

Novel therapeutic agents in acute myeloid leukemia

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Acute myeloid leukemia (AML) is an intrinsically resistant disease. Prognosis is poor for the majority of AML patients, based on age and/or adverse biologic features. Standard therapy for AML is highly toxic and poorly tolerated, particularly by the group of older patients for whom few useful therapies exist. Allogeneic hematopoietic stem cell transplantation is an important option for patients with high-risk AML during first remission, as well as for any patient in second or subsequent remission. Use of reduced intensity conditioning transplantations has made allogeneic stem cell transplantation available for a wider group of individuals, but the impact of this novel procedure on the natural history of AML is unknown. The major thrust of novel therapeutics in AML is development of so-called targeted therapies, which are based on exploitation of newly understood pathophysiological events critical for leukemogenesis. Such events include unbridled proliferation, failure to differentiate, stromal cell-mediated survival factors, and failure to undergo normal programmed cell death. Therapies developed to deal with these problems include inhibitors of ras physiology and activated tyrosine kinases, such as fms-like tyrosine kinase 3; histone deacetylase inhibitors, and DNA-hypomethylating agents, which promote transcription of silenced genes; angiogenesis inhibitors; and anti-bcl-2 agents, respectively. Challenges in therapeutic development include the likelihood that only a subset of AML patients will respond to any of these therapies, based on the patient's intrinsic pathophysiology as well as the fact that many of these agents will only work in conjunction with chemotherapy or other viable antileukemic therapies. © 2007 International Society for Experimental Hematology. Published by Elsevier Inc.

Acute myeloid leukemia (AML) patients under the age of 60 years usually (70–80%) achieve complete remission with standard chemotherapy, but only 40% of those who achieve remission can expect to enjoy long-term disease-free survival [1]. Results in older adults are even more disappointing, with 20% dying of complications during induction, complete remissions achievable in 40% to 50%, and no more than 10% to 20% of those patients in initial remission living 3 years beyond their diagnosis [2].

AML is a heterogeneous disease. The French-American-British classification system [3], which subdivided AML patients into one of eight categories based on morphological, cytochemical, and immunophenotypic characteristics of the leukemic blasts is being supplanted by recently adopted World Health Organization classification system [4], which attempts to acknowledge the more-recently described cytogenetic abnormalities that can be used to parse patients into those with a favorable, intermediate, or poor

prognosis. AML patients whose blasts contain one of the balanced translocations, i.e., t(8;21), inversion 16, or t(15;17), can expect an approximately 60% cure rate. Those with abnormalities more typical of myelodysplastic syndrome, such as loss of all or part of chromosomes 5, 7, and complex karyotypes, have a dismal outlook [5]. The 70% of patients presenting with normal chromosomes have an intermediate prognosis, with an approximate 40% likelihood of long-term disease-free survival [5]. These results are achieved with a uniform therapeutic approach, except acute promyelocytic leukemia (APML), in which combination therapy with all transretinoic acid and anthracycline-based chemotherapy has led to a high cure rate and obviated the need for stem cell transplantation in most cases [6]. Moreover, the unique activity of such agents as arsenic trioxide [7] and gemtuzumab ozogamicin (GO) [8] in this disease represent specific therapies designed to take advantage of the unique biology of APML. Can similar and specific, at least equally efficacious, therapy be derived for other subtypes of AML?

Based on cloning genes at cytogenetic breakpoints, as well as on disparate biological observations, the pathophysiology of AML may depend on unbridled proliferation of

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the leukemic stem cell, failure to differentiate stromal cell-related survival factors, and/or defects in programmed cell death (apoptosis) [9]. A therapeutic development strategy pertains to each of these issues (Table 1), as well immunotherapeutic approaches and novel chemotherapeutic agents.

Inhibiting proliferation: targeting gain-of-function oncogene mutations

Ras mutations can be found in 10% to 40% of AML cases. Ras activation requires a posttranslational modification step in which a farnesyl lipid moiety is attached to the molecule, allowing activation, thereby suggesting a therapeutic strategy of farnesyl transferase inhibition [10]. A Phase I study with one such agent, tipifarnib, documented activity in advanced AML, albeit without regard to ras mutational status [11]. However, tipifarnib led to a low response rate in an international trial of patients with patients relapsed or refractory AML [12]. Nonetheless, untreated older patients with AML (generally older than 65 years and/or those with adverse prognostic chromosomal abnormalities) responded (10–20% complete response rate) to tipifarnib as a single agent [13]. An ongoing Phase III trial in Europe in which patients older than age 70 years are randomized to receive tipifarnib or supportive care monitors survival as the major endpoint.

Mutations of the proliferation-promoting fms-like tyrosine kinase (FLT3) transmembrane enzyme occur in one of two types: 1) a repeat of 3 to 100 amino acids in the juxtamembrane region (internal tandem duplication in 25% of AML cases) and 2) point mutations in the activation loop (5–10% of AML) [14]. The internal tandem duplication mutations carry an adverse prognostic impact, and parse out poor survival in those patients with normal chromosomes [15]. Both types of mutations of FLT3 confer factor-independent growth in leukemic cell lines [16] and are associated with a fatal murine myeloproliferative syn-

drome in a transplant model [17]. Orally bioavailable drugs that inhibit activated FLT3 specifically kill factor-independent cell lines and can “cure” mice with the model leukemia [18].

Strong preclinical evidence supporting the use of FLT3 inhibitors in mutant FLT3 AML has led to the expected developmental pathway. The oral agents in active trials are MLN518 (Millennium, Cambridge, MA, USA) [19,20], CEP701 (Cephalon, Frazer, PA, USA) [21], and PKC412 (Novartis, East Hanover, NJ, USA) [22].

In Phase II trials in patients with mutant FLT3, AML peripheral blasts counts declined [20–22], but more profound clinical responses were rarely noted. The relative lack of single-agent activity has been attributed to: 1) insufficient inhibitory drug levels; 2) the preeminence of alternate leukemic cell-survival pathways; 3) inherent resistance (either pharmacokinetic or pharmacodynamic) in the marrow stem cell niche; and 4) selection for novel FLT3 mutation that will not allow binding by the drug [23]. FLT3 inhibitors differ according to side-effect profile and spectrum of kinases they inhibit. For example, PKC412 also inhibits the serine-threonine kinase protein kinase C [24].

In part because of the lack of preclinical activity as single agents and because of, albeit sequence-specific, synergy between FLT3 inhibitors and chemotherapy [25], combination trials are now underway. PKC412 was combined with chemotherapy in a nearly completed Phase IB trial. Despite nausea and vomiting at a higher PKC412 dose, 50 mg orally twice daily can be tolerably added to standard induction and postremission chemotherapy [26]. An international Phase III trial of chemotherapy plus or minus PKC412 in newly diagnosed patients is being planned. Chemotherapy plus or minus CEP701 is the design of a trial for patients with mutant FLT3-relapsed AML [27]. Ultimately, it might be optimal to combine inhibitors with rationally targeted biological therapy, such as heat shock protein 90 inhibitors, which can enhance degradation of protooncogene proteins [28].

Table 1. New therapies in acute myeloid leukemia

New chemotherapy regimens
Direct drug-resistance modulation (e.g., cyclosporine A, PSC-833)
Cytokine (e.g., GM-CSF priming)
Antiangiogenic (e.g., PTK787, bevacizumab)
Proapoptotic (e.g., α -bcl-2 antisense)
Cell-signaling modulation
Tyrosine kinase (e.g., FLT3) inhibition
Farnesyl transferase inhibition
Immunotherapeutic
Antibody-based (e.g., gemtuzumab, ozogamicin [α -CD33])
Vaccines
Leukemic cell–dendritic cell fusion
Antigenic peptide (e.g., WT1)
Allogeneic stem cell transplantation, including reduced intensity conditioning

FLT3 = fms-like tyrosine kinase; GM-CSF = granulocyte-macrophage colony-stimulating factor.

Inhibition of drug resistance

So-called multidrug resistance inhibitors have been developed to prevent drug efflux, which can account for the phenomenon of pleiotropic drug resistance. Most trials with multidrug resistance inhibitors in AML have been negative. One reason why the nonimmunosuppressive cyclosporine analog PSC833 did not enhance the effects of chemotherapy could be reliance on alternative resistance mechanisms; but perhaps if used only in those patients whose blasts extrude chemotherapy, a more relevant subset to treat could be defined [29]. A Phase III trial comparing continuous infusion daunorubicin and cytarabine with or without cyclosporin A in relapsed AML documented superior survival in the experimental arm [30] and is being followed up by Southwest Oncology Group Phase III randomized trial in older adults with AML.

While the mechanisms that prevent apoptosis in leukemic cells may be varied, the known overexpression of the antiapoptotic protein bcl-2 has been targeted with oblimersen, an 18-mer antisense oligonucleotide [31]. The Cancer and Leukemia Group B is conducting a prospective randomized Phase III trial of chemotherapy plus or minus this bcl-2 inhibitor in newly diagnosed older adults with AML.

Proangiogenic cytokines are released by marrow stromal cells, such as fibroblasts, monocytes, and endothelial cells and can also mediate chemotherapy resistance. Inhibition of the vascular endothelial growth factor receptor pathway with drugs such as PTK787 and bevacizumab is currently being evaluated both alone and with chemotherapy [32]. Cytokinetic resistance is defined as failure of the leukemic stem cell to enter the cell cycle. Myeloid growth factor pretreatment can sensitize leukemic cells by promoting entry into the cell cycle. Most studies have not shown a value to such priming “strategies,” yet a recent trial in younger adults with AML did suggest a benefit for pretreatment with granulocyte colony-stimulating factor [33].

Immunotherapy

The antibody-toxin conjugate GO (Mylotarg, Wyeth Pharmaceuticals, Madison, NJ, USA) was approved for use as a single agent in (non-APML) AML based on activity (30% response rate) in relapsed CD33⁺ AML [34]. CD33 is expressed by normal myeloid stem cells, explaining the myelosuppressive nature of GO, which is also hepatotoxic, particularly if used close to allogeneic bone marrow transplant [35]. A Phase III trial comparing chemotherapy with or without the addition of the nonconjugated anti-CD33 antibody HM195 in relapsed AML was negative [36].

Another immunotherapeutic approach is the strategy of making the leukemic cell more visible to the immune system. One can vaccinate with antigenic leukemic peptides [37] or fuse of leukemic cells with antigen-presenting cells [38]. Moreover, studies have demonstrated the feasibility and potentially beneficial effect of nonmyeloablative transplants, which depend on the “graft vs leukemia effect” [39].

Chemotherapy

New chemotherapeutic drugs, such as cloretazine (an alkylating agent) [40], and the novel nucleoside analogs troxycitabine [41] and clofarabine [42] are being tested. Clofarabine has been approved for use in relapsed pediatric acute lymphoblastic leukemia and has activity in AML. It is a challenge to prove that any of these drugs will be superior to existing agents that are associated with a relatively high response rate.

Summary

Novel therapies capitalizing on newly identified targets, such as mutant FLT3, are in active development. However,

AML is an uncommon disease and many of these drugs must be used in combination with other agents. Nonetheless, if such challenges can be overcome, a new generation of less toxic and more specific anti-AML therapy will be at hand.

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