Pharmacological and Clinical Studies on Purine Nucleoside Analogs- New Anticancer Agents

E. Lech-Maranda, A. Korycka and T. Robak*

Department of Hematology, Medical University of Lodz and Copernicus Memorial Hospital, 93-513 Lodz, Pabianicka 62, Poland

Abstract: More recently, three novel purine nucleoside analogs, including clofarabine, nelarabine and immucillin H, have been introduced into clinical trials. These agents have different metabolic properties, novel mechanism of action, and are undergoing phase I-II clinical studies for the treatment of hematopoietic malignancies. Pharmacology and anticancer activity of PNA are the subjects of this review.

Keywords: Cladribine, fludarabine, pentostatin, clofarabine, nelarabine, immucillin H.

INTRODUCTION

The purine nucleoside analogs (PNA) are an important class of drugs that are used in the treatment of cancer, especially hematopoietic malignancies [1]. Three PNA, fludarabine (9-β-D-arabinosyl-2-fluoroadenine, FA), pentostatin (2'-deoxycoformycin, DCF) and cladribine (2-chlorodeoxyadenosine, 2-CdA) were approved for clinical use in 1991 and 1992 (Fig. **1**). These drugs have chemical structure similar to adenosine (Ado) or deoxyadenosine (dAdo) and are made up a purine base (e.g. adenine), which is linked to a deoxyribose sugar through a glycosidic bond [2, 3]. Deactivation of PNA occurs through deamination by adenosine deaminase (ADA) and by cleavage of the glycosidic bond by the bacterial enzyme purine nucleoside phosphorylase (PNP). PNA block nucleotide metabolism by incorporation into DNA and inhibition of ribonucleotide reductase (RR) [4]. All PNA share many other similar characteristics such as transportation into the cells and phosphorylation by deoxycytidine kinase (dCK), deoxyguanosine kinase (dGK) and dephosphorylation by 5'-nucleotidase (5'-NT) [5]. However, these agents have different activity against hematological malignancies. Although PNA could be successfully used in monotherapy, several studies proved that the combination of PNA with other cytotoxic drugs or monoclonal antibodies (MoAbs) may be more effective [6].

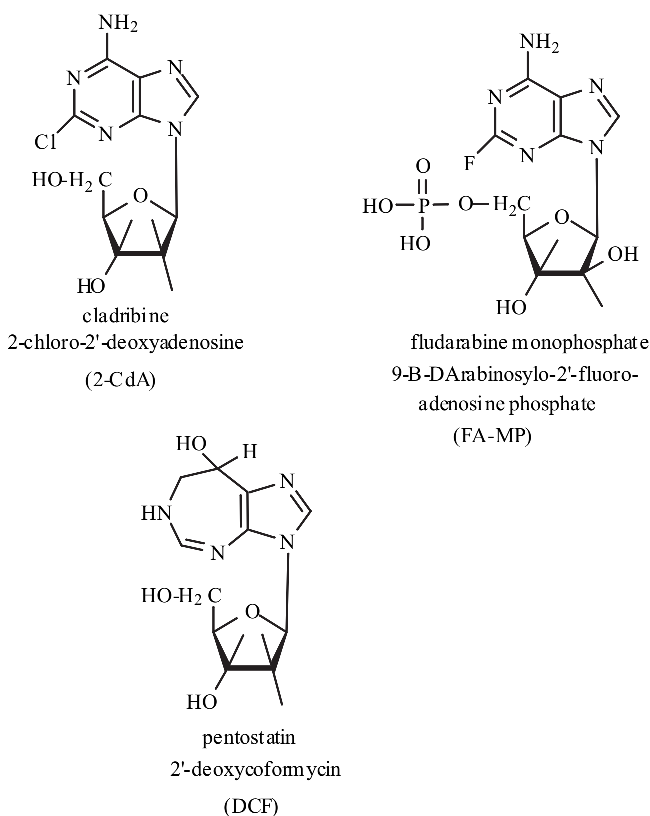

Fig. (1). Chemical structure of cladribine, fludarabine monophosphate and pentostatin.

More recently, a novel group of PNA has been developed. These agents, including clofarabine, nelarabine and immucillin H (Fig. **2**), have different metabolic properties and novel mechanism of action. Currently there are three PNA that are being, or will be evaluated in the clinic for anticancer activity [2].

In this paper, we summarise the current knowledge about mechanism of action, pharmacokinetics and possible therapeutic activity of new PNA in different malignancies.

Clofarabine

Clofarabine (2-chloro-2'-arabino-fluoro-2'-deoxyadenosine; CAFdA) is a next generation of deoxyadenosine analogs that was synthesized as a rational extension of the experience with FA and 2-CdA. Its structure differs from that of 2-CdA in that it contains a fluorine atom at the 2'-position in the deoxyribose [7, 8]. This structural difference significantly increases the stability of the glycosidic bond, resulting in enhanced acid stability of the compound, and makes it a poor substrate for PNP. These structural properties of CAFdA increase its oral bioavailability [9, 10].

Mechanism of Action

Clofarabine, similarly to other PNA, is phosphorylated to the monophosphate form by dCK and this reaction is

*Address correspondence to this author at the Department of Hematology, Medical University of Lodz and Copernicus Memorial Hospital, 93-513 Lodz, Pabianicka 62, Poland; Tel: +48 42689 5191; Fax: +48 426895192; E-mail: robaktad@csk.umed.lodz.pl

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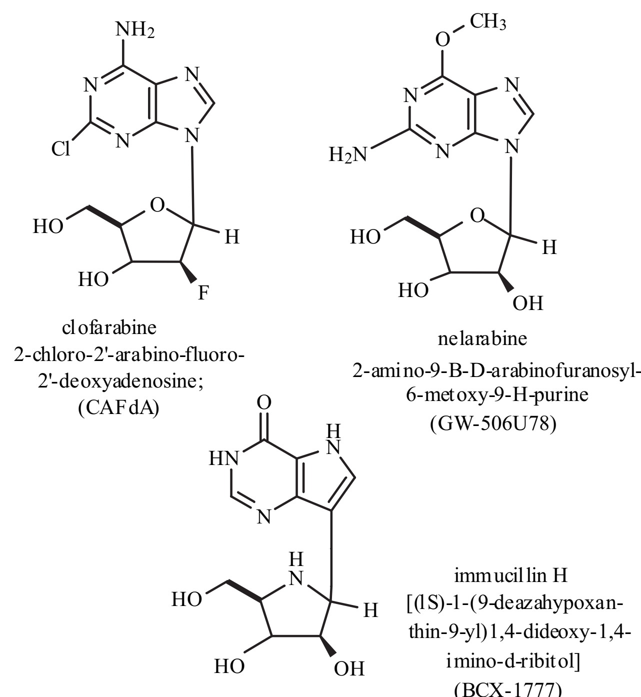

Fig. (2). Chemical structure of clofarabine, nelarabine and Immucillin H.

necessary for its cytotoxic activity. The monophosphate is the major metabolite of CAFdA and serves as a depot for active triphosphate form (CAFdA-TP) [11, 12]. CAFdA seems to be a more efficient substrate for dCK than other PNA [13]. Additionally, CAFdA is intracellularly phosphorylated not only by dCK, but also by mitochondrial dGK [14]. CAFdA-TP is slowly eliminated from the cells and its retention is longer than 2-chlorodeoxyadenosine triphosphate (2-CdA-TP) or fludarabine triphosphate (FA-TP). The mechanism of action of CAFdA is complex and comprises inhibition of DNA polymerases and RR as well as induction of apoptosis [7, 15]. It has been reported that CAFdA is a potent inhibitor of DNA polymerases α and ε that are involved in nuclear DNA replication. DNA polymerases β (involved in DNA repair process) and γ (mitochondrial) are much less sensitive to CAFdA [16]. Despite the fact that 2-CdA and FA are structurally similar to CAFdA, differences in clinical response observed between their triphosphates may be explained by different influence on enzymes. CAFdA combines the features of 2-CdA and FA since FA-TP primarily inhibits DNA polimerases, 2-CdA-TP particularly inhibits RR, whereas CAFdA-TP has the favorable properties of both agents with regard to inhibition of each enzyme [16, 17]. The influence of CAFdA on apoptosis process appears through induction of DNA strand breaks and disruption of mitochondrial integrity, resulting in the release of proapoptotic proteins [18, 19].

Pharmacokinetics and Administration

The phase I clinical studies were performed in adult and pediatric patients with acute leukemias, chronic lymphoproliferative disorders (LPDs), and solid tumors to evaluate dose-limiting toxicities (DLT) and the maximum tolerated doses (MTD) [15, 20-22]. CAFdA was given as 1-hour infusion daily for 5 days, every 3 to 6 weeks. Dose-escalation studies in acute leukemias started at 7.5mg/m^2, with escalation to 55mg/m^2 daily for 5 days. The DLT was reversible hepatotoxicity at 55mg/m^2, therefore, the recommended dose for phase II studies was 40mg/m^2 in patients with acute leukemias, myelodysplastic syndrome (MDS) and chronic myeloid leukemia in blast phase (CML-BP) [15, 20, 21]. In patients with LPDs and solid tumors, the DLT was myelosuppression at the dose of 15mg/m^2. Therefore, CAFdA at the doses of 2mg/m^2 or 4mg/m^2 daily for 5 days were recommended for phase II clinical trials in these patients [20]. The phase I study conducted in pediatric patients with refractory or relapsed leukemia, led to the recommendation of CAFdA at a dose of 52mg/m^2 intravenously (iv) over 2 hours for 5 consecutive days. The DLT was reversible hepatotoxicity and skin rash at 70mg/m^2 daily for 5 days [22].

During the phase I studies plasma and cellular pharmacology assessments were performed. The peak levels of CAFdA in plasma occurred at the end of the infusion and a linear increase between plasma concentration and increasing dose of CAFdA was observed [15]. A dose-proportional accumulation of intracellular CAFdA-TP and its prolonged retention in blast cells, irrespective of lymphoid or myeloid lineage, were shown. In blast cells of responding patients, the accumulation of CAFdA-TP retained more than 50% of the initial concentration of CAFdA-TP at 24 hours after the first infusion of CAFdA. This slow elimination of triphosphate forms of this drug was not observed for other PNA [15].

Clinical Trials

CAFdA is the most promising PNA in current clinical trials in leukemias as well as in solid tumors (Table **1**). This agent has established single-agent antileukemic activity at tolerable doses for the treatment of relapsed ALL in pediatric patients.

Acute Leukemias and Myelodysplastic Syndromes (MDS)

The phase II study with CAFdA was performed in 62 patients with relapsed or refractory acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), CML-BP and MDS. In all patients, the overall response (OR) rate was 48%, however, it differed by diagnosis, salvage status, and duration of first remission. The OR rate was 55% in AML, 50% in MDS, 58% in CML-BP, and 16% in ALL patients. The most frequently observed adverse events included hepatotoxicity, skin rashes and mucositis [23].

The combined phase I and II study was performed in 29 adults AML and high-risk MDS patients using the combination of clofarabine and cytarabine (Ara-C). CAFdA was given at a dose of 40mg/m^2 on days 2-6 and Ara-C at a dose of 1g/m^2 iv on days 1-5. The OR rate was 41% with the median remission duration of 3,2 months (range, 0.5-14 months). The median overall survival (OS) time for responders was 8 months (range, 2-8 months) [24].

The phase II trial was conducted with CAFdA as first line treatment in 28 elderly patients (> 70 years) with AML

Table 1. Activity of Clofarabine in Hematologic Malignancies and Solid Tumors

Study	Treatment schedule	Patients characteristics	No of pts	OR rate (%)	Comments
Kantarjian *et al.* 2003 [20] Phase I	Clofarabine 2mg/m^2 daily for 5 days	Solid tumors patients CLL, NHL patients	13 6	No objective response	Optimal dose schedule needs to be defined
Kantarjian *et al.* 2003 [23] Phase II	Clofarabine 40mg/ m^2 daily for 5 days. Cycles every 3-6 weeks.	Adult patients with relapsed/refractory hematologic malignancies - AML - MDS - ALL - CML-BP	31 8 12 11	55 50 16 58	Hepatotoxicity, skin rashes and mucositis were the most frequently side effects.
Burnett *et al.* 2004 [*1] Phase II	Clofarabine 30mg/m^2 daily for 5 days. Cycles every 4 weeks.	Elderly patients (> 70 years) with newly diagnosed AML	28	68	CR rate was 59%.
Jeha *et al.* 2004 [*4] Phase II	Clofarabine 52mg/m^2 daily for 5 days. Cycles every 2-6 weeks.	Children with relapsed/refractory acute leukemias -AML - ALL	35 49	26 31	The median OS was 39 weeks for AML and 42 weeks for ALL responders.
Faderl *et al.* 2004 [*3] Phase II	Clofarabine 40mg/m^2 on days 2-6 and Ara-C 1g/m^2 on days 1-5	Newly diagnosed patients (> 50 years) with AML and high-risk MDS	60	60	CR rate was 60% in the group of patients with diploid karyotype as compared to 43% in the abnormal karyotype group
Faderl *et al.* 2005 [24] Phase I/II	Clofarabine 40mg/m^2 on days 2-6 and Ara-C 1g/m^2 on days 1-5	Adult patients with relapsed/refractory AML and high-risk MDS	29	41	The median OS was 8 months for responders.

Abbreviations: OR- overall response, CR – complete response, OS-overall survival, AML –acute myelogenous leukaemia, ALL – acute lymhoblastic leukaemia, MDS – myelodysplastic syndrome, CML-BP- chronic myeloid leukemia in blast phase, CLL- chronic lymphocytic leukemia, NHL- non Hodgkin's lymphoma, Ara-C- cytarabine.

who were not suitable for intensive chemotherapy. CAFdA was used at a dose of 30mg/m^2 iv daily for 5 days every 4 weeks[*1]. Since the high CR rate of 59% was observed, this study encouraged for the initiation of the randomized study with CAFdA at the same schedule with or without low-dose of Ara-C (20mg/m^2 subcutaneously daily for 7 to 14 days). It has been reported that a trend for better response rates with the combination of these drugs is present[*2].

Another phase II study, with combination of CAFdA and Ara-C, was performed in older (>50 years) patients with AML and high-risk MDS as the frontline treatment. The complete response (CR) rate was 52% in all 60 patients, however the CR rate was 60% for the subgroup of patients with diploid karyotype as compared to 43% in the abnormal karyotype group[*3].

In the pediatric phase II study, CAFdA was given at a dose of 52mg/m^2 daily for 5 days every 2-6 weeks to children with relapsed or refractory acute leukemias. The OR rate was 26% in AML and 31% in ALL patients. The median OS time was 42 weeks (range, 7.0-63.1 weeks) and 39 weeks (range, 7.7-93.6 weeks) for ALL and AML responders, respectively[*4]. CAFdA has been approved by the U.S. Food and Drug Administration in December 2004 as treatment for children with relapsed ALL who have received at least two prior regimes [7].

LPDs and Solid Tumors

Experience with CAFdA in patients with LPDs and solid tumors is limited [5]. In the phase I trial in patients with CLL and non-Hodgkin's lymphoma (NHL), a significant myelosuppression was observed which led to the decreasing of CAFdA dose to 2mg/m^2 daily for 5 days. The evidence of its activity, including decrease in lymphadenopathy and peripheral lymphocytosis, was seen in these patients even at low doses of CAFdA, however, no objective response was observed [20]. The role of CAFdA and its optimal dose schedule in LPDs and solid tumors patients needs to be defined [7].

Nelarabine

Nelarabine (2-amino-9-β-D-arabinofuranosyl-6-metoxy-9-*H*-purine) is a water-soluble prodrug of guanine nucleoside analog, 9-β-D-arabinosylguanine (Ara-G) [25]. However, Ara-G was synthesized in 1964 but has not been in clinical use because of its poor solubility properties [26, 27]. Therefore, nelarabine, the 6-methoxy derivative of Ara-G, has been synthesized enzymatically from diaminopurine arabinoside, and is 10 times more soluble than Ara-G [25, 28].

Mechanism of Action

The demethoxylation of nelarabine by ADA converts it to biologically active Ara-G [25]. Nelarabine is a poor substrate for ADA, having a substrate efficiency of less than 1% of that of Ado, however, the high specific activity of ADA in the red blood cells (RBCs) and body organs, resulted in rapid demethoxylation to Ara-G after iv

administration of nelarabine [25, 29]. Afterwards, Ara-G is transported into T- cells via nitrobenzylthioinosine-sensitive and -insensitive equilibrative nucleoside transporters (NT) [30]. The rate-limiting step in the formation of active Ara-GTP is the phosphorylation of Ara-G to monophosphate form (Ara-GMP) [31]. This phosphorylation is catalyzed *in vitro* by high-affinity, low specific activity mitochondrial deoxyguanosine kinase (dGK) and low-affinity, high specific activity cytosolic dCK [25]. dGK activity is found in the most of mitochondria-rich tissue [32], however the specific activity of dGK is lower than that of dCK [33, 34]. The accumulation of Ara-GTP is augmented when either specific activity of dCK or dGK is increased. Interestingly, at low concentrations of Ara-G, dGK is the preferred enzyme, but at high concentration of the substrate dCK phosphorylates more efficiently [34]. The Ara-GTP competes with native deoxynucleotides as a substrate for incorporation into DNA by DNA polymerases [31, 35]. It results in inhibition of DNA synthesis and the initiation of apoptosis [36].

Ara-G is selectively toxic to mature T-cells [37, 38] and immature T-lymphoblasts as compared with B-lymphoblasts, null-cells or myeloid human leukemia cell lines which are resistant to Ara-G [39-42]. The differential accumulation of Ara-GTP in these cells seems to be responsible for T-cell selective cytotoxicity of Ara-G [39, 41-43]. Moreover, the recent *in vitro* studies revealed that high Ara-GTP accumulation in T cells and its incorporation into replicating DNA initiates S phase-specific apoptosis. The signal for apoptosis may be also augmented by cytosolic concentration of Ara-GTP by binding to apoptosome complexes. Ara-G is also able to induce apoptosis in T cells by involvement of Fas/FasL system resulting in release of soluble FasL (sFasL) and triggering death receptor-mediated cell death in the bystander cells. In contrast, myeloid and B-cells accumulated lower levels of Ara-GTP and arrested in S phase, blocking any apoptotic signaling [44]. The concentration of Ara-GTP in leukemic cells is reported to correlate with clinical response. The patients who achieved complete or partial remission after nelarabine treatment accumulated significantly higher levels of Ara-GTP compared with patients who failed to respond [45].

Pharmacokinetics and Administration

The limited-center phase I clinical study was conducted to assess the MTD, toxicity profile, and pharmacokinetics in 93 pediatric and adult patients with refractory hematologic malignancies. Nelarabine was given as 1 hour iv infusion daily for 5 consecutive days in cycles of every 21-28 days . The MTD was 40mg/kg for 5 days in adults and 60 mg/kg for 5 days in children. DLT was mainly neurological, and affected both central and peripheral nervous system usually occurring within the first week after the course of therapy. Myelosuppression and other significant non-hematological toxicity did not occur. [46].

Pharmacokinetics of nelarabine was evaluated in 71 of the 93 patients on the first day of therapy. The mean half-life ($T_{1/2}$) of nelarabine in pediatric and adult patients was 14.1 min. and 16.5 min., respectively. The maximum concentration (C_{max}) of Ara-G occurred at the end of the 1-hour infusion of nelarabine. The C_{max} of Ara-G ranged from 11.6 μmol/L to 308.7 μmol/L at nelarabine doses of 5 to 75 mg/kg and was linearly related to the dose. The pharmacokinetic parameter estimates of Ara-G between patients with different diagnoses were similar. The clearance of Ara-G was higher in pediatric patients as compared with adults, however, it may be associated with age-related differences in renal function [27].

Clinical Observations

Nelarabine is a potent agent for treatment of hematological malignancies with major efficacy in T-cell disorders (Table **2**). Kurtzberg *et al* [46] reported the clinical outcome of pediatric and adults patients with refractory hematological malignancies treated with nelarabine. The OR rate was 31%, however this rate was 54% in the subgroups of patients with T-cell ALL who achieved a complete or partial response after one or two cycles of nelarabine. Additionally, accumulation of Ara-GTP in leukemic blasts was correlated, as reported before [45], with cytotoxic activity of the drug.

A phase II trial in 106 pediatric patients with relapsed or refractory T-cell malignancies revealed the activity of nelarabine with an objective response rate of more than 50% in patients with first bone marrow relapse. The initial nelarabine dose was 1.2 g/m^2 daily for 5 consecutive days every 21 days. The most significant side effects of nelarabine were neurological complications [47].

In a pilot trial, a combination of nelarabine and FA was evaluated in 13 patients with a variety of refractory hematological malignancies. Nine patients had indolent leukemias, including six whose disease failed prior FA therapy, 2 patients had T-ALL, one had CML, and one had mycosis fungoides. Nelarabine was infused on days 1, 3 and 5 at a dose of 1.2g/m^2. On day 3 and 5, fludarabine at a dose 30 mg/m^2 was administered 4 hours before the nelarabine infusion. Seven patients (54%) responded to this combination regimen achieving a partial or complete response. The median peak of intracellular Ara-GTP concentration was significantly higher in responders compared with nonresponders. Additionally, among six patients who were refractory to PNA (2-CdA or FA), four had remission and one achieved stable disease. This result may suggest the utility of nelarabine in diseases refractory to other PNA [29].

Immucillin-H

Immucillin H ((1S)-1,4-dideoxy-1-C-(4-hydroxypyrolo [3,2-d]pyrimidin-7-yl)-1,4-imino-D-ribitol hydrochloride, BCX-1777, forodesine) is a potent inhibitor of human, rat, monkey, dog and mouse purine nucleoside phosphorylase (PNP) [48].

Mechanism of Action

PNP is an important enzyme in the salvage of PNA and catalyzes the reversible phosphorolysis of N-ribosidic bonds of both purine nucleosides and deoxynucleosides, except Ado, generating purine base and ribose (or deoxyribose) 1-phosphate [49]. The major physiological substrates for mammalian PNP are inosine, guanosine, and 2'-

Table 2. Clinical Trials with Nelarabine in Hematologic Malignancies

Study	Treatment schedule	Patients characteristics	No of pts	OR rate (%)	Comments
Kurtzberg *et al.* 2005 [46] Phase I/II	Nelarabine 60mg/kg in children and 40mg/kg in adults daily for 5 days in 1-hour infusion . Cycles every 21-28 days	Pediatric and adult patients with refractory hematologic malignancies (B-cell, T-cell, myeloid)	93	31	OR rate was 54% in patients with T-ALL
Berg *et al.* 2005 [47] Phase II	Nelarabine 1.2g/m^2 (as an initial dose) daily for 5 days in 1-hour infusion.	Pediatric patients with relapsed/refractory T-cell malignancies (ALL, NHL) - 1st relapse - ≥ 2nd repalse - CSF relapse - extramedullary relapse	 33 30 21 22	 55 27 33 14	The study of Children's Oncology Group
Gandhi *et al.* 2001 [29] Pilot study	Nelarabine 1.2g/m^2 on days 1, 3, and 5 + FA 30mg/m^2 on days 3 and 5	Adult patients with refractory hematologic malignancies	13	54	Among 6 patients who were refractory to PNA, 4 had an objective response and 1 achieved stable disease.

Abbreviations: OR- overall response, ALL – acute lymhoblastic leukaemia, NHL- non Hodgkin's lymphoma, FA- fludarabine, PNA- purine nucleoside analogs,

deoxyguanosine [50]. Several cases of a rare genetic deficiency of this enzyme have been reported in children [51]. The PNP-deficient patients exhibit profound T-cell depletion and significant cellular immunodeficiency. DNA synthesis of B-cells and nonlymphoid cells remained normal in these patients suggesting that PNP activity may be required for normal human T-cell proliferation [51-53]. This observation led to the development of PNP inhibitors that could be useful in the treatment of T-cell proliferative disorders [54].

Several agents have been reported to inhibit PNP activity, however pharmacokinetic studies have demonstrated that greater than 95% continuous inhibition of PNP is required for significant reduction in T cell function [55]. Schramm's *et al* [50] used the special approach for designing more potent PNP inhibitors by identification of the transition-state structure stabilized by the target enzyme [48, 50]. Using inosine as a substrate for transition-state analysis, 9-deazanucleoside analogs (immucillins) were designed to mimic the transition-state [56]. Two immucillins, immucillin H and immucillin G, have a carbon-carbon linkage between a cyclic amine moiety that replaces ribose, and 9-deaza-hypoxanthine or 9-deaza-guanine, respectively [56, 57]. *In vitro* studies using cell lines established that in the presence of deoxyguanosine (dGuo), immucillin H selectively inhibited the growth of malignant T-cells [58] and activated human lymphocytes [59]. Immucillin H is 100-to 1000-fold more potent than other known PNP inhibitors [58, 60]. PNP inhibition results in accumulation of inosine, guanosine, 2'-deoxyinosine and 2'-dGuo nucleoside levels in plasma and urine [54]. The intracellular accumulation of dGuo inhibits T-cell proliferation, while the other nucleosides do not [61]. Afterwards, the dGuo is phosphorylated by dCK to dGTP that accumulates and inhibits RR, thus preventing the conversion of ribonucleoside diphosphates to corresponding deoxyribonucleoside diphosphates. Depletion of deoxyribonucleosides results in the inhibition of cellular DNA synthesis and cells replication [53].

Pharmacokinetics and Administration

In *in vitro* studies, immucillin-H inhibits the proliferation of T-ALL cells with an IC_{50} of 0.015µM. The proliferation inhibition correlates with dGTP levels in the cells. In the presence of BCX-1777 and dGuo, a 154-fold higher accumulation of dGTP is observed in T-ALL cells compared with a 15-fold accumulation in human lymphocytes. In addition, the $T_{1/2}$ of dGTP in T-ALL cells was 18 h, which is longer than that observed in human lymphocytes (4 h). These results suggest that the low nucleotide levels and high dCK level in T-ALL cells make them more sensitive than human lymphocytes to inhibition by BCX-1777 [58].

In murine models, the IC_{50} value for BCX-1777 ranges from 0.48 to 1.57nM. The bioavailability after oral administration of BCX-1777 in mice is 63%. At a single dose of 10mg/kg in mice, immucillin-H increased of dGuo accumulation to approximately 5µM [59].

In vivo studies in primates revealed that oral and iv administration of immucillin-H induces a rapid elevation of plasma 2'-dGuo and that oral dosing at 8.8 and 17.6 mg/kg are at least equivalent to 4.4 mg/kg iv twice daily in effecting 2'-dGuo accumulation. Increasing the iv dose of immucillin-H did not increase dGuo accumulation, however plasma dGuo concentration remained longer elevated. In contrast, the oral dose increasing resulted in elevated plasma dGuo accumulation [54].

A phase I clinical trial performed by Gandhi *et al* [57], was designed to determine the MTD of immucillin-H and correlate the drug pharmacodynamics to the administered dose. Five patients with relapsed or refractory T-cell lymphoblastic lymphoma, acute leukemia and T-cell prolymphocytic leukemia were treated with immucillin-H at

a dose of 40 mg/m^2 over 30 minutes of iv infusion on the first day. The treatment was continued for days 2-5 at the same dose administered twice daily. Cycles were repeated every 21-28 days. Median peak level of immucillin-H (5.4μM) was achieved at the end of the infusion. This concentration was sufficient to elevate plasma dGuo accumulation. The intracellular dGTP levels increased by 2 to 40-fold in 4 of 5 patients, and were correlated with antileukemic activity of the drug in these patients. In this study no objective responses to immucillin-H were observed.

Clinical Observations

Immucillin-H is undergoing phase II clinical trials for treatment of T-cell NHL, which includes cutaneous T-cell lymphoma (CTCL) [2]. However, the results are not available yet.

CONCLUSIONS

Currently used purine nucleoside analogs, FA, 2-CdA and DCF, represent a group of cytotoxic agents with established activity in indolent lymphoid and myeloid malignancies. These three agents share similar structure and mechanism of cytotoxic action. More recently, a novel group of PNA, including CAFdA, nelarabine and immucillin, H, has been developed. These agents have novel metabolic properties as well as mechanism of action, and are under investigation in clinical trials. CAFdA is the most promising PNA in current clinical development. This agent has single-agent antileukemic activity as treatment for children with relapsed ALL who have received at least two prior regimes.

ACKNOWLEGEMENTS

This work was supported in part by the grants from Medical University of Lodz, Poland (No 503-193-1) and by Foundation for Development of Diagnostics and Therapy, Warsaw, Poland.

ABBREVIATIONS

2-CdA	=	2-chlorodeoxyadenosine; cladribine
5'-NT	=	5'-nucleotidase
Ado	=	Adenosine
ALL	=	Acute lymphoblastic leukemia
AML	=	Acute myelogenous leukemia
Ara-C	=	Arabinoside cytosine; cytarabine
Ara-G	=	9-β-D-arabinosylguanine
ATP	=	Adenosine triphosphate
BCX-1777	=	Immucillin H
CAFdA	=	2-chloro-2'-arabino-fluoro-2'-deoxyadenosine; clofarabine
CLL	=	Chronic lymphocytic leukemia
CML	=	Chronic myelogenous leukemia
CML-BC	=	Blast crisis of CML
CR	=	Complete response
CTCL	=	Cutaneous T-cell lymphoma
dAdo	=	Deoxyadenosine
DCF	=	2'-deoxycoformycin; pentostatin
dCK	=	Deoxycytidine kinase
dGK	=	Deoxyguanosine kinase
dGuo	=	2'-deoxyguanosine
DLT	=	Dose limiting toxicity
FA	=	9-β-D-arabinosyl-2-fluoroadenine; fludarabine
FA-MP	=	Fludarabine monophosphate, soluble form of fludarabine
i.v	=	Intravenously
MDS	=	Myelodysplastic syndrome
MTD	=	Maximum tolerated dose
NHL	=	Non-Hodgkin's Lymphoma
NT	=	Nucleoside transporters
OR	=	Overall response
OS	=	Overall survival
PNA	=	Purine nucleoside analogs
PNA-TP	=	Triphosphate forms of purine nucleoside analogs
PNP	=	Purine nucleoside phosphorylase
PR	=	Partial response
RR	=	Ribonucleotide reductase

FOOTNOTES

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Received: September 17, 2005 Revised: October 21, 2005 Accepted: October 22, 2005

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