Nucleosides as anticancer agents: from concept to the clinic

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ABSTRACT

The continuing use of nucleosides as anticancer agents is discussed. Examples include the newly approved drug clofarabine as well as 4'-thio-ara-C, a drug that has initiated clinical trials. New directions in anticancer drug discovery will also be discussed.

INTRODUCTION

At the end of 2004 the FDA approved another nucleoside as an anticancer agent. Clofarabine, a purine nucleoside analog, was approved for the treatment of a pediatric cancer. This approval continues to demonstrate the value of the anticancer selectivity found in certain nucleosides. We have learned much about the design of such nucleosides over the years, though rational design remains a challenge because of the multiple points of interaction that nucleosides have. This multiplicity of biological interaction is very likely a prime reason that certain nucleosides have selectivity. As we understand more about these points of interaction, we are better able to design new anticancer drugs.

RESULTS AND DISCUSSION

Over the years nucleosides have been in and out of favor as potential anticancer drugs. The reasons for this view included 1) concerns about the toxicity of nucleoside analogs and 2) concerns that perhaps new nucleoside analogs would not be sufficiently different from those already known and approved for human use, and therefore no further advances were likely. An objective examination of U. S. FDA-approved anticancer agents shows that nucleosides comprise a significant sized class of anticancer agents. Nucleosides are also the largest class of approved antiviral agents. Of the sixty or so small molecule therapeutics for cancer treatment that have been approved by the FDA, 11 of them are antimetabolites and 10 of those 11 are nucleosides or related compounds affecting DNA synthesis in a variety of ways.

The most recently approved anticancer FDA-approved anticancer drug is clofarabine, a drug that we discovered and developed over a period of years.\textsuperscript{1-4} This drug was initially approved for the treatment of refractory pediatric acute lymphoblastic leukemia, and is currently being examined for efficacy against other forms of cancer. In addition, 1-(4-thio-β-D-arabinofuranosyl)cytosine (4'-thio-ara-C),\textsuperscript{5,7} selected from a larger series of compounds, has also entered clinical trials.

The future directions of cancer chemotherapy involve both small molecule drugs and biologics, with new agents targeting specific proteins or pathways, and with some agents having multiple sites of action. Within this framework for the future, there clearly is still a role for nucleosides, which are a continuing focus of our cancer research effort.

Research and clinical progress with nucleosides have made it clear that even modest changes in nucleoside structure can have a significant effect not only on mechanism of action and clinical indication, but also on toxicity. As we have learned more over the years about nucleosides as anticancer agents, this fact has become critical to our design approaches. Nucleosides have always had multiple points of action, and this fact has been one of the reasons that the class has been so successful in the clinic. The multiple points of mechanistic action, however, bring with them challenges in terms of rational drug design as defined above. As we have learned more about the relevant enzymes such as deoxyctydine kinase and DNA polymerases, however, our ability to apply rational design concepts has increased.

The focus of the presentation will be threefold. First, the successful transition of clofarabine from concept to approval will be discussed. Then the current status of 4'-thio-ara-C will be presented. Finally, progress on one or two new directions in our laboratory, focusing on 2', 4' and 5'-modified nucleosides including specific enzyme targeting, will be presented.

CONCLUSION

Nucleosides continue to be excellent candidates as anticancer drugs, as our experience with clofarabine and 4'-thio-ara-C demonstrates. Additional clinical candidates
will certainly develop from efforts in our laboratory and others around the world.

REFERENCES