

Developing Drugs for Leukemia's

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At present, available therapies are only partially effective in patients with leukemia and the vast majority of patients cannot be cured with current treatment strategies. Hence, there is an obvious need to develop more specific and effective drugs for the treatment of these diseases. In the last twenty years, significant progress in molecular and cellular biology has resulted in a better characterization and understanding of the molecular abnormalities in acute and chronic leukemia. These achievements have provided new opportunities for the development of innovative drugs, and leukemia mortality rates have begun to decline. Molecular-targeted drugs were first introduced for the treatment of hematological malignancies. Imatinib was the first small molecule-targeted drug successfully used for the treatment of chronic myeloid leukemia (CML), and rituximab was the first tumor-specific antibody to be introduced for the treatment of CD20-positive lymphomas and chronic lymphocytic leukemia (CLL). The introduction of imatinib and rituximab has changed the mortality rates associated with CML and B-cell lymphoid malignancies. In CML the availability of tyrosine kinase inhibitors (TKIs) changed the management and prognosis of this disease [1]. However, about 20% of CML patients do not achieve optimal response on imatinib treatment and they need alternative drugs. The availability of second generation TKIs, such as dasatinib and nilotinib, has provided new therapeutic hope for patients with imatinib resistance [2]. In addition, new molecules with different modes of action have demonstrated activity in patients with highly-resistant mutants such as MK0457 and dasatinib, which exhibit inhibitory activity against Aurora kinases [3]. Current therapies are frequently inappropriate and unsuccessful for acute myeloid leukemia (AML), especially for older patients. For these patients, there is an obvious need to develop better strategies and new, more specific and active drugs. The search for new drugs in AML has led to the development of many new antileukemic agents potentially active in this form of leukemia [4]. Novel agents potentially useful in the treatment of patients with AML include monoclonal antibodies, molecular target drugs, newer nucleoside analogs and other drugs. These new agents seem unlikely to be curative when administered as monotherapy. They will rather have to be used in combination with other new agents or with more standard therapy. Nucleoside analogs are clinically important antileukemic drugs which compete with physiologic nucleosides and consequently, interact with a large number of intracellular targets. Recently, three novel nucleoside analogs, clofarabine, troxacitabine and sapacitabine, have been introduced into clinical trials in AML and shown promise. However, phase II and III randomized trials are necessary to verify whether these drugs confer an advantage in the treatment of this disease. Gemtuzumab ozogamicin is a humanized IgG4 anti-CD33 monoclonal antibody conjugated to calicheamicin, a potent antitumour antibiotic that had demonstrated activity in recurrent and previously untreated AML [5]. This drug was used to treat AML from 2000-2010 but was withdrawn from market in June 2010 when a clinical trial showed the drug increased patient death and added no benefit over conventional leukemia therapies. Another antibody with potential in the treatment of AML is lintuzumab. This is a humanized monoclonal antibody directed against CD33. However the phase IIb trial of lintuzumab (SGN-33) in patients with AML did not meet the primary endpoint of extending overall survival and its development program will be discontinued by the producer (Seattle Genetics, Inc.). These examples indicate that the

usefulness of originally promising antileukemic drugs is frequently not confirmed in well-designed clinical trials. In recent years, FMS-like tyrosine kinase 3 (FLT3) inhibitors, lestaurinib, tandutinib and PKC 412 have been also developed and tested in AML [6]. Preclinical observations and clinical studies indicate that FLT3 inhibitors are promising agents in the treatment of FLT3-mutated AML patients, especially when used in combination with chemotherapy. The most common adult leukemia in the Western world is chronic lymphocytic leukemia (CLL). Recent treatment of CLL is combined cytotoxic chemotherapy with monoclonal antibodies, which has significantly improved the quality of response, duration of response, and survival [7]. However, intensive treatment is often too toxic, particularly in older patients. Therefore, the development of novel treatment strategies is highly desirable, especially those with targeted actions and lower toxicities. Recently, several new agents have been explored and have shown promise in CLL treatment including new mAbs and BCL-2 inhibitors, such as oblimersen, obatoclax, and ABT-263 [8]. In addition, protein kinase inhibitors, such as flavopiridol, spleen tyrosine kinase inhibitors (Fostamatinib disodium), Bruton's tyrosine kinase (PCI-32765), and phosphatidylinositol 3-kinase inhibitors (CAL-101) are highly active and well tolerated in CLL patients, irrespective of high-risk genomic abnormalities and suggest that these drugs may be an important new targeted treatment approach for CLL. This is also an exciting time in drug development for acute lymphoblastic leukemia (ALL). Recently, three novel PNAs, clofarabine, nelarabine and forodesine (immucillin H, BCX-1777), have demonstrated promising activity in patients with relapsed and refractory ALL [9]. Another important trend in ALL drug development is the increasing understanding of the molecular level of the genomic changes that occur in B- and T-cell ALL. Drugs targeting the molecules relevant to the biology of ALL are in early clinical trials: inhibitors of FLT-3, BCR-ABL, mTOR, Bcl-2, ribonucleotide reductase, Aurora A kinase and the proteasome complex. The use of anti-NOTCH1 therapies for T-ALL, including combination therapies with molecularly-targeted drugs are also promising [10]. Currently available inhibitors of these targets have the potential to increase treatment efficacy, and usually have non-overlapping toxicities with standard cytotoxic chemotherapy agents. The development of new drugs with novel mechanisms of action remains vital to success in fighting leukemias. It is expected that a better understanding of the molecular pathogenesis of leukemias will contribute to the discovery and clinical application of novel drugs that will revolutionize therapeutic strategies and bring renewed hope to leukemia patients. Novel therapies are being evaluated both in pre-

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clinical studies and in early clinical trials. This is an exciting time for the development of new, effective drugs for the treatment of leukemia, which should significantly improve the prognosis of this frequently fatal disease in the near future.

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