Critical Reviews in Oncology/Hematology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Polo-like kinase inhibitors in hematologic malignancies

Chetasi Talati, Elizabeth A. Griffiths, Meir Wetzler, Eunice S. Wang*

Leukemia Section, Department of Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA

Contents

ARTICLE INFO

Article history:
Received 11 December 2014
Received in revised form 12 October 2015
Accepted 27 October 2015

Keywords:
Polo-like kinase
Acute myeloid leukemia
Myelodysplastic syndromes
Drug development

ABSTRACT

Polo-like kinases (Plk) are key regulators of the cell cycle and multiple aspects of mitosis. Two agents that inhibit the Plk signaling pathway have shown promising activity in patients with hematologic malignancies and are currently in phase III trials. Volasertib is a Plk inhibitor under evaluation combined with low-dose cytarabine in older patients with acute myeloid leukemia (AML) ineligible for intensive induction therapy. Rigosertib, a dual inhibitor of the Plk and phosphatidylinositol 3-kinase pathways, is under investigation in patients with myelodysplastic syndrome (MDS) who have failed azacitidine or decitabine treatment. The prognosis for patients with AML, who are ineligible for intensive induction therapy, and for those with MDS refractory/relapsed after a hypomethylating agent, remains poor. Novel approaches, such as Plk inhibitors, are urgently needed for these patients. Here, we provide a comprehensive overview of the current state of development of Plk inhibitors for the treatment of hematologic malignancies.

1. Polo-like kinase inhibitors in mitosis and cancer

Loss of control of cellular proliferation is one of the hallmarks of cancer (Hanahan and Weinberg, 2011). Cell division, or mitosis, is a complex and highly orchestrated process, and the effective regulation of mitotic events is crucial to the maintenance of cellular integrity. The Polo-like kinase (Plk) family is a group of five serine/threonine protein kinases that, in coordination with other kinases, play essential roles in cell division and checkpoint regulation of mitosis (Schöffski, 2009; Strebhardt, 2010; Strebhardt and Ullrich, 2006; Andrysik et al., 2010). The most extensively characterized member of the Plk family is Plk1 (Strebhardt and Ullrich, 2006), a kinase that directly promotes mitotic entry and is involved in centrosome maturation and separation, formation of the bipolar spindle, transition from metaphase to anaphase, and initiation of cytokinesis (Barr et al., 2004; Degenhardt and Lampkin, 2010) (Fig. 1). Plk1 has also been reported to contribute to the response

* Corresponding author. Tel.: +1 716 845 3544; fax: +1 716 845 8741.
E-mail addresses: Chetasi.Talati@RoswellPark.org (C. Talati), Elizabeth.Griffiths@RoswellPark.org (E.A. Griffiths), Eunice.Wang@RoswellPark.org (E.S. Wang).

http://dx.doi.org/10.1016/j.critrevonc.2015.10.013
1040-8428/

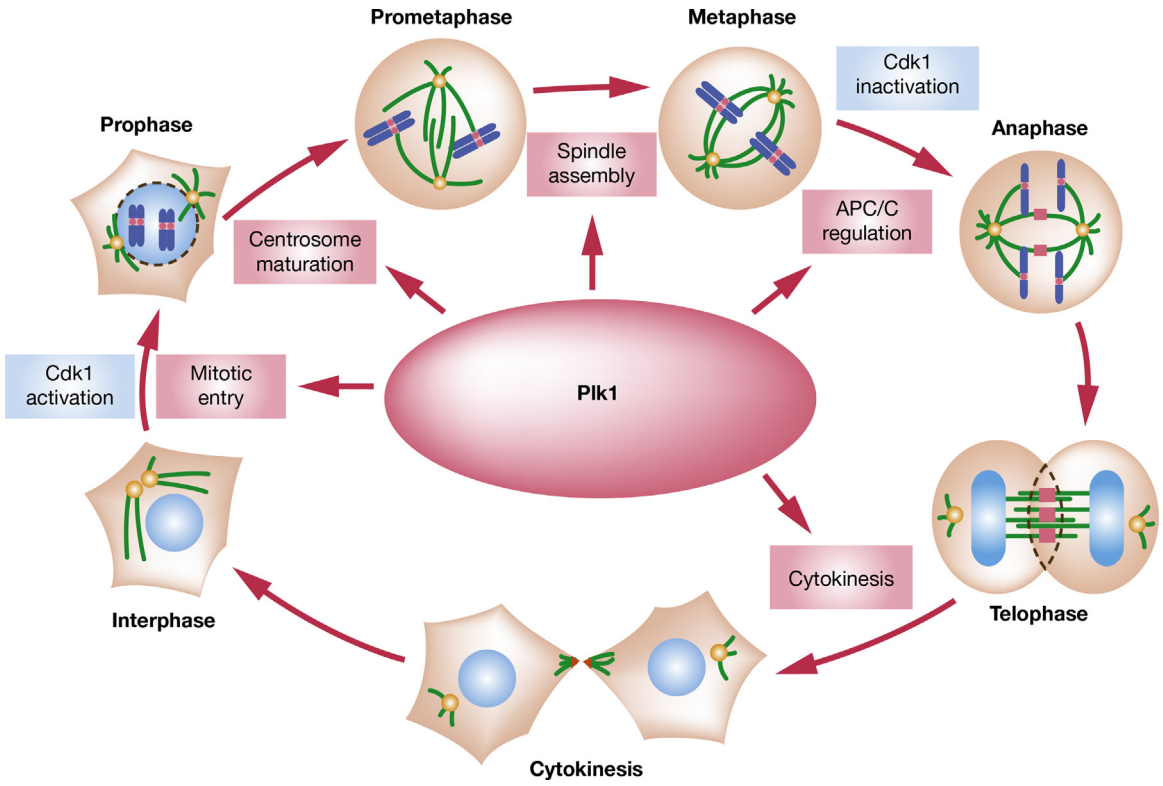

Fig. 1. The multiple roles of Plk1 in the regulation of mitosis.
APC/C, anaphase-promoting complex/cyclosome. Reprinted by permission from Macmillan Publishers Ltd.: *Nature Reviews Molecular Cell Biology* (Barr et al., 2004), copyright 2004.

of cells to DNA damage and replication stress (Degenhardt and Lampkin, 2010; Li et al., 2008; Trenz et al., 2008; Shen et al., 2013; Yim and Erikson, 2009).

Plk1 is overexpressed in a number of different types of tumor (Strebhardt and Ullrich, 2006; Eckerdt et al., 2005; Takai et al., 2005; Weiss and Efferth, 2012). Studies have shown an association between Plk1 overexpression and increased tumor stage/grade and worsened prognosis, including a low rate of overall survival (OS) in patients with some tumor types (Strebhardt and Ullrich, 2006; Eckerdt et al., 2005; Takai et al., 2005; Weiss and Efferth, 2012). Elevated Plk1 expression has also been demonstrated in hematologic malignancies (Holtrich et al., 1994; Ikezoe et al., 2009; Mito et al., 2005; Renner et al., 2009; Gleixner et al., 2010). Plk1 is overexpressed in acute myeloid leukemia (AML) cell lines and primary AML patient samples (Renner et al., 2009). Pharmacologic inhibition or RNA interference (RNAi)-mediated knockdown of Plk1 preferentially blocks proliferation of leukemic rather than normal cells (Renner et al., 2009). Overexpression of Plk1 has been linked to shortened event-free survival (EFS) in patients with diffuse large B-cell lymphomas (DLBCL) (Liu et al., 2007). Plk1 is also expressed in chronic myeloid leukemia (CML) cell lines and primary CML patient samples, and Plk1 downregulation leads to growth arrest and apoptosis (Gleixner et al., 2010). Depletion of Plk1 in cancer cells has been shown to perturb mitotic spindle assembly, leading to activation of the mitotic checkpoint, prolonged mitotic arrest, and subsequent apoptosis (Schöffski, 2009; Barr et al., 2004; Liu and Erikson, 2003).

The essential role of Plk1 in mitosis indicated by its expression in dividing cells and its increased expression in hematologic malignancies makes Plk1 an attractive therapeutic target. To date, volasertib (BI 6727; Boehringer Ingelheim), rigosertib (ON 01910.Na; Onconova Therapeutics, Inc.; a multikinase inhibitor whose targets include the Plk1 and phosphatidylinositol 3-kinase [PI3K] pathways), and another Boehringer Ingelheim agent, BI 2536, are the only Plk inhibitors that have undergone clinical assessment in this setting. Although BI 2536 was evaluated in patients with AML and other hematologic malignancies, its clinical development was discontinued in favor of volasertib, which has an improved pharmacokinetic profile. Other Plk inhibitors (TKM-080301, MK-1496, NMS-1286937, GSK461364, and HMN-214) have, to date, only been investigated in solid tumors (ClinicalTrials.gov., 2014a; Doi et al., 2011; Olmos et al., 2011; Ramanathan et al., 2013; Garland et al., 2006). Additionally, the Plk inhibitors MLN0905 and TAK-960 have shown promise in preclinical models of hematologic malignancies, but have not yet entered the clinic.

2. Plk inhibitors in clinical development in hematologic malignancies

2.1. Compounds in phase III development

2.1.1. Volasertib

Volasertib is a dihydropteridinone derivative that acts as a small-molecule, adenosine triphosphate (ATP)-competitive kinase inhibitor of Plk1 (Rudolph et al., 2009). In-vitro kinase assays showed that volasertib potently inhibited Plk1 (half maximal inhibitory concentration [IC_{50}] 0.87 nmol/L), as well as the closely related kinases Plk2 (IC_{50} 5 nmol/L), and Plk3 (IC_{50} 56 nmol/L), but had no inhibitory activity against a panel of >50 unrelated kinases at concentrations up to 10 μmol/L (Rudolph et al., 2009). Potent inhibition of proliferation has been observed with volasertib in a wide range of cancer cell lines. In HL-60 and THP-1 AML cells, volasertib inhibited proliferation with half maximal effective concentration (EC_{50}) values of 32 and 36 nmol/L, respectively (Rudolph et al., 2009). Volasertib causes the formation of abnormal, monopo-

Please cite this article in press as: Talati, C., et al., Polo-like kinase inhibitors in hematologic malignancies. Crit Rev Oncol/Hematol (2015), http://dx.doi.org/10.1016/j.critrevonc.2015.10.013