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Cyclin-dependent kinase inhibitors for the treatment of chronic lymphocytic leukemia

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ABSTRACT

In the last 10 years, oncology has been transformed by the development and broad availability of small molecule therapies for cancer. Compounds have been and are being developed to target nearly every known relevant component of the cell's machinery. One class of compounds, the cyclin-dependent kinase (CDK) inhibitors, was originally conceived as an anticancer therapeutic based on the premise that as cancer is (in part) defined by loss of cell-cycle control, the interruption of cell cycle could arrest cancer growth. While CDKs do play critical roles in cell cycle, including in cancer, the study of CDK inhibitors in the relatively non-proliferative disease chronic lymphocytic leukemia (CLL) revealed alternate mechanisms both for CDKs, as well as for the role of CDK inhibitors in cancer therapy. In this review, we will consider three CDK inhibitors: alvocidib (flavopiridol), dinaciclib, and TG02. We will discuss their preclinical and clinical development for the treatment of CLL, and suggest that CDK inhibitors remain relevant in CLL, with potential utility in several scenarios.

1. Introduction

Modern medical oncology is presently transforming from a medical specialty chiefly concerned with chemotherapy to a discipline of molecular biology, complete with armamentarium of small molecule targeted therapies. These small molecules are usually inhibitory in nature, frequently inhibit intrinsic kinase activities, and purport to be relatively specific. In contrast to the blunt weapon of cytotoxic chemotherapy, targeted therapies aim to disrupt specific components within the machinery of the cancer cell, directing and concentrating toxic effects chiefly upon the cancer itself thereby limiting systemic toxicities traditionally associated with cancer therapy like hair loss, nausea, and hematopoietic suppression.

One particular class of targeted agents that merits consideration is the cyclin dependent kinase (CDK) inhibitors. Cyclins, as might be guessed from the name, fluctuate with and are indispensible components of eukaryotic cell cycle, and the discovery of these proteins and their cyclic expression was instrumental in helping to understand and develop the model of the cell cycle [1]. Subsequent studies have shown that their regular rise and fall is critical to eukaryotic cell cycle progression, and that their orderly fluctuations are controlled by internal and external stimuli and anti-stimuli. Cyclins are actually components of a complex consisting of cyclins and CDKs; the cyclin subunit serves to activate the CDK (and by virtue of its variable level it is a *de facto* regulator of CDKs), while the CDK itself is the effector subunit [2]. CDKs act as serine/threonine protein kinases, which directly or indirectly activate factors integral to cell cycle. For example, CDK4 and CDK6 in cooperation with cyclin D inactivates retinoblastoma (Rb), in turn releasing the transcription factor E2F; the transcription factor is then free to awaken a number of genes important to mitosis [3]. Rb is among the most well known among the tumor-suppressor genes, and the potential importance of CDKs in cancer is readily apparent. Thinking along these lines, CDK inhibitors have been explored as a class of novel therapeutic agents with a goal to disrupt CDKs' control of cell cycle.

Indeed, some cancers may even be defined by dysregulated cyclin and thus CDK activity: mantle cell lymphoma, an uncommon lymphoma of mature B cells, is defined by the presence of overexpressed cyclin D1, usually as a result of a translocation between chromosomes 11 and 14 with the net result that cyclin D1 is driven under influence of powerful immunoglobulin heavy chain enhancers on chromosome 14. Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western adults [4] and shares many features with mantle cell lymphoma including mature B-cell derivation, B-cell receptor stereotypy, overactive

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