Aurora B: A new promising therapeutic target in cancer

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Summary

A critical step for maintenance of genetic stability is chromosome segregation, which requires a high coordination of cellular processes. Loss of mitotic regulation is a possible cause of aneuploidy in human epithelial malignancy and it is thought to create an abnormal nuclear morphology in cancer cells. Serine/threonine protein kinase Aurora B gene plays a regulatory role from G2 to cytokinesis, encompassing key cell cycle events such as centrosome duplication, chromosome bi-orientation, and segregation. The overexpression of Aurora B has been observed in several tumour types, and has been linked with a poor prognosis for cancer patients. Therapeutic inhibition of Aurora kinase showed great promise as a probable anticancer regime because of its important role during cell division.

Keywords: Aurora kinase, Aurora B, serine-threonine kinase, mitosis, cytokinesis, cancer, inhibitors

1. Aurora B and cancer

In the last decade, a large number of studies have linked the aberrant expression of Aurora kinases to cancer and this has lead to a great effort on the development of Aurora kinases inhibitors.

Aurora B is involved in chromosome segregation, spindle-checkpoint and cytokinesis, and alteration of each of these steps could induce aneuploidy, one of main features and driving force of cancer cells (1-3).

In vitro studies performed with several Aurora B inhibitors, dominant negative mutants or RNAi, show that Aurora B deficiency interferes with the cell cycle. Treated cells cannot divide after mitosis and become tetraploid, with two copies of centrosomes. Moreover, cells expressing catalytically inactive Aurora B do not arrest in mitosis in the presence of nocodazole or taxol. These observations concur with Aurora B’s presumed roles: spindle checkpoint suppression allows cells to go through mitosis, despite a number of chromosomes being oriented in a syntenic manner (both kinetocores attached to the same pole), while the lack of phosphorylation of cleavage furrow components prevents cytokinesis.

The effects of longer depletion of Aurora B seem to be cell line dependent. Some cells either enter additional cell cycles but, because of cell division failure, they become massively polyploid, whereas other cell lines undergo apoptosis or arrest in a pseudo G1 state. These differences are probably due to the p53-dependent post-mitotic checkpoint (4-6).

Aurora B is located on chromosome 17p13.1, a chromosomal region that has not been frequently associated with amplification in tumours, with the exception of glioblastoma (7). Aurora B gene is dramatically up-regulated in highly proliferating compared with non-proliferating cells. Although Aurora B overexpression has been shown in many tumours types, this is not the result of gene amplification, and it is still under debate whether the observed overexpression of Aurora B is a reflection of the high proliferative rate of neoplastic cells or whether it is causally related to tumorigenesis.

Aurora B is overexpressed in several human cancers, such as non small cell lung carcinoma (8), mesothelioma (9), glioblastoma (7) oral cancer (10), malignant endometrium, hepatocellular carcinoma (11), testicular germ cell tumours (12-15), ovarian (16,17), thyroid (18,19), colon (20) and prostate (21,22). Aurora B expression is positively correlated with poor prognosis and displays a tendency to group in higher grades of malignancy in different neoplastic lesions. Aurora B expression directly correlates with Gleason grade in prostate cancer (21,22), Duke's grade

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in colorectal cancer (20) and dedifferentiation in ovary and thyroid carcinoma (16,18). In thyroid tumours, an increase of Aurora B expression has been observed in papillary and anaplastic thyroid carcinomas. In the late stages of thyroid tumour progression a further increase of Aurora B expression was observed indicating that Aurora B overexpression might confer a growth advantage to neoplastic cells (18,19). In all lesions overexpressing Aurora B, phosphorylation of histone H3 was clearly detectable.

Several studies have suggested that commonly occurring gene polymorphisms of Aurora B are associated with cancer risk. An alternative splicing variant of Aurora B (Aurora B-Sv2) has been found frequently associated with advanced stages of hepatocellular carcinoma; and this variant appears to be more frequently associated with tumour recurrence and poor prognosis (11).

Aurora B kinase expression in epithelial ovarian cancer patients has been evaluated. Expression of Aurora B in poorly and moderately differentiated carcinomas of the ovary was significantly higher than in

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tumor Type</th>
<th>Title of the Study</th>
<th>Phase</th>
<th>Sponsored by</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>VX-680 (MK0457)</td>
<td>Advanced Cancer</td>
<td>A Phase I, Open Label, Multi-centre Study to Assess the Safety, Tolerability, and Pharmacokinetics of AZD1152 in Japanese Patients With Acute Myeloid Leukaemia</td>
<td>Phase I</td>
<td>MERCK</td>
<td>NCT00104351</td>
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<tr>
<td>VX-680 (MK0457)</td>
<td>Leukemia</td>
<td>A Phase I/II Dose Escalation Study of MK0457 in Patients With Leukaemia</td>
<td>Phase I</td>
<td>MERCK</td>
<td>NCT00111683</td>
</tr>
<tr>
<td>VX-680 (MK0457)</td>
<td>Carcinoma, Non-Small-Cell Lung</td>
<td>A Phase II Study Evaluating the Efficacy of MK0457 as a 5-Day Continuous Infusion in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC)</td>
<td>Phase II</td>
<td>MERCK</td>
<td>NCT00290550</td>
</tr>
<tr>
<td>VX-680 (MK0457)</td>
<td>Leukemia</td>
<td>A Phase II Study of MK0457 in Patients With T315I Mutant Chronic Myelogenous Leukaemia and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukaemia</td>
<td>Phase II</td>
<td>MERCK</td>
<td>NCT00405054</td>
</tr>
<tr>
<td>VX-680 (MK0457)</td>
<td>Chronic Myelogenous Leukaemia, Leukemia, Lymphoblastic Acute Philadelphia Positive</td>
<td>A Phase I Dose Escalation of MK0457 in Combination With Dasatinib in Patients With Chronic Myelogenous Leukaemia and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukaemia</td>
<td>Phase I</td>
<td>AstraZeneca</td>
<td>NCT00500006</td>
</tr>
<tr>
<td>AZD1152</td>
<td>Acute Myeloid Leukaemia</td>
<td>A Phase I, Open Label, Multi-centre Study to Assess the Safety, Tolerability, and Pharmacokinetics of AZD1152 in Japanese Patients With Acute Myeloid Leukaemia</td>
<td>Phase I</td>
<td>AstraZeneca</td>
<td>NCT00530699</td>
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<tr>
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<td>Myeloid Leukemia</td>
<td>A Phase I/II, Open Label, Multi-Centre Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of AZD1152 in Patients With Acute Myeloid Leukaemia</td>
<td>Phase I</td>
<td>AstraZeneca</td>
<td>NCT00497991</td>
</tr>
<tr>
<td>AZD1152 + LDAC</td>
<td>Acute Myeloid Leukaemia</td>
<td>A Randomised, Open-label, Multi-centre, 2-stage, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of AZD1152 Alone and in Combination With Low Dose Cytosine Arabinoside (LDAC) in Comparison With LDAC Alone in Patients Aged 60 With Newly Diagnosed Acute Myeloid Leukaemia (AML)</td>
<td>Phase II</td>
<td>AstraZeneca</td>
<td>NCT00952588</td>
</tr>
<tr>
<td>AZD1152 + LDAC</td>
<td>Acute Myeloid Leukaemia</td>
<td>A Phase I, Open-Label, Multi-Centre, Multiple Ascending Dose Study to Assess the Safety and Tolerability of AZD1152 in Combination With Low Dose Cytosine Arabinoside (LDAC) in Patients With Acute Myeloid Leukaemia (AML)</td>
<td>Phase I</td>
<td>AstraZeneca</td>
<td>NCT00926731</td>
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<td>AZD1152</td>
<td>Solid Tumours</td>
<td>A Phase I, Open-Label, Multi-Centre Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD1152 Given as a Continuous 48-Hour Intravenous Infusion in Patients With Advanced Solid Malignancies</td>
<td>Phase I</td>
<td>AstraZeneca</td>
<td>NCT00338182</td>
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<td>Solid Tumours</td>
<td>A Phase I, Open-Label, Multi-Centre Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD1152 Given as a Continuous 7-Day Intravenous Infusion in Patients With Advanced Solid Malignancies</td>
<td>Phase I</td>
<td>AstraZeneca</td>
<td>NCT00497679</td>
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well-differentiated carcinomas and overall, the Aurora B overexpression group demonstrated a significantly shorter progression-free survival and survival than a low expression group (16). In human colorectal cancer samples the correlation of Aurora B expression with overall survival was also evaluated, showing that patients with a high expression level of Aurora B lived significantly shorter lives compared with patients with low expression levels. Furthermore single-nucleotide polymorphism analysis showed that patients harboring G-allele in 885A>G showed a significantly decreased overall survival (17). These studies suggest that Aurora B expression could be used as a predictor of aggressive lesions and as a prognostic marker.

2. Aurora B as therapeutic target

The inhibition of Aurora B kinase has an anti-proliferative effect and causes regression in several animal models of human cancers, including breast, colon, lung, leukemia, prostate and thyroid (15-22). These observations strongly suggest a potential role for Aurora B inhibition in patients. To target the enzymatic activity of Aurora kinases, small molecules able to occupy the catalytic binding site have been identified, however due to the high homology of Aurora kinases catalytic subunit most of the inhibitors developed so far lack selectivity and inhibit both Aurora Kinases. Despite this lack of selectivity of Aurora Kinases inhibitors the number of Aurora inhibitors is rapidly increasing: approximately 15 Aurora inhibitors are under Phase I/II evaluation and others are in preclinical testing (Table 1) (3,23).

Inhibition of Aurora B by specific inhibitors interferes with normal chromosome alignment during mitosis and overrides the mitotic spindle checkpoint inducing endoreduplication. Aurora B seems to be more suitable as an anticancer drug target, since inhibition of Aurora B rapidly results in catastrophic mitosis, leading to cell death (23-28).

In order to block Aurora B functions, several anticancer drugs targeting its catalytic binding site have been developed. However, given the high homology of the catalytic domain of Aurora kinases, small molecules do not differentiate between them, and could be considered dual inhibitors (Aurora A and B inhibitors), however the phenotype observed in cells treated with these dual inhibitors closely resemble those exerted by specific inhibition of Aurora B. The first three small-molecule dual inhibitors of Aurora(s) described include Hesperadin, VX-680, and ZM447439. These three drugs have similar potency versus Aurora A, and Aurora B. Each induces a similar phenotype in cell-based assays, characterized by inhibition of phosphorylation of histone H3 on Ser10 and Ser28, inhibition of cytokinesis, and development of polyploidy (28-34).

In addition, selective inhibitors of Aurora B have been developed: AZD1152 (highly potent and selective inhibitor of Aurora B), and GSK1070916 (a potent and selective inhibitor of Aurora B and Aurora C kinases) (3,19,23).

The role of Aurora B in human tumourigenesis remains to be fully clarified, however, overexpression of Aurora B occurs in many tumours and accumulating evidence indicates that its expression negatively correlates with patient's survival and prognosis.

Aurora B inhibitors have been obtained and are currently under clinical trials. However, antimitotic drugs frequently show the appearance of drug resistance, adverse side effects (neurotoxicity) and their clinical effects are not predictable. Aurora inhibitors lack neurotoxicity and could contribute to the treatment of human neoplasia (31-34).

Furthermore, preclinical data are predicting that the association of these inhibitors with conventional chemotherapy and radiotherapy display additive or even synergistic anticancer effect thus opening new avenues towards the cure of cancer.

References


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