/-C	Several kinases	C19H19ClN6O4S3	Sunesis	phase I	Solid tumors, Leukemia
		AKI-001	Aurora-A/-B/-C	-	C21H24N4O	Roche	Preclinical	Solid tumors
		ZM-447439	Aurora-A/ -B	-	C29H31N5O4	AstraZeneca	Preclinical	Solid tumor, Leukemia
	Multikinase inhibitor	KW-2449	FLT3, ABL, ABL-T315I, Aurora-A/-B	-	C20H20N4O	Kyowa Hakko Kirin	Phase 1 (Terminated)	Acute myelogenous leukemia, Acute lymphoblastic leukemia, Myelodysplastic syndromes, Chronic myelogenous leukemia
		CYC116	VEGFR2	Aurora-A/-B/-C	C18H20N6OS	Cyclacel	Phase 1 (Terminated)	Solid tumor
		R763/AS703569	Flt1, Flt3, Abl, Akt, VEGFR3	Aurora-A/-B/-C	C24H30N7OF	Rigel	Phase 1	Solid tumor, Hematological malignancies
		XL-228	IGF1R, FGFR1-3, ABL, SRC family kinases, Aurora-A/-B/-C	-	C22H31N9O	Exelixis	Phase 1	Ph+ leukemia, Multiple myeloma, Colorectal cancer
		PHA-739358/Danusertib	Bcr-Abl, Aurora-A/-B/-C	Abl, c-RET, FGFR1, Trk-A	C26H30N6O3	Nerviano/Pfizer Italia	Phase 2	Hormone refractory prostate cancer, Multiple myeloma, Hepatocellular carcinoma, Solid tumors, Chronicmyelogenous leukemia
		JNJ-7706621	CDK1/2/3/4/6, Aurora-A/-B	-	C15H12F2N6O3S	Johnson & Johnson	Preclinical	Breast cancer
		SU-6668/TSU-68/Orantinib	PDGFRβ, VEGFR2, FGFR1	Aurora-B/-C, TANK-binding kinase 1	C18H18N2O3	Taiho Pharmaceutical Co., Ltd.	Phase 3 (Terminated)	Hepatocellular Carcinoma
							Phase 1/2	Hepatocellular Carcinoma
							Phase 1	Unspecified adult solid tumor, Multiple myeloma, Plasma cell neoplasm
		AT-9283	Bcr-Abl, JAK2, JAK3, TYK2, RSK2, Aurora-A/-B	-	C19H23N7O2	Astex	Phase 2	Multiple myeloma
							Phase 1	Solid tumor, Acute leukemia, Advanced solid tumor, Non-Hodgkin lymphoma
		PF-03814735	FLT1, FAK, Trk-A, MET, FGFR1, Aurora-A/-B	-	C23H25F3N6O2	Pfizer	Phase 1	Solid tumor
Selective Aurora kinase inhibitor	Aurora-A	MLN8054	Aurora-A	Aurora-B	C25H15ClF2N4O2	Millennium	Phase 1 (Terminated)	Advanced malignancies, Breast , Colon, Pancreatic, Bladder cancer
		MLN8237/Alisertib	Aurora-A, ABL-T315I	-	C27H20ClFN4O4	Millennium	Phase 3	Peripheral T-cell lymphoma
							Phase 2	Periodic epithelial ovarian cancer, Fallopian tube cancer, Early peritoneal cancer, Advanced solid tumors, Advanced types of blood malignancy
		ENMD-2076	Aurora-A	mutiple tyrosine kinases (SRC, cKit, FAK, VEGFR2)	C21H25N7	EntreMed	Phase 2	Fibrolamellar carcinomas, Triple-negative breast cancer, Advanced/metastatic soft tissue sarcoma, Advanced ovarian clear cell carcinomas
							Phase 1	Acute myelogenous leukemia
		VX-689/MK-5108	Aurora-A	Aurora-B/-C, Trk-A	C22H21ClFN3O3S	Vertex/Merck	Phase 1	Solid tumor, Neoplasm
		TC-A 2317 hydrochloride	Aurora-A	-	C19H28N6O.HCl	Mitsubishi Tanabe Pharma Co.	Preclinical	Colon cancer cell line
		MP529	Aurora-A	-	-	SuperGen	Preclinical	Cancer cell lines
		Aurora-A inhibitor I	Aurora-A	-	C31H31ClFN7O2	Genentech	Preclinical	Colon cancer cell line, Leukemia cell lines
	Aurora-B	GSK1070916	Aurora-B/-C	FLT1, TIE2, SIK, FLT4, FGFR1	C30H33N7O	GlaxoSmith Kline	Phase 1	Advanced solid tumor
		BI 811283	Aurora-B	-	-	Boehringer Ingelheim	Phase 2	Acute myelogenous leukemia
							Phase 1	advanced and metastatic solid tumors
		Hesperadin	Aurora-B	-	C29H32N4O3S	Boehringer Ingelheim	Preclinical	Research tool
		AZD-1152/Barasertib	Aurora-B	Aurora-A/-C	C26H31FN7O6P	AstraZeneca	Phase 2	Advanced solid tumors, Acute myelogenous leukemia
							Phase 1	Diffuse large B-cell lymphoma