Editorial

New and Emerging Drug Targets for the Treatment of Hematological Malignancies

As a group, hematological malignancies represent the fourth most common cancer accounting for a little less than 10% of all cancer diagnoses. Overall outcomes for patients with hematological malignancies have improved as a result of chemotherapy and radiotherapy, however the heterogeneous nature of the biological characteristics of hematological malignancies necessitates a diverse range of treatments strategies. Currently outcomes vary dramatically between the various hematological malignancies with childhood acute lymphoblastic leukemia and Hodgkin's lymphoma having 5-year survival rates in the vicinity of 90% [1, 2], while those for patients with multiple myeloma and adults with acute leukemias remain less than 50% [3, 4]. Novel approaches to treatment and the introduction of new agents are essential to improve outcomes for patients who do not obtain cures with the currently available therapeutic options. A variety of approaches are likely to be needed for this diverse group of diseases.

This special edition of Current Drug Targets focuses on new and emerging drug targets for the treatment of hematological malignancies with an emphasis on the diversity of therapeutic strategies. The first therapeutic agents for the treatment of malignancies were taken directly from the environment, with subsequent structural modifications often enhancing the utility of these agents. Such empirical treatments have played a major role in the management of hematological malignancies over the last few decades and include agents such as vincristine and etoposide. The introduction of high throughput screens has enabled new agents that impact on the growth and survival of malignant cells to be identified from among the multitude of chemically diverse compounds provided by nature. Lucas et al have reviewed the development of agents derived from higher plants for the treatment of leukemias and lymphomas and the rationale behind these developments, underpinning the enormous resource provided by naturally occurring compounds and the essential role they play in modern oncology.

As our understanding of the biology of hematological malignancies has increased there has been a shift from empirical treatments to targeted therapies. Although it needs to be remembered that many empirically developed drugs do indeed hit specific targets in malignant cells. As the treatment of cancers with chemotherapeutic agents was pioneered in hematological malignancies so too targeted treatments are also having their greatest impact in this group of malignancies. Some of the outstanding additions over the last two decades are Rutuximab and Imatinib. Rutuximab, a humanised antibody to CD20, has dramatically improved the cure rate for patients with diffuse large B-cell lymphoma making it the most important single new agent for the treatment of B-cell lymphomas. As reviewed by Capietto et al in this issue, the success of this initial therapeutic antibody has been followed by a growing list of antibody-based therapies with a range of targets and mechanisms of action. There are now antibodies in clinical trial for the treatment of many hematological malignancies, and with an expanding list of these agent currently in clinical trial it appears these agents will play a significant role in future treatment strategies.

Imatinib was the first agent specifically designed to directly target the protein product of an oncogene. It has revolutionized the treatment of chronic myeloid leukemia, the principal malignancy bearing the relevant genetic lesion. As with the development of Rutuximab, Imatinib has been followed by a plethora of targeted agents. The vast majority of these target enzymes that are constitutively activated in malignant cells, providing survival and proliferative advantages. Unlike CML, most hematological malignancies lack dominant cytogenetic abnormalities and so do not have such clearly defined targets. However, a number of inhibitors of cell signaling pathways that support malignant cell proliferation and survival are in clinical trial, including inhibitors of the PI-3K/AKT/mTOR and NF-κB pathways. In addition a number of agents that directly target the apoptotic machinery are being investigated with varying degrees of success and are reviewed here by Saborit-Villarroya et al. One of the more promising emerging target is the receptor tyrosine kinase Flt-3, the over activation of which is present in more that 30% of AML patients and is associated with a poor prognosis [5]. An agent that counters the actions of aberrant Flt-3 signaling has the potential to dramatically improve outcomes for this subset of AML patients and Pratz and Levis have reviewed the development of such agents and their progress towards the clinic.

Over recent years there has been increasing interest in disrupting the microenvironment to enhance the efficacy of chemotherapeutic agents. These have included strategies for mobilizing malignant hematopoietic cells out of their protective bone marrow environment with agents such as chemokine inhibitors [6]. Other approaches include altering the behavior of the cells within the micro-environment. Perhaps one of the more developed is the use of inhibitors of p38MAPK, reviewed by Gaundar and Bendall. This strategy is of particular interest to multiple myeloma where the understanding of stromal/malignant cell interactions is well more mature and appreciated.

One of the new and relatively untapped areas for the development of new therapeutic agents for the treatment of hematological malignancies are micro-RNAs. These small non-coding RNAs regulate the translation and stability of mRNA, altering the balance of proteins present in cells. miRNAs are abnormally expressed in leukemias [7] and an understanding of which mRNAs are targeted is evolving. The developing understanding of miRNAs and how their deregulation contributes to hematological malignancies and the potential of modifying the expression of miRNAs using pharmacological agents is reviewed by Mian and Zeleznik-Le.

Despite the host of new and emerging therapies for the treatment of hematological malignancies we are still a long way short of having successful treatments for all patients. This is at least partially due to the heterogeneity of these diseases. Currently there are more than 50 different agents in use and an even larger number in clinical trial. Even if the majority of these agents progress to the clinic they are unlikely to provide the desired outcome for all patients. Like traditional chemotherapeutic agents, new, targeted treatments are also limited by the development of resistance. Undoubtedly complex combinations and timings of drug administration will avoid or overcome this to some degree. Learning how to best use new agents as they become available presents a significant challenge. However the major advances resulting from a select number of agents introduced in recent decades and the diversity of agents and therapeutic strategies under development provide an optimistic base on which to build.

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