Editorial: Novel and Emerging Drugs for Leukemias

Tadeusz Robak*

Department of Hematology, Medical University of Lodz and Copernicus Memorial Hospital, 93-510 Lodz, ul. Ciołkowskiego 2, Poland

Abstract: For the last twenty years, significant progress in molecular and cellular biology has resulted in a better characterization and understanding of the molecular abnormalities in leukemias. These achievements have provided new opportunities for the development of innovative, more effective drugs. Novel therapies are being evaluated both in pre-clinical studies and in early clinical trials. In this editorial, we demonstrate a brief review of the present insights into new therapeutic strategies for acute and chronic leukemias.

Keywords: ALL, AML, CLL, CML, HCL, LGLL, new drugs, PLL.

For the last twenty years, significant progress in molecular and cellular biology has resulted in a better characterization and understanding of the biology and prognosis of acute and chronic leukemias. These achievements have provided new opportunities for the development of innovative and more effective therapies [1]. Novel therapies are being evaluated both in pre-clinical studies and in early clinical trials. However, despite the significant progress made in recent years, available therapies for leukemias are only partially efficient and there is an obvious need to develop better strategies and new, more specific and active drugs.

ACUTE MYELOID LEUKEMIA

Together with increasing understanding of the biology of acute myeloid leukemia (AML), several new agents have been explored and have shown promise in treating this leukemia [2]. Novel agents potentially useful in the treatment of patients with AML include newer nucleoside analogs, monoclonal antibodies, molecular target drugs, new formulations of established drugs and other agents. Three newer nucleoside analogs, clofarabine, troxacitabine and sapacitabine have been recently investigated in patients with AML. Clofarabine is a second generation of purine nucleoside analogs (PNA) synthesized to combine the most favorable pharmacokinetic properties of fludarabine and cladribine [3]. Clofarabine acts by inhibiting DNA polymerases and ribonucleotide reductase as well as by inducing apoptosis in cycling and non-cycling cells. The recent studies have demonstrated that clofarabine used in monotherapy or in combination with other agents shows good efficacy in the treatment of lymphoid and myeloid malignancies. Troxacitabine is a novel L-enantiomer of the nucleoside analog, different from cytarabine in its structure and mechanism of action and resistance. The results of phase I and phase I/II studies in AML have shown 10-15% of CR in patients refractory to previous therapies [4]. Sapacitabine is a novel 2'-deoxycytidine analog, which displayed antiproliferative activity in a variety of leukemic cell lines, including those, shown to be resistant to several anticancer drugs. In a phase I study of sapacitabine in relapsed or refractory AML the OR and CR rates were 28% and 9%, respectively [5]. The role of these agents in AML treatment needs to be defined in further phase II and III studies.

Two methylation inhibitors, 5-azacyticline and decitabine are pyrimidine analogs incorporated into RNA and/or DNA. Although the antileukemic capacity of these agents has been known for almost 40 years, their therapeutic potential in hematologic malignancies is still under extensive investigation [6,7]. Demethylating agents have proven their efficacy in monotherapy in myelodysplastic syndrome (MDS) in phase III trials. Lower doses of these agents are active in AML and are extensively investigated especially in the secondary AML and AML in elderly patients. Azacytidine is the first drug in the history of MDS treatment which has prolonged overall survival (OS). The activity of demethylating agents in elderly patients with AML is encouraging, although it still needs further clinical evaluation. Azacytidine and decitabine seem to be the best choice for patients with high-risk MDS and AML, neither eligible for intensive chemotherapy, nor for allogeneic stem cell transplantation.

Tipifarnib, lonafarnib and BMS-214662 are farnesyltransferase inhibitors with *in vitro* and *in vivo* activity against AML. These drugs are currently under development in AML and demonstrate therapeutic activity in poor risk patients. In addition, farnesyltransferase inhibitors may be more active when combined with other antileukemic agents. Cloretazine is a novel alkylating agent, which belongs to the group of sulfonyl hydrazine prodrugs. This drug spontaneously generates nucleophilic species that can efficiently alkylate DNA resulting in DNA cross-linking and cell death. In the *in vitro* studies, cloretazine showed significant antileukemic activity against myeloid leukemia blast cells both as a single agent and in combination with AraC or daunorubicin.

FMS-like tyrosine kinase 3 (FLT3) is a class III receptor of the tyrosine kinase family that is normally expressed on the surface of hematopoietic progenitor cells. In the recent years FLT3 inhibitors, lestaurinib, tandutinib and PKC 412 have been developed and tested in AML. The predinical observations and clinical studies indicate that FLT3 inhibitors are promising agents in the treatment of FLT3

*Address correspondence to this author at the Department of Hematology, Medical University of Lodz, 93-510 Lodz, ul. Ciołkowskiego 2, Poland; Tel: 048 42 689-15-91; Fax: 048 42 689-51-92;
E-mail: robaktad@csk.umed.lodz.pl

1873-5576/12 $58.00+.00

mutated AML patients, especially when used in combinations with chemotherapy.

Gemtuzumab ozogamicin (GO) is a humanized IgG4 anti-CD33 monoclonal antibody (Mab) conjugated to calicheamicin, a potent antitumor antibiotic that had demonstrated activity in recurrent and previously untreated AML. GO was granted an accelerated approval in May 2000 to treat patients aged 60 years and older with recurrent AML not considered eligible for other therapies. Recently published results of the MRC AML15 trial showed that a substantial proportion of younger patients with AML have improved survival with the addition of GO to induction chemotherapy with little additional toxicity [8]. However, results in unselected patients with newly diagnosed AML have been rather disappointing and no improvement was found in clinical benefit and the increased number of deaths occurred in patients assigned to the drug when compared with those assigned to chemotherapy alone in a post approval clinical trial. In consequence, currently GO is not commercially available to AML patients. Lintuzumab (SGN-33, Seattle Genetics) is a humanized monoclonal antibody also directed against CD33. It consists of a human IgG1 framework combined with complementarity-determining regions of murine M195 antibody [9]. Humanization led to a higher binding affinity for the CD33 antigen and avoidance of neutralizing responses. This antibody has been studied in several trials in AML and has modest single-agent activity. However, lintuzumab has some potential in a combination therapy [10]. Novel therapies for AML are discussed in details in this issue of the journal [11].

ACUTE LYMPHOBLASTIC LEUKEMIA

This is also an exciting time in drug development for acute lymphoblastic leukemia (ALL). One contributory factor is the development of more representative preclinical models of ALL for testing and prioritizing novel agents. Recently three novel PNAs: clofarabine, nelarabine and forodesine have demonstrated promising activity in patients with relapsed and refractory ALL [12]. Phase I/II clinical studies revealed efficacy of clofarabine and nelarabine in ALL. In 2004, clofarabine was approved by the US Food and Drug Administration (FDA) and in 2004 by the European Commission (EMEA), for the treatment of relapsed or refractory ALL in children after at least two prior chemotherapy regimens. Nelarabine belongs to the guanosine analogs in which the hydrogen of hydroxide group at 6-position of guanine ring is substituted by the methoxy group. The OR rates in refractory or relapsed ALL were11 to 60% [13]. Nelarabine is recommended for T-ALL and T-cell lymphoblastic lymphoma (T-LBL) which did not respond to or relapsed after treatment with at least two chemotherapy regimens. However, the use of the drug is limited by potentially severe neurotoxicity. In June 2005, nelarabine received EMEA orphan drug status and in October 2005, the drug was approved by the US FDA for the treatment of relapsed T-ALL and T-LBL [14].

Another important trend in ALL drug development is the increasing understanding of the genomic changes at the molecular level, which occur in B- and T-cell ALL. A final important trend is the increasing availability of new agents against relevant molecular targets. Molecularly targeted agents include novel antibody-based drugs targeted against leukemia surface antigens, proteasome inhibitors, mTOR inhibitors, JAK inhibitors, Aurora A kinase inhibitors, and inhibitors of Bcl-2 family proteins. The use of anti-NOTCH1 therapies for T-ALL, including combination therapies with molecularly targeted drugs is also promising [15]. Currently available inhibitors of these targets have the potential to increase treatment efficacy, and usually have non-overlapping toxicities with standard cytotoxic chemotherapy agents [16]. Development of new drugs with novel mechanisms, unique formulations of existing medications, as well as manipulation of current combinations of drugs remain vital to the success in ALL. Novel and emerging drugs for ALL are discussed in this issue of the journal [17].

CHRONIC LYMPHOCYTIC LEUKEMIA

The most common adult leukemia in the Western world is chronic lymphocytic leukemia (CLL). While treatment options for CLL have increased over the past two decades with the introduction of purine analogs, combined chemo-immunotherapy, alemtuzumab and recently bendamustine, none of these therapies are curative. Therefore, identifying new therapies for CLL represents a major scientific goal. Recently, several new agents have been explored and have shown promise in CLL treatment including new mAbs, BCL-2 inhibitors, such as oblimersen, obatoclax, and ABT-263; and protein kinase inhibitors, such as flavopiridol, spleen tyrosine kinase inhibitors, and phosphatidylinositol 3-kinase inhibitors. The promising drugs are also new mAbs targeting CD20 molecule, lumiliximab, epratuzumab, apolizumab, galiximab and anti-CD40 mAbs. New generations of anti-CD20 mAbs have been developed for potential benefits over the classical, 1st generation mAb – rituximab [18]. New mAbs have augmented antitumor activity by increasing complement dependent cytotoxicity (CDC) and/or antibody dependent cellular cytotoxicity (ADCC) and increased Fc binding affinity as compared with the classical 1st generation mAb – rituximab. The 2nd generation mAbs are humanized or fully human to reduce immunogenicity, but with an unmodified Fc region. They include ofatumumab, veltuzumab and ocrelizumab. Ofatumumab is a fully human, anti-CD20, IgG1 mAb in phase I, II, and III trials for hematological malignancies and autoimmune diseases. Ofatumumab specifically recognizes an epitope encompassing both the small and large extracellular loops of the CD20 molecule and is more effective than rituximab at CDC induction and killing target cells. Ofatumumab has demonstrated superior response rates in 2 challenging groups of CLL patients: those refractory to fludarabine and alemtuzumab; and those refractory to fludarabine and considered inappropriate candidates for alemtuzumab [19]. In October, 2009, the FDA approved ofatumumab for patients with CLL refractory to fludarabine and alemtuzumab [20]. Data concerning activity and toxicity of ofatumumab combined with fludarabine and cyclophosphamide (O-FC) in previously untreated patients with CLL were recently reported [21]. The encouraging activity of ofatumumab used as a single agent and in combination with chemotherapy in patients with refractory and previously untreated CLL warrants its further

investigation in these disorders. The 3rd generation mAbs are also humanized mAbs but in addition, they have an engineered Fc to increase their binding affinity for the FcγRIIIa receptor. The 3rd generation mAbs include AME-133, PRO131921 and GA-101. GA-101 (RO5072759), a fully humanized type II IgG1 mAb derived from humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering using GlycoMab technology. GA-101 was designed for enhanced ADCC and superior direct cell-killing properties, in comparison with currently available Type I antibodies. Compared with classical Type I CD20 antibodies, GA-101 binds with high affinity to the CD20 epitope and, as a result, induction of ADCC is 5-100 times greater than rituximab [22]. It also exhibits superior caspase–independent apoptosis induction than rituximab. However, CDC activity is low. GA-101 was investigated in phase I study as a single agent in patients with CLL for whom no therapy of higher priority was available. The antibody has shown a similar safety profile to rituximab and promising efficacy. Thirteen patients were treated, including 8 who previously received rituximab-containing therapy [23]. OR was observed in 8/13 (62%) with one CR, and seven PR. Based on this data, GA-101 mAb is a promising therapeutic agent for CD20 positive B-cell lymphoid malignances. It is currently being explored as a single agent and in combination with chemotherapy in phase II and III in CLL. TRU-015 is a small modular immunopharmaceutical (SMIP) derived from key domains of an anti-CD20 antibody. TRU-015 represents a novel biological compound that retains Fc mediated effector functions and is smaller than mAbs. TRU-016 is a SMIP derived from key domains of an anti-CD37 antibody, for the potential treatment of CLL. This compound showed significant antitumor activity against human B cell tumors in several subcutaneous xenograft models, including a model resistant to CD20-directed treatment. In preclinical studies, TRU-016 has demonstrated significantly greater direct and NK-cell mediated killing of CLL cells compared with other therapeutic antibodies used in CLL [24]. Encouraging reductions in tumor lymphocyte blood counts, lymph node/spleen size and improvement in normal hematopoietic function in patients with high-risk genomic CLL were demonstrated at low, non-saturating doses of TRU-016.

Bendamustine is a bifunctional alkylating agent composed of an alkylating nitrogen mustard group and a purine-like benzimidazole ring. Bendamustine causes DNA damage that leads to cell death *via* activation of DNA-damage, stress response, and apoptosis. Although it was synthesized in 1963 only more recently, its peculiar mechanism of action has reawakened interest in this drug. Recent data indicates that bendamustine, especially when combined with rituximab, is a valid therapeutic choice for patients with CLL demonstrating refractoriness to standard chemotherapy regimens [25]. In March 2008, bendamustine was approved by the USA FDA for the treatment of CLL. Alvocidib (flavopiridol) is a synthetic derivative of the flavonoid rohitukine. Alvocidib was originally described as an inhibitor of cyclin-dependent kinase (CDK) and other protein kinases because of its interaction with adenosine triphosphate (ATP) binding sites [26]. Studies *in vitro* showed that alvocidib promoted CLL-cell apoptosis independent of p53 function and prior to fludarabine exposure. Recently presented updated results confirm that alvocidib given as a 30-minute loading dose followed by a 4-hour infusion administered weekly for 4 of 6 weeks induces durable responses in heavily pre-treated, relapsed CLL patients with bulky lymphadenopathy (>5 cm) and poor-risk cytogenetic features [27]. New agents potentially useful in CLL are also being evaluated both in pre-clinical studies and in early clinical trials and are discussed in this review [28].

RARER INDOLENT LYMPHOID LEUKEMIAS

Rarer indolent lymphoid leukemias include well defined mature B-cell and T-cell neoplasm with widely varying natural history and specific morphological, immunophenotypic and molecular characteristics [29]. The World Health Organization (WHO) classification has defined these disease entities on the basis of their molecular, histological, immunophenotypic and clinical features [30]. In this classification, lymphoid neoplasms are divided into B-cell type and T-cell type and include hairy cell leukemia (HCL), B-cell prolymphocytic leukemia (B-PLL), T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocyte leukemia (LGLL), mature T-cell and natural killer (NK) cell neoplasms and adult T-cell leukemia/lymphoma (ATLL). Moreover, hairy cell leukemia variant (HCL-V), included in the WHO classification as provisional entity, can be recognized [30]. In the past 20 years, there has been a considerable progress in the treatment of patients with rarer chronic lymphoid leukemias, especially in HCL [31].

The introduction of purine nucleoside analogs (PNA), cladribine (2-CdA, 2-chlorodeoxyadenosine) and pentostatin (DCF, deoxycoformycin) has significantly improved the prognosis in HCL. Both agents induce complete response (CR) in the majority of patients and give long OS. Moreover, they are active in relapsed patients. However, responses are not universal and the refractory patients often respond poorly to subsequent treatments. Additionally, relapse free survival curves do not reach a plateau and a significant proportion of patients who relapse require re-treatment. Moreover, patients with HCL-V seem to be resistant to PNA. On the other hand, minimal residual disease (MRD) is present in responders and cure is rather not achievable. Additionally, patients with HCL-V are usually resistant to PNA [30]. Therefore, more effective therapies are still required for the treatment of HCL and especially for HCL-V. Promising results have been obtained with immunotoxin BL22 targeting CD22 [32]. CD22 is highly expressed in HCL, even in chemoresistant disease, and is therefore a potential target for antibody-directed therapy in refractory/resistant HCL and HCL-V. In addition, newer anti-CD22 immunotoxin, Moxetumomab Pasudotox (CAT-8015, HA22) is highly active in refractory/relapsed HCL-C and HCL-V [33]. Moxetumomab Pasudotox is a new generation of CD22-specific targeted immunotoxin composed of anti-CD22 antibody fused to the modified form of *Pseudomonas* exotoxin. This agent has a novel mechanism of action as compared to other anti-CD22 monoclonal antibodies. Moxetumomab Pasudotox is internalized upon binding to CD22, inhibiting protein translation and promoting apoptosis. In this issue of the

journal, current therapies and emerging drugs for patients with prolymphocytic leukemia, hairy cell leukemia, large granular lymphocyte leukemia and T-cell leukemia/lymphoma are also presented [34].

CHRONIC MYELOID LEUKEMIA

The availability of tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib and nilotinib, which inhibit the molecular processes driving chronic myeloid leukemia (CML), revolutionized the management of this disease. Imatinib mesylate was the first TKI introduced into clinical practice in 1998. It is clear from the evidence available that imatinib has advantages over IFNα, the previous best treatment for chronic-phase CML, such as reduced toxicity, more rapid hematological response, higher rate of cytogenetic response and oral administration. However, about 20% of patients do not achieve optimal response to imatinib treatment and they will need alternative drugs. The availability of second-generation TKIs has provided new therapeutic option for patients with imatinib resistance [35]. Dasatinib and nilotinib belonging to second-generation TKIs have shown promising results in imatinib-resistant or intolerant CML patients. These drugs were approved in the US and the European Union for CML patients resistant or intolerant to imatinib. The presence of T315I mutation of Bcr-Abl kinase still remains the unsolved problem. However, the new molecules with different mode of action have demonstrated activity also in patiets with this highly resistant mutant. Several new compounds have been developed in recent years in an attempt to manage TKI-resistant CML. These comprise third-generation TKIs including ponatinib (AP24534) and danusertib (formerly PHA-739358) [34]. These drugs are active against T315I and all other BCR-ABL mutants and could be the next treatment of choice in CML and other hematological malignancies with Philadelphia-positive chromosome, particularly Ph(+) ALL known for its frequent occurrence of T315I mutation [36]. Danusertib also exhibits inhibitory activity against all known Aurora kinases. Inhibitors of Aurora family of serine-treonine kinases are the promising, new group of molecules effective in CML. One of these molecules, MK0457, has entered the clinical trials and initial reports indicate that this compound could be also active in disease associated with T315I mutation [37]. In addition, omacetaxine, which was developed before imatinib, could be also a useful drug in the treatment of imatinib-resistant CML [38]. Overall, many of new agents, with different mode of action, are in clinical development for CML and are discussed in this issue of the journal [39].

CONCLUSION

It is expected that a better understanding of the molecular pathogenesis of leukemias will contribute to discovery and clinical application of novel drugs that will revolutionize therapeutic strategies and bring renewed hope to leukemia patients. The recent findings in pharmacology, adverse effects, and efficacy of the emerging new treatments will be discussed in this special issue of Current Cancer Drug Targets .

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Received: September 30, 2011 **Accepted: January 13, 2012**