Neutropenia and Low Infection Rates Dilemma of the CDK Inhibitors: A New Theory

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Dear Editor,

In a multicellular organism like us, all cells constantly make a very important and obligatory decision: "Divide" or "Stay Quiescent". This essential task is regulated by several molecules in our cells, including cyclin-dependent kinases (CDKs).[1] The CDKs have an important regulatory role in cell cycle and can be found in nearly all eukaryotic organisms.[2] As a matter of fact, a fission yeast *Schizosaccharomyces pombe* can divide properly even if we change their CDK gene with an equivalent homologous human gene. This shows that CDKs might have been stayed similar throughout evolution.[3]

Dysregulation in the cell cycle could be seen in nearly all emergent cancer cells. These cells can maintain this dysregulation through genetic or epigenetic alterations in CDK proteins or the related pathways. After learning the importance of the CDKs in cancer development, some drugs that inhibit CDKs were developed to limit the overproliferation of the neoplastic cells.[4]

The first FDA approved drug of this type is palbociclib for use in hormone receptor positive (HR+) HER2 negative advanced breast cancer patients[5], followed by several other ribociclib and abemaciclib. These CDK inhibitors improved the survival outcomes in HR+-HER2 negative breast cancer and became the standard-of-care treatments in advanced disease. Currently, many combination and new CDK inhibitor drugs are being researched in the scientific community, such as ribociclib, abemaciclib, dinaciclib.[6]

The CDK inhibitors are mostly well tolerated by the patients. The most common and most important side effect of them is neutropenia. Grade 3 or higher neutropenia occurs in 2/3 of the patients receiving palbociclib or ribociclib, and 4/5 of the patients taking these drugs develop any grade of neutropenia during the treatment.[7] The other side effects such as nausea, diarrhea, ALT/AST increase, alopecia, and fatigue occur mostly in lower grades, and are mostly well tolerated.[7]

Even though patients receving CDK inhibitors tend to have lower white blood cell counts, we usually don't see an increase in infection and neutropenic fever rates (< 1% of the patients).[8] Because of the evolutionary importance of CDK proteins; even if bacteria don't have any CDKs like humans, some of their cell cycle regulator proteins might share some similarities with human CDKs.[3] For instance; c-di-GMP is an important intracellular messenger of the bacteria Pseudomonas aeruginosa that controls the biofilm lifecycle. Inhibition of this messenger results in dispersal of the previously formed biofilms. Suprisingly; these inhibitor compounds share some pharmacological similarities with CDK inhibitors.[9]

These similarities between human CDK proteins and some bacterial virulence factors (such as c-di-GMP) may be the reason why we don't see an increase in neutropenic fever and infection rates at the patients who are receiving these drugs.

Based on these associations, we firmly believe that CDK inhibitors could also have a strong antibacterial effect in addition to their antineoplastic effect.[10] Further research can shed light this dilemma and change our perception on toxicity profile of CDK inhibitors and could lead the repurposing of CDK inhibitors as anti-bacterial agents.

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