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Older and new purine nucleoside analogs for patients with acute leukemias

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ABSTRACT

Purine nucleoside analogs (PNAs) compose a class of cytotoxic drugs that have played an important role in the treatment of hematological neoplasms, especially lymphoid and myeloid malignancies. All PNA drugs have a chemical structure similar to adenosine or guanosine, and they have similar mechanisms of action. They have many intracellular targets: they act as antimetabolites, competing with natural nucleosides during DNA or RNA synthesis, and as inhibitors of key cell enzymes. In contrast to other antineoplastic drugs, PNAs act cytotoxically, both in the mitotic and quiescent cell cycle phases. In the last few years, three PNAs have been approved for the treatment of lymphoid malignancies and other hematological disorders: 2-chlorodeoxyadenosine (2-CdA), fludarabine and pentostatin. 2-CdA and fludarabine are also active in the treatment of acute myeloid leukemia (AML). These drugs, in combination with cytarabine and other agents, are commonly used as salvage regimens in relapsed or refractory AML. Moreover, the addition of 2-CdA to the standard induction regimen is associated with an increased rate of complete remission and improved survival of adult patients with AML. More recently three novel PNAs have been synthesized and introduced into clinical trials: clofarabine, nelarabine and forodesine. Clofarabine is the most promising PNA in current clinical trials in pediatric and adult patients with acute leukemias. Nelarabine is more cytotoxic in T-lineage than in B-lineage leukemias. Clofarabine and nelarabine have been approved for the treatment of refractory patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma. Clofarabine is also an active drug in AML treatment when administered either alone or in combination regimens as front-line treatment and in relapsed or refractory patients. Unlike other PNA, forodesine is not incorporated into DNA but displays a highly selective purine nucleoside phosphorylase inhibitory action. Forodesine is undergoing clinical trials for the treatment of T-cell malignancies, including T-cell ALL. This article summarizes recent achievements in the mechanism of action, pharmacological properties and clinical activity and toxicity of PNAs, as well as their emerging role in lymphoid and myeloid acute leukemias.

Introduction

Acute leukemia is a clonal disease characterized by the proliferation and accumulation of myeloid or lymphoid progenitor cells in the bone marrow, leading to hematopoietic failure. Acute myeloid leukemia (AML) is the most common type of leukemia in adults, yet continues to have the lowest survival rate.[1] Although AML accounts for approximately 25% of all leukemias in adults in the Western world it comprises only 15–20% of cases in patients aged <15 years.[2] In the US, 47,150 projected new cases of leukemia were reported in 2012, of which 13,780 were examples of AML and 6050 with acute lymphoblastic leukemia (ALL).[3] AML is a heterogeneous disease with a variable response to therapy. The standard treatment for AML is remission induction chemotherapy with an anthracycline/cytarabine combination, followed by either consolidation chemotherapy or allogeneic stem cell transplantation.[4,5] Despite substantial progress in the treatment of newly diagnosed AML, 20–40% of patients do not achieve remission with standard induction chemotherapy and 50–70% of first CR patients are expected to relapse over 3 years.

Acute lymphoblastic leukemia is the most common malignant disease in childhood and accounts for only approximately 20% of acute leukemias in adults.[6] In contrast to AML, ALL remains a rare disorder in the elderly. In the developed countries, the peak incidence of ALL is in young children aged 2–4 years, but in adults the incidence is approximately 1 per 100,000, and has remained constant over all age ranges in subsequent decades.[7] With present chemotherapy protocols, up to 90% of children with ALL and about 60–85% of adults will achieve a CR, but only 50–70% of children and 20–30% of adult patients will be cured.[8,9]

Purine nucleoside analogs (PNAs), such as fludarabine, cladribine (2-CdA) and pentostatin, have been approved for the treatment of hematological malignancies (Fig. 1). These drugs have a chemical structure similar to adenosine or deoxyadenosine and a similar mechanism of action, such as inhibition of DNA synthesis,

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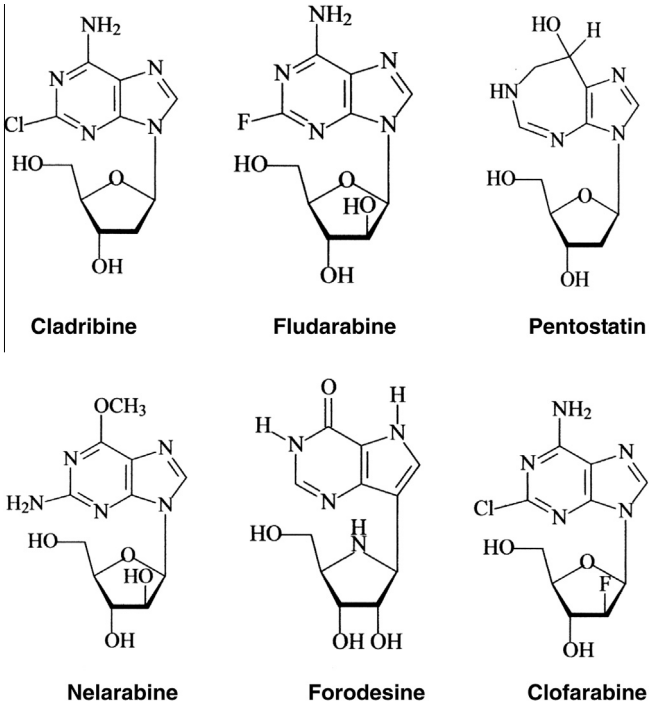

Fig. 1. Chemical structure of purine nucleoside analogs, useful in hematological malignancies.

inhibition of DNA repair and accumulation of DNA strand breaks.[10–12] In addition, PNAs induce apoptosis which is the endpoint of their action. PNAs compete with physiologic nucleosides, and, consequently, interact with a large number of intracellular targets, inducing cytotoxicity.[13] These compounds act as antimetabolites, competing with natural nucleosides during DNA or RNA synthesis and as inhibitors of key cell enzymes.[12,14] However, these agents also exhibit significant differences, especially in their interactions with enzymes involved in purine metabolism activity. Fludarabine and 2-CdA are useful drugs for therapy of indolent lymphoid malignancies and acute leukemias.[15,16] In contrast, pentostatin has not been used in the induction or consolidation of remission in patients with acute leukemias.

Recently three novel second-generation purine nucleoside analogs, clofarabine, nelarabine and forodesine, have been synthesized and introduced into preclinical studies and clinical trials (Fig. 1).[17] These agents have demonstrated promising activity in patients with acute leukemias.

This review article summarizes the mechanism of action and clinical activity and toxicity of PNAs in acute leukemias – AML and ALL. A literature review was conducted of the MEDLINE database PubMed for articles in English. Publications from 1980 through January 2013 were scrutinized. The search terms used were pentostatin, cladribine, 2-chloro-2′-deoxyadenosine, 2-CdA, fludarabine, clofarabine, nelarabine and forodesine in conjunction with acute myeloid leukemia and acute lymphoblastic leukemia. Conference proceedings from the previous 5 years of The American Society of Hematology, The European Hematology Association, and American Society of Clinical Oncology were searched manually. Additional relevant publications were obtained by reviewing the references from the selected articles.

Fludarabine

Fludarabine is a purine analog highly effective in the treatment of CLL and other indolent lymphoid malignancies. The limited solubility of fludarabine and difficulties in its formulation led to the synthesis of the fludarabine prodrug – fludarabine 5′-monophosphate (FA-MP), which is commercially available. After the uptake into the cells, fludarabine must be converted by deoxycytidine kinase (dCK) or deoxyguanine kinase (dGK) into its triphosphate form, which is the active metabolite required for its cytotoxicity.[18] FA-MP was converted to fludarabine by an apparent first-pass metabolism within five minutes after rapid intravenous (i.v.) infusion, and a linear relationship between the dose of FA-MP and fludarabine concentration was observed.[19,20] Fludarabine is usually administered at a dose of 25 mg/m2/day in a 30 min infusion or i.v. bolus injection for 3–5 days, and the courses are repeated every 3–5 weeks.[21–23]

Fludarabine used as a single agent and in combination with other drugs has some activity in patients with AML (Table 1).[24–47] However, although fludarabine demonstrates some activity in AML when used alone in higher doses, the severe toxicity seen at doses producing responses was not acceptable.[24] Subsequently, a combination of fludarabine and cytarabine (Ara-C) was investigated in refractory or relapsed AML in several trials (Table 1). The CR rate with this regimen was from 36% to 44%, and median CR duration from 39 weeks to 4.7 months. Recently, Ferrara et al. evaluated the efficacy and toxicity of fludarabine and Ara-C given as sequential continuous infusion in 64 untreated elderly AML patients aged >60 years, in which AML was diagnosed after MDS.[27] Overall, 43 (67%) of the patients achieved a CR and 11 patients (17%) were refractory to induction treatment. Median disease free survival (DFS) was 10 months and OS was 9. A combination of fludarabine and Ara-C was more effective in AML patients with good or intermediate-risk karyotype. A combination of fludarabine, Ara-C and granulocyte-colony stimulating factor (G-CSF) (FLAG) is also an active regimen in refractory/relapsed AML with CR rates between 30–81%.[29–34] Promising results have been published using fludarabine-containing combination therapy for AML, most commonly FLAG, FLAG + mitoxantrone (FLANG), or FLAG + idarubicin (FLAG-I). The FLAG regimen was also combined with idarubicin (FLAG-I). This programme induced CR rates from 50% to 70%, although with substantial myelotoxicity.[35–40] More recently, Kim et al. performed a Phase II trial to evaluate the efficacy and safety of the modified fludarabine, Ara-C, and attenuated-dose idarubicin (m-FLAI) regimen in 108 previously untreated AML patients aged 60 years and older.[38] The patients received two consecutive cycles of m-FLAI induction chemotherapy consisting of fludarabine at a dose of 25 mg/m^2 on days 1–4, Ara-C at a dose of 1000 mg/m^2 on days 1–4, and attenuated-dose idarubicin at a dose of 5 mg/m^2 on days 1–3. Complete response was observed in 56.5% of patients, and the treatment related mortality (TRM) rate was 21.3%. Median OS was 10.2 and median evidence free survival (EFS) was 6.6 months. These results indicate that m-FLAI is an effective induction regimen for previously untreated older AML patients.

In elderly patients with AML, FLAG combined with non-pegylated liposomal formulations of doxorubicin (Myocet™) showed a promising efficacy response with acceptable toxicity. Melillo et al. evaluated the efficacy and safety of this regimen in 35 elderly patients with median age 69 years (range 61–83 years).[41] Nineteen patients had newly-diagnosed AML, 12 patients had secondary AML and 4 patients had a late relapsed AML. Complete remission was observed in 22 (63%) and PR was obtained in 3 (8.5%) patients. The median OS was 12 months with a median disease free survival (DFS) of 20 months. One-year and two-year DFS were 78.9% and 26.7%, respectively. Fludarabine was also assesed in combination with liposomal daunorubicin (DNR) and Ara-C (FLAD regimen) in 42 patients with poor-risk AML.[42] The CR rate was above 60% for both previously untreated or relapsed AML patients. Fludarabine combined with carboplatin and topotecan was tested in refractory or relapsed leukemia patients. In a phase I study, 31 patients (28 with AML) received fludarabine and carboplatin, followed by