Abstract. Aurora kinases are a family of serine/threonine protein kinases that play a central role in eukaryotic cell division. Overexpression of aurora kinases in cancer and their role as major regulators of the cell cycle quickly inspired the idea that their inhibition might be a potential pathway when treating oncologic patients. Over the past couple of decades, the search for designing and testing of molecules capable of inhibiting aurora activities fueled many pre-clinical and clinical studies. In this study, data from the past 10 years of in vitro and in vivo investigations, as well as clinical trials, utilizing aurora kinase inhibitors as therapeutics for hematological malignancies were compiled and discussed, aiming to highlight potential uses of these inhibitors as a novel monotherapy model or alongside conventional chemotherapies. While there is still much to be elucidated, it is clear that these kinases play a key role in oncogenesis and their manageable toxicity and potentially synergistic effects still render them a focus of interest for future investigations in combinatorial clinical trials.

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From the first reports of them being essential in cell division to the recent years of thorough molecular studies, the auroras have been described as oncogenes relevant to many human malignancies (9, 10). Their gene amplification and overexpression is detected particularly in solid tumors, however, their correlation with leukemia development has also been reported (10, 11).

The family name as aurora was conceived when it was first discovered that aurora-mutated Drosophila cells failed to properly duplicate and separate their centrosomes during mitosis, inducing the formation of monopolar spindles that, when observed under a microscope, would bear resemblance to the aurora borealis phenomenon (12). Later studies led to the determination of the localization of these kinases (Figure 1) and their actual cellular roles in humans.

**AURKA**

Prior to bipolar spindle formation, from late S phase to prometaphase, AURKA is mainly concentrated at centrosomes (13, 14) due to an increase in cyclin-dependent kinase 11 (CDK11) activity (15). AURKA is then a part of important processes for centrosome maturation such as pericentriolar matrix recruitment and microtubule nucleation and stabilization (16, 17).

The role of AURKA in maturation occurs through phosphorylation loops and protein-protein interactions with many different kinases. One such pathway is AURKA-mediated phosphorylation of a large tumor suppressor 2 (LATS2) and ajuba LIM protein (AJUBA) complex which acts on an auto-phosphorylation loop that directs AURKA to the centrosomes and induces the recruitment of a centrosomal pool of γ-tubulin, an essential step for microtubule nucleation and later spindle assembly (17-20).

During metaphase and throughout mitosis, the bipolar spindle assembly begins and AURKA also localizes to spindle microtubules, as well as the centrosomes (21, 22). AURKA localization to spindle microtubules is dependent on activity of TPX2 microtubule nucleation factor (TPX2) which binds to and activates AURKA at the spindles, inhibiting dephosphorylation by protein phosphatase 1 (PP1) (22-24).

Aurora-related proteins have been shown to phosphorylate kinesin family member 11 (EG5), an important microtubule-motor protein responsible for centrosome separation, in the Xenopus laevis model, thus conferring it a major role in bipolar spindle formation (25, 26). However, it has been demonstrated that AURKA is also involved in EG5-independent pathways for bipolar spindle assembly through phosphorylation of another motor protein, kinesin-12 (KIF15/HKLP2), in human cell models (27, 28).

Besides its role in cellular spatial organization, AURKA also exerts a series of nuclear functions related to the control of mitotic checkpoint G2/M (Figure 2), making it a key factor in initiation of mitosis (20, 29).

**AURKB**

Along with the regulatory proteins inner centromere protein, survivin and borealin, AURKB forms the chromosomal passenger complex (CPC) and takes part in regulating crucial pathways for chromosome condensation, sister chromatid separation and cytokinesis (30).

During the G2 phase, at mitosis onset, AURKB is responsible for phosphorylation of histone H3 (Figure 2), an event that coincides with heterochromatin condensation and proper chromosome formation (31-33). *In vitro* experiments utilizing analogous animal models have demonstrated AURKA to be a better kinase for the phosphorylation of H3 than AURKB, however, the intracellular colocalization of AURKB and phosphorylated H3, and the knowledge that a decrease in AURKB level implicates in reduced H3 phosphorylation, leads to the understanding that *in vivo* models favor AURKB activity for histone phosphorylation (33, 34).

After chromosome condensation, during prophase in early mitosis, the activation of phosphorylated histones H3 and H2A recruits AURKB to the centromeres (35-37). It has been suggested that recruitment of AURKB happens in a two-step process where H2A phosphorylation by BUB1 mitotic checkpoint serine/threonine protein kinase (BUB1) firstly creates a pool of kinetochore-bound AURKB and then H3 phosphorylation by haspin kinase translocates this AURKB pool to the inner centromere, where it is mainly located during prophase (38).

Until the onset of anaphase, AURKB phosphorylation of the KMN network, an association of the conserved kinetochore proteins kinetochore null protein 1 (KNL1), mis-segregation 12 (MIS12) and nuclear division cycle 80 (NDC80), takes part in regulating kinetochore-microtubule attachment stabilization (39, 40). While during early mitosis the attachment turnover is high, ensuring quickly destabilization of incorrect attachments, it tends to slow down alongside mitosis progression after correct and stable attachments are formed and the spindle assembly checkpoint is satisfied, allowing for increased activity of anaphase-promoting complex/cyclosome and proper chromosomal separation in anaphase (38, 40-42).

AURKB also exerts major roles in cytokinesis, from initial anaphase through telophase and the end of mitosis, being relocated from inner centromeres to the spindle midzone by the action of mitotic kinesin MKLP2 and then interacting with kinesins KIF4A and KIF2A to promote microtubule bundling and consequent central spindle formation, as well as proper cleavage furrow completion (43-45). It has been shown that after chromosomal segregation, the activity of AURKB at the spindle midzone functions as a checkpoint for the regulation of incorrectly segregated chromatin, inhibiting the formation of tetraploid daughter cells and protecting lagging chromosomes from breakage (45, 46).
AURKC

The activity and metabolic role of AURKC is still poorly understood when compared to the other two aurora kinases expressed by humans, being mostly described by its overlapping functions with AURKB (47, 48). Although poorly expressed in most somatic cells, high AURKC expression in germ cells and its ability to interact with chromosomal passenger complex proteins has led to the understanding that AURKC exerts many functions that overlap with activities of AURKB in meiotic cells, being responsible for the regulation of kinetochore-microtubule attachment and proper sister chromatid segregation (48, 49).

AURKC has also been observed to be highly expressed in pre-implantation embryo cells, being able to carry out
normal cell division in AURKB-null mice with death occurring only after implantation takes place, making it clear that AURKC may be relevant in the division of somatic cells (50, 51). While the non-overlapping functions of AURKB and AURKC are not fully elucidated, both kinases are known to form distinct complexes with chromosomal passenger complex proteins and act through distinct mechanisms, while still being able to interfere with each other’s activities, as shown by experiments of selective inhibition of one or both kinases (52).

**Aurora Family as Targets in Oncohematological Therapy**

The finding of overexpression of aurora kinases in cancer and their role as major regulators of the cell cycle quickly led to the idea that their inhibition might be a potential pathway when treating oncological patients. Over the past couple of decades, the quest to design and test molecules capable of inhibiting aurora activities fueled many pre-clinical and clinical studies, resulting in the development of a series of pan-aurora inhibitors as well as selective inhibitors of one of the three human kinases (53). While some aurora kinase inhibitors (AKIs) demonstrate promising results as single treatments, it is also important to perceive their potential as synergistic compounds, being able to restore sensitivity to chemotherapy agents in tumor cells and interact with other targeted therapies for increased efficacy (54).

In this scenario, hematological malignant disorders as leukemia presents overexpression of AURK, and the use of AKIs seems to be an effective pharmacological approach to treating these diseases (14). Table I presents studies published in the past 10 years describing the mechanism of action of several AKIs in different leukemia cell lines, as well as in in vivo models, and validation of AURKA and B overexpression in patient samples. The studies showed that the antileukemic effect of AKI AURKA and AURKB are consistently related to G2/M cell-cycle arrest, modulation of the expression of cell cycle regulators, and polyploidy induction resulting in apoptotic cell death.

AURKA and AURKB have an important role in cell-cycle progression, in fact, the transcription of AURK is cell cycle-regulated. AURKA mRNA is found at higher concentrations in the G2/M phase, its protein level reaching higher a little later; the same happens to AURKB, with enhanced levels of mRNA and protein expression just after those of AURKA (14). Inhibition of AURKA expression by genetic knockdown was shown to lead to errors in cell mitotic processes, once the spindle checkpoint detects a failure in chromosome alignment, it culminates in mitotic arrest and cellular death by apoptosis (71). The knockdown of AURKB leads to reduction in histone H3 phosphorylation required in chromosome condensation and cytokinesis, these errors are associated with abnormal segregation, resulting in polyploid cells (34). Otherwise, cells lacking both genes are able to finish mitosis without completing anaphase, resulting in polyploid cells with just one nucleus (72).

Most studies evaluating the mechanism of AKI action in hematologic cell lines focus on acute myeloid leukemia (AML). This neoplasia is characterized by clonal expansion of undifferentiated myeloid precursors, leading to impaired hematopoiesis and bone marrow failure (73). In in vitro studies, AKIs were evaluated alone or in combination with cytarabine, a nucleoside analog that is incorporated into DNA in cell replication (S-phase) (74). The synergism of cytarabine with pan-AKI AMG 900 enhanced the antileukemic effect and attenuated polyploidization (60). In another study, the AURKB inhibitor barasertib used in combination with cytarabine showed a greater-than-additive cytotoxic effect with evidence of apoptosis, since barasertib does not prevent DNA synthesis, enabling cytarabine incorporation into DNA (66).

Internal tandem duplication of FMS-like receptor tyrosine kinase 3 (FLT3) is one of the most common somatic mutations characterized in AML. It results in the constant activation of FLT3 kinase, which is linked to cancer resurgence and poor patient survival (75). The dual FLT3 inhibitor/ AKI CCT241736 showed promising antileukemic effect in vitro and in vivo, as well as in primary samples from patients with AML, including those who were resistant to the FLT3 inhibitor quinatinib, indicating that dual inhibition can be a tool to manage therapies in patients with AML presenting internal tandem duplication of FLT3 with resistance to current chemotherapy (56).

Translocation t(8;21) is frequent in 4-8% of patients with AML and results in the chimeric protein RUNX family transcription factor 1-RUNX1 partner transcriptional co-repressor 1 (RUNX1-RUNXIT1); 40-60% of patients harboring this translocation are susceptible to relapse after complete remission, this being one of the major causes of treatment failure (76-78). Qi et al. showed that AURKB inhibitor barasertib was more successful in inhibiting proliferation of AML cell lines with t(8;21) than cytarabine and AURKA inhibitor alisertib, and combination of the two AKIs did not show a synergistic effect, indicating that AURKB inhibitor may be a more efficient inhibitor in the treatment of patients with a specific subtype of AML (58).

Acute lymphoblastic leukemia (ALL) is the most common leukemia diagnosed in adults and the second most frequent acute subtype in children worldwide, this neoplasia presents chromosomal and genetic alterations related to the differentiation and proliferation of T and B precursor cells (79, 80). AURKA and AURKB are overexpressed in samples from patients with ALL (55, 65, 81) and some research described the mechanism of action of AKI in ALL cell lines alone or in combination with other antineoplastics agents.
Genetic alterations as t(4;11) with mixed lineage leukemia (MLL) fusion–associated gene AF4 (MLL–AF4) and t(9;22) with breakpoint cluster region–Abelson murine leukemia 1 (BCR–ABL1) are frequent in ALL and are related to treatment resistance, poor outcome, and disease relapse (65, 82). Rearrangements of MLL gene represents 10% of ALL cases and MLL–AF4 fusion is present in the majority of ALL cases (57%), is highly associated with rapid cancer development, fast progression, and poor prognosis in comparison with patients without this rearrangement (83, 84).

In in vitro studies evaluating the cytotoxicity of the pan-AKIs VX-680 and VE-465 against a panel of ALL cell lines, cell lines with MLL–AF4 fusion showed higher sensitivity to AKI treatment, and VE-465 gave better results when compared to VX-68. Curiously, the same study reported that these cell lines presented AURKB protein expression higher than AURKA (65). A recent study conducted by Moreira-Nunes et al. observed no difference between AURKA and AURKB gene expression in samples with MLL–AF4 fusion from patients with ALL when compared to other frequent fusions in leukemia [BCR–ABL1, translocation factor 3 (E2A immunoglobulin enhancer-binding factors E12/E47) and pre-B-cell leukemia translocation factor 1 (E2A–PBX1) translocation, stem leukemia cell interrupting locus and T-cell acute lymphocytic leukemia protein 1 (SIL–TALL) fusion, translocation–Ets–leukemia and acute myeloid leukemia 1 protein (TEL–AML1) fusion]. In contrast, when the expression of AUKA and B were analyzed in all patients in the study, AURKB expression was higher than that of AURKA and overexpression was correlated with lower survival rates (55). Thus, due to the role of AURKB in ALL, and even the lack of evidence that correlates the expression of this kinase with outcome in those with MLL–AF4, more studies evaluating AURKB inhibitors in therapy of MLL–AF4 ALL are still necessary.

The Philadelphia chromosome (Ph+) is characterized by the translocation between chromosomes 9 and 22, generating the chimeric gene BCR–ABL1 (85, 86). Although this translocation is more described in chronic myeloid leukemia (CML), the presence of Ph affects around 3-5% of children and 25% of adults with ALL, and is related to a poor prognosis (87-89). The chimeric BCR–ABL1 gene is constitutively active and overexpresses a tyrosine-kinase receptor that is involved in signaling pathways linked to cellular proliferation, de-differentiation, and apoptosis escape (90). Although tyrosine-kinase inhibitors (TKIs) such as imatinib, bosutinib, dasatinib, and nilotinib were developed, mutations in catalytic enzymatic domains as ABL1T315I result in TKI resistance, leading to risk of treatment failure in patients with CML or ALL Ph+ (67, 91-93).

Due to the efficacy of AKIs in leukemia cell lines in vitro and in vivo studies, Fei et al. evaluated the pan-AKI danusertib (PHA-739358) in human ALL cell lines with and without BCR–ABL1T315I mutation, and also in ALL Ph− cell lines. Danusertib induced cytotoxicity in all cells independently of BCR–ABL1T315I mutation and Ph presence, as well as reducing the percentage of leukemia cells (CD10+/CD19+) and enhancing the survival rates of mice transplanted with cells with BCR–ABL1T315I mutation (67). The study also attested to synergy in the cytotoxic effect of the pan-AKI danusertib in combination with farnesyltransferase inhibitor, vincristine, and with the TKI dasatinib independently of BCR–ABL1T315I mutation, suggesting danusertib as a new option for chemotherapy in patients with ALL, since it is effective independently of Ph presence or BCR–ABL1T315I mutation, and, especially for patients with BCR–ABL1T315I mutation who are resistant to actual treatment with TKIs.

CML is basically, but not only, characterized by the presence of Ph+ cells, since around 95% of cases present this translocation (94, 95). Thus, the malignant potential of CML cells is related to the BCR–ABL1 chimeric gene, which is also its pharmacologic target (85, 96). Resistance to TKIs in CML is widely documented and occurs in 20-40% of cases (97), furthermore, the overexpression of AURKA in several cancer types is described as one mechanism of chemoresistance (98-104).

In vitro studies monitored the antileukemia effect of pan-AKIs GW809897X and GW806742X in a non-resistant CML cell line, with promising results (55). Long et al. showed that AURKA inhibitor AKI603 suppressed cell growth and induced cell differentiation of both imatinib-resistant (BCR–ABL1T315I) and non-resistant cell lines (64). A similar study showed that AURKA inhibitor alisertib, when used alone, reduced viability of CML cell lines, both non-resistant and resistant to imatinib and nilotinib, as well as cells harboring BCR–ABL1T315I mutations. Moreover, when administered in combination with the TKIs imatinib, ponatinib or nilotinib, there was a disruption in the resistance mechanism and reduced rates of cell growth were observed in the respective resistant cell lines. Moreover, alisertib plus ponatinib showed an additive effect in reducing tumor volume and enhanced the rate of survival in mice transplanted with CML BCR–ABL1T315I+ cells (61).

Inhibition of AURKA seems to reduce the profile of resistance in CML cell lines in vitro and in vivo; the utilization of AKIs in combination with conventional chemotherapy may improve the outcome of patients that are unresponsive to chemotherapy for CML.

Lymphomas are a group of malignant diseases that can be derived from constituent cells of the lymphoid tissue, lymphocytes and histiocytes. Malignant lymphomas are divided into Hodgkin’s and non-Hodgkin’s lymphoma (NHL) and are more common in the head and neck region, but NHL can also be found in extranodal regions (25% of the cases), with or without lymph node involvement. NHL is
### Table I. In vitro studies utilizing Aurora-kinase inhibitors as a monotherapy or in combination with synergetic treatments in the past 10 years.

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<td>GW8099897X GW806742X</td>
<td>NR</td>
<td>Cell death</td>
<td>Caspase 3 and 7 activation</td>
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<tr>
<td>AURKA/B/C</td>
<td>In vitro, in vivo with validation in patient samples</td>
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<td>FLT3–ITD</td>
<td>CCT241736</td>
<td>NR</td>
<td>Reduced viability</td>
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<td>NR</td>
<td>AKI604</td>
<td>NR</td>
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<td>Alisertib (MLN8237) Barasertib (AZD1152-HQPA)</td>
<td>NR</td>
<td>Reduction in proliferation</td>
<td>Modulation in the expression of cell cycle regulators</td>
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<td>AURKA</td>
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<td>Cytotoxicity</td>
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<td>AURKA/B/C</td>
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<td>AMG 900 Cytarabine P–gp</td>
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<td>Reduction in proliferation</td>
<td>Induces polyploidization and apoptosis</td>
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<td>AURKA</td>
<td>In vitro and in vivo</td>
<td>CML</td>
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<td>AURKA</td>
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### Table I. Continued

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<th>Leukemia subtype</th>
<th>Cell line</th>
<th>Genetic alterations assessed</th>
<th>Aurora inhibitor</th>
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<td>\textit{In vitro}</td>
<td>CML</td>
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<td>AKI603 NR</td>
<td>Apoptosis</td>
<td>Reduced cell viability</td>
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<td>AURKA/B/C</td>
<td>\textit{In vitro} \textit{with validation in patient samples}</td>
<td>ALL</td>
<td>RS4:11 MV4:11 CCRF-SB MOLT-3 MOLT-4 RPMI-8402 SUP-B15 CCRF-CEM</td>
<td>\textit{MLL–AF4 TP53}</td>
<td>VE-465 VX-680 NR</td>
<td>Cytotoxicity Inhibition of AURKA phosphorylation</td>
<td>G2/M cell-cycle arrest Apoptosis and accumulation of polyploidy</td>
<td>65</td>
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<tr>
<td>AURKB</td>
<td>\textit{In vitro}</td>
<td>AML</td>
<td>HL-60</td>
<td>U937</td>
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<td>Induced polyploidy Apoptosis Inhibited AURKB auto-phosphorylation</td>
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<tr>
<td>AURKA/B/C</td>
<td>\textit{In vitro} \textit{and \textit{in vivo}}</td>
<td>ALL</td>
<td>UCSF02 TXL2 BLQ1 P2 US6 US7 US7R</td>
<td>\textit{BRC–ABL1 BRC–ABL1T315I TP53}</td>
<td>Danusertib (PHA-739358) Lonafarnib, Vinblastine, and Dasatinib</td>
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<tr>
<td>AURKB</td>
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<td>NHL (DLBCL, MCL, T-FL, Burkitt’s lymphoma)</td>
<td>Toledo RL MCL Granta-519 Granta-4 SudHl-4 SudHl-6 Raji</td>
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<td>AT9283 Docetaxel</td>
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<tr>
<td>AURKA</td>
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<tr>
<td>AURKA</td>
<td>\textit{In vitro}</td>
<td>NHL (MCL, Burkitt’s Lymphoma, and NK-cells lymphoma)</td>
<td>Granta-519 Jeko1 JVM2 Z138 Akata DHL16 SudHl-16 KAI3 SNK6</td>
<td>\textit{TP53}</td>
<td>MK-8745 NR</td>
<td>G2/M cell-cycle arrest Inhibited phosphorylation of AURKA</td>
<td>Apoptosis</td>
<td>70</td>
</tr>
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</table>

ALL: Acute lymphoblastic leukemia; AML: acute myeloid leukemia; ARA-C: cytarabine; AURKA: aurora kinase a; AURKB: aurora kinase b; CML: chronic myeloid leukemia; CLL: chronic lymphoblastic leukemia; NHL: non-Hodgkin lymphoma; NR: not reported; NK: natural killer; NILR: nilotinib resistant; MCL: mantle-cell lymphoma; T-FL: transformed follicular lymphoma.
more frequent than Hodgkin’s disease and corresponds to around 90% of head and neck malignancies (105, 106). Of NHL subtypes, follicular and diffuse large B-cell lymphomas are the most frequently diagnosed, corresponding to about 20% and 30%, respectively. Other subtypes account for fewer than 10% of the cases (107).

Studies have shown that AURKA is overexpressed in several NHL subtypes when compared to normal tissues and B-cells, Chowdhury et al. evaluated the protein expression of AURKA and the potential of AURKA inhibitor, MK-8745, in NHL derived from Mantle cell, Burkitt’s, and natural killer-cell lymphomas. Most of the cell lines analyzed presented enhanced AURKA expression but the results showed that treatment with pan-AKI VE-465 and taxol, when used alone, had higher toxicity than the selective inhibitor. However, the antitumoral effect of AURKA inhibitor was correlated with the expression of AURKA activator TPX2 (70).

Moreover, the pan-AKI AT9283 exhibited highly cytotoxic effects in NHL cells and, when used in combination with docetaxel, enhanced apoptosis, as well as survival rates and reduced tumor volume in the mouse mantle cell lymphoma xenograft model (68). The synergistic effect of AURK inhibition was observed with other antitumoral agents that target the cell cycle and microtubular constituents. The disruption in replication machinery leads to selective cancer cell death, enhancing the antitumoral potential of AKI in oncological treatment (108, 109).

Kong et al. evaluated the synergism between the inhibitors of AURKA, alisertib, and BCL2 apoptosis regulator (BCL2) ABT-199, in cell lines of the NHL subtype double-hit lymphoma. Interestingly, the BCL2 inhibitor showed better results in vitro than AURKA inhibitor but the ABT-199 plus alisertib treatment synergistically inhibited viability in double-hit lymphoma cells (62). This subtype of NHL is characterized by MYC proto-oncogene (MYC) and BCL2 translocation, MYC and AURKA are regulated by each other in a feedback pathway and exert a strong role in the cell cycle and replicative process (110). BCL2 regulates the apoptotic process and has a function in survival and chemoresistance in hematological malignancies (111, 112). Thus, dual inhibitory therapy focusing on AURKA and BCL2 may be an interesting option for treatment in patients with double-hit lymphoma with these specific mutations.

Table II presents clinical trials from the past 10 years utilizing AKIs as a therapeutic option for patients afflicted by leukemia and other hematological disorders. The most common studied disorder was AML, appearing in seven out of 12 studies (113-117, 122, 124), while the most targeted kinase was AURKA, appearing in 10 of 12 studies (113-118, 120-123). AURKC was not a main target in any of the selected studies.

In all clinical trials presented, the most prevalent therapeutic option was alisertib (113, 114, 118, 120, 122, 123), a selective inhibitor of AURKA that is also under investigation for relevance in the treatment of non-hematological malignancies (125). While it was most effective when treating patients with AML, this finding may also be correlated to its use as a synergistic compound alongside conventional induction chemotherapy (113, 114).

A study cohort by Goldberg et al. demonstrated alisertib to be potentially clinically effective for patients with AML, while having no efficacy when treating those with myelodysplastic syndrome, hinting towards a better understanding of the drug mechanism of action and biological pathway (122).

While most investigated drugs were AURKA-selective inhibitors or pan-AKIs, AURKB was selectively targeted by the use of barasertib in two studies (119, 124). Although its efficacy was demonstrated in the treatment of patients with diffuse large B-cell lymphoma, the low progression-free survival of 60 days attested to by Collins et al. discredits its use as a monotherapy for this disease (119). When treating patients with AML, Kantarjian et al. demonstrated barasertib to achieve better complete response rates as a monotherapy than low-dose cytosine arabinoside, an agent previously demonstrated to be clinically beneficial in clinical trials (124, 126).

Other inhibitors that were reported in only one study include AMG 900, AT9283, ENMD-2076 and MK-0457. These drugs had only modest to no efficacy when utilized as single agents and in low, tolerable doses, although ENMD-2076 monotherapy still achieved a 25% overall response rate when treating patients with AML and CML, and should be taken into account when considering possible synergistic interactions (115-117, 121).

Overall, the usage of AKIs did not cause unexpected or unmanageable adverse effects in patients and the main ones were related to blood or gastrointestinal disorders (115, 117, 119-121, 123), which is in accordance with the expected effects of aurora inhibition in non-malignant rapidly dividing cells due to mitosis impairment (127, 128).

Conclusion

The interest in understanding the involvement of aurora in biological pathways in non-malignant as well as in malignant cells has only grown over the years. While there is still much to be elucidated, it is clear that these kinases and their upstream and downstream regulators play a key role in mitosis and oncogenesis, motivating their investigation as potential targets for oncological treatments. Even though the clinical trials using AKIs as a monotherapy for hematological disorders have not shown great results, the manageable toxicity and potentially synergistic effects still render them a focus of interest for future investigations in combinatorial clinical trials.
Table II. Clinical trials utilizing aurora-kinase inhibitors as a monotherapy or in combination with synergetic treatments in the past 10 years.

<table>
<thead>
<tr>
<th>Kinase assessed</th>
<th>Study phase</th>
<th>Patients enrolled</th>
<th>Leukemia subtype</th>
<th>Aurora inhibitor</th>
<th>Synergistic treatment</th>
<th>Prognostic significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AURKA</td>
<td>II</td>
<td>39 (64% Male)</td>
<td>AML</td>
<td>Alisertib</td>
<td>Cytarabine and idarubicin</td>
<td>Remission was achieved in 64%</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=67 years</td>
<td></td>
<td>(MLN8237)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AURKA</td>
<td>I</td>
<td>22 (68% Male)</td>
<td>AML</td>
<td>Alisertib</td>
<td>Cytarabine and idarubicin</td>
<td>Remission was achieved in 86%</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=62.7 years</td>
<td></td>
<td>(MLN8237)</td>
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</tr>
<tr>
<td>AURKA/B</td>
<td>I</td>
<td>35 (66% Male)</td>
<td>AML</td>
<td>AMG 900</td>
<td>NR</td>
<td>Complete response with incomplete count recovery was achieved in 9%</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=69 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AURKA/B</td>
<td>I/II</td>
<td>7 (71% Male)</td>
<td>ALL</td>
<td>AT9283</td>
<td>NR</td>
<td>None of the patients achieved a partial or complete remission</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=3 years</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AURKA</td>
<td>I</td>
<td>27 (74% Male)</td>
<td>CML</td>
<td>ENMD-2076</td>
<td>NR</td>
<td>Overall response rate was 25%</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=69 years</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AURKA</td>
<td>I</td>
<td>26 (61.5% Male)</td>
<td>MM</td>
<td>Alisertib</td>
<td>Bortezomib</td>
<td>Overall response rate was 26.9%</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=64.5 years</td>
<td></td>
<td>(MLN8237)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AURKB</td>
<td>II</td>
<td>15 (53% Male)</td>
<td>DLBCL</td>
<td>Barasertib</td>
<td>NR</td>
<td>Overall response rate was 20%</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=65 years</td>
<td></td>
<td>(AZD1152-HQPA)</td>
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</tr>
<tr>
<td>AURKA</td>
<td>II</td>
<td>48 (73% Male)</td>
<td>Non-Hodgkin</td>
<td>Alisertib</td>
<td>NR</td>
<td>Overall response rate was 27%</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=67.5 years</td>
<td>lymphoma</td>
<td>(MLN8237)</td>
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<td></td>
</tr>
<tr>
<td>AURKA/B</td>
<td>II</td>
<td>52 (65% Male)</td>
<td>CML</td>
<td>MK-0457</td>
<td>NR</td>
<td>Only 3.8% had complete cytogenetic and hematological response</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=52 years</td>
<td></td>
<td>ALL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AURKA</td>
<td>II</td>
<td>57 (56% Male)</td>
<td>MDS</td>
<td>Alisertib</td>
<td>NR</td>
<td>Overall response rate was 13%</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=72 years</td>
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<td>(MLN8237)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AURKA</td>
<td>I</td>
<td>58 (47% Male)</td>
<td>NHL</td>
<td>Alisertib</td>
<td>NR</td>
<td>Overall response rate was 27%</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age=61 years</td>
<td></td>
<td>(MLN8237)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AURKB</td>
<td>II</td>
<td>77 (58.4% Male)</td>
<td>AML</td>
<td>Barasertib</td>
<td>NR</td>
<td>Complete response rate of 35.4%</td>
<td>124</td>
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<tr>
<td></td>
<td></td>
<td>Median age=76 years</td>
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<td>(AZD1152-HQPA)</td>
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</table>


Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors’ Contributions

Machado CB, da Silva EL and Moreira-Nunes CA, performed the study design; Machado CB and Nogueira BMD, prepared the figures; Machado CB, da Silva EL, Nogueira BMD, da Silva JBS, Moraes-Filho MO, Moraes MEA, Montenegro RC and Moreira-Nunes CA wrote the article. All Authors read and approved the final article.

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