REVIEW ARTICLE

Purine Nucleoside Analogs: Emerging Roles in Indolent Lymphoproliferative Disorders

By Martin S. Tallman and David Hakimian

RECENTLY, a great deal of interest has been generated in three new purine nucleoside analogs because of their remarkable activity in a variety of incurable malignant lymphoproliferative disorders. 2-Fluoro-ara-AMP (fludarabine), 2-deoxycoformycin (2-DCF, pentostatin), and 2-chlorodeoxyadenosine (2-CdA) are all structurally similar analogs of adenosine, but they differ in their interaction with adenosine deaminase (ADA) (Fig 1). This enzyme normally regulates intracellular adenosine levels through the irreversible deamination of adenosine to inosine and thereby serves to degrade purine and deoxypurine nucleotides. The development of these drugs resulted from the systematic search for compounds that could interfere with ADA activity. This enzyme became a specific target because of the observation that approximately 30% of children with severe combined immunodeficiency syndrome (SCIDS) are congenitally deficient in ADA. 

The unique observation that the nucleoside analogs are effective against common and generally incurable malignancies is a luxury not often afforded the clinical hematologist/oncologist. Furthermore, each has now been approved by the Food and Drug Administration for clinical use. Therefore, another mechanism of action has been implicated. The intracellular accumulation of deoxyadenosine triphosphates affects both dividing and nondividing cells.

MECHANISMS OF ACTION

2-DCF

2-DCF is an irreversible inhibitor of ADA (Fig 2). As a result of the high ratio of the phosphorylating enzyme deoxyxycytidine kinase (dCK) to the dephosphorylating enzyme 5-nucleotidase in lymphocytes, adenosine and deoxyadenosine are converted to triphosphate metabolites. The accumulation of these metabolites inhibits ribonucleotide reductase, which in turn inhibits DNA synthesis. This is believed to be the mechanism of action of 2-DCF in dividing cells.

In contrast to 2-DCF, fludarabine and 2-CdA do not inhibit ADA, but rather are resistant to the enzyme. Similar to other nucleoside analogs, fludarabine must be phosphorylated to be active. Fludarabine is initially phosphorylated by DCK intracellularly to 2-fluoroadenosine-arabinoside monophosphate (2-fluoro-ara-AMP). 2-Fluoro-ara-AMP is sequentially phosphorylated first to the diphosphate by adenylic kinase, then to the active metabolite 2-fluoroadenosine arabinoside triphosphate (2-fluoro-ara-ATP) by nucleoside diphosphate kinase, which inhibits DNA synthesis by interfering with two enzymes, DNA polymerase and ribonucleotide reductase. 2-Fluoro-ara-ATP directly competes with dATP required by DNA polymerases.

The incorporation of 2-fluoro-ara-AMP acts as a DNA chain terminator. Similarly, 2-CdA is phosphorylated by DCK, resulting in an intracellular accumulation of 2-chlorodeoxyadenosine triphosphate, which inhibits ribonucleotide reductase. Unlike conventional chemotherapy, which affects dividing cells, the purine nucleosides affect both dividing and nondividing cells.

The unique observation that the nucleoside analogs are effective against nondividing cells has not been completely explained, particularly in view of the fact that very little ribonucleotide reductase is present in resting cells. Therefore, another mechanism of action has been implicated. The intracellular accumulation of deoxyadenosine triphosphates after administration of these three drugs also causes DNA strand breaks which activate two enzymes, a Ca2+/Mg2+-dependent endonuclease (itself producing further double-strand DNA breaks), and a poly-(ADP-ribose)polymerase that consumes nicotinamide adenosine dinucleotides (NAD) and ATP. The consumption of these vital cofactors together with inhibition of the polymerase prevents DNA repair. Oligonucleosomal fragments result, which are the hallmark of apoptosis or programmed cell death.

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PHARMACOKINETICS/PHARMACOLOGY

Fludarabine

The parent drug fludarabine, 2-fluoro-ara-AMP, is converted to 2-fluoro-ara-A by an apparent first-pass metabolism within minutes after rapid intravenous infusion (Table 1). Plasma concentrations of 2-fluoro-ara-A have been best fitted to a three-compartment open model. The mean apparent volume of distribution (Vdr) is 62.28 ± 16.88 L/m², and the mean steady-state volume of distribution (Vdss) is 44.17 ± 10.82 L/m². These data indicate extensive tissue binding, because Vdr is greater than Vdss. Urinary excretion appears to be the primary means of elimination as approximately 60% of 2-fluoro-ara-A is present in the urine within 24 hours of administration. Furthermore, total body clearance (67.98 mL/min/m² ± 19.58) correlates well with creatinine clearance, suggesting renal excretion as well. The drug is administered most commonly as a short daily intravenous (IV) infusion for 5 days every 21 days. Oral bioavailability has recently been studied and is approximately 75% of the IV dose with a similar terminal half-life.

2-DCF

Plasma concentration of 2-DCF is best fitted to a two-compartment open model. The rapid disposition phase is short, with a mean T½α of 8.72 to 60 minutes, followed by a terminal phase (T½β) of 4.93 to 10 hours. The mean apparent Vdr is 23.1 ± 6.16 L/m², and the mean Vdss is 20.0 ± 5.01 L/m². The similarity of these values suggests that extensive tissue binding does not occur. Peak cerebral spinal fluid levels of approximately one tenth of simultaneous plasma levels have been shown in monkeys and in a single human patient. Mean urinary excretion of 2-DCF is 95.9% ± 12.2% of the administered dose, suggesting that DCF is not converted to a metabolite and that renal excretion is a primary method of elimination. Total body clearance is 52.4 ± 16 mL/min/m² and correlates with creatinine clearance, confirming renal excretion of the drug. In an early dose-seeking study, Grever et al. established that a dose of 4 mg/m² inhibited ADA and induced responses in lymphoid malignancies. This dose administered IV every 2 weeks is the schedule frequently used.

2-CdA

Plasma concentrations of 2-CdA can be fitted into either a two- or three-compartment model. A two-compartment...
2-CdA IN LYMPHOPROLIFERATIVE DISORDERS

Table 1. Comparison of Pharmacokinetic Properties of the Newer Purine Analogs

<table>
<thead>
<tr>
<th>Property</th>
<th>Fludarabine</th>
<th>2-DCF</th>
<th>2-CdA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose/schedule</td>
<td>25 mg/m² IV bolus daily for 5 d every 21 d</td>
<td>4 mg/m² IV every 2 wks</td>
<td>0.09-0.1 mg/kg continuous IV infusion daily for 7 d or 0.14 mg/kg daily as a 2-h bolus for 5 d</td>
</tr>
<tr>
<td>Peak plasma drug concentration</td>
<td>1.4-2.2 µmol/L, undetectable at 4 min</td>
<td>1 µmol/L decreasing to 6-30 nmol/L in 2 h</td>
<td>1.98 nmol/L</td>
</tr>
<tr>
<td>Terminal elimination half-life</td>
<td>10.41 h</td>
<td>4.93-10 h</td>
<td>6.7 ± 2.5 h</td>
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<tr>
<td>Mean volume of distribution</td>
<td>62.28 ± 16.88 L/m²</td>
<td>23.1 ± 6.16 L/m²</td>
<td>9.2 ± 5.4 L/kg</td>
</tr>
<tr>
<td>Mean steady-state volume of distribution</td>
<td>44.17 ± 10.82 L/m²</td>
<td>20.0 ± 5.01 L/m²</td>
<td>22.52</td>
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<tr>
<td>Primary means of elimination</td>
<td>Urinary</td>
<td>Urinary</td>
<td>Urinary</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>75%</td>
<td>NA</td>
<td>50%</td>
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</table>

Abbreviation: NA, not available.

The model shows a $T_{1/2\alpha}$ of 35 ± 12 minutes and a $T_{1/2\beta}$ of 6.7 ± 2.5 hours. The Vdr is 9.2 ± 5.4 L/kg. Urinary excretion appears the primary means of elimination. 2-CdA penetrates the cerebrospinal fluid and achieves concentrations approximately one fourth those of the plasma. In phase I trials, 2-CdA was administered by continuous IV infusion for 7 days, establishing the maximum tolerated dose of 0.1 mg/kg/d. Because there was a long-terminal half-life, it was suggested that 2-CdA could be administered intermittently rather than by continuous infusion without loss of efficacy. Indeed, Lilisemark and Juliusson showed that the area under the concentration-time curves (AUC) is similar for both 2-hour bolus and continuous infusion. Recently, these same investigators have shown that the drug can be administered subcutaneously or orally with a bioavailability of 100% and 50%, respectively. Compared with a 2-hour bolus IV infusion, similar AUCs of 2-CdA are obtained when the drug is administered orally at a dose of 0.28 mg/kg/d or by subcutaneous injection at a dose of 0.14 mg/kg/d.

**ANALYSIS OF CLINICAL TRIAL DATA**

Multiple phase II studies have shown significant activity of fludarabine, 2-DCF, and 2-CdA in the treatment of a variety of indolent B-cell lymphoproliferative disorders, including hairy cell leukemia (HCL), chronic lymphocytic leukemia (CLL), low-grade non-Hodgkin's lymphomas (NHL), Waldenström's macroglobulinemia, and cutaneous T-cell lymphomas (CTCL). Despite their similar chemical structures, emerging clinical data suggest that certain nucleoside analogs have greater activity in some diseases than others. The most encouraging results with the nucleoside analogs have been achieved in patients with HCL.

**HCL**

**2-DCF.** 2-DCF was the first agent to produce complete and durable remissions in patients with HCL (Table 2). Several studies using various dosing schedules have been published. High complete remission (CR) rates of 64% to

Table 2. Activity of Nucleoside Analogs in HCL

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. Patients</th>
<th>Prior Therapy</th>
<th>Complete (%)</th>
<th>Partial (%)</th>
<th>None (%)</th>
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<td><strong>DCF</strong></td>
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<td>Cassileth et al[21]</td>
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<td>18</td>
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<td>Ho et al[25]</td>
<td>33</td>
<td>30</td>
<td>11 (33)</td>
<td>15 (45)</td>
<td>4 (13)†</td>
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<td>23‡</td>
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<td>85</td>
<td>36 (42)</td>
<td>35 (42)</td>
<td>14 (15)§</td>
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<td>12</td>
<td>29 (78)</td>
<td>8 (22)</td>
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<td>Kantarjian et al[33]</td>
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<td>0</td>
<td>2 (66)</td>
<td>1 (33)</td>
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<td>Kraut and Chun[34]</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1 (100)</td>
<td>0</td>
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</tbody>
</table>

* Includes 1 patient with minor response.
† Reported as stable disease (3 additional patients had early deaths).
‡ 23/159. 159 patients includes 8 variants (3 died of infection).
§ Includes 8 patients with stable disease, 3 patients who had early deaths, and 2 not evaluable.
pressed. The other common side effect is fever, generally occurring 5 to 7 days after therapy, which seems to be noninfectious in etiology and has been attributed to cytokine release from lysed hairy cells. Third, most patients achieving PR have complete resolution of profound peripheral cytopenias, but have either a small amount of residual hairy cells in the marrow or minimal residual splenomegaly. Fourth, durable CRs are achieved in the majority of patients with only a single cycle of the drug, an observation unprecedented in the treatment of malignant disease.

Although the CR rate appears to be comparable with 2-DCF and 2-CdA, the short treatment course, the ease of administration, and lack of side effects suggest that 2-CdA has emerged as the treatment of choice for all patients with this disease. However, an important question remains: Will the prolonged remissions achieved with 2-CdA or 2-DCF translate into cures? Emerging data suggest that, although high CR rates are attained and disease-free survival is prolonged with purine analogs compared to IFN, the disease is not completely eradicated. In one of the most mature series evaluating 2-CdA, the actuarial disease-free survival rate is 77% at a median of 30 months after treatment. In this cohort of 40 patients, 8 patients (20%) have relapsed at a median of 16 months (range, 3 to 23 months). In the recently updated series by Kraut et al evaluating 2-DCF, 11 of 23 patients (48%) have relapsed at a median of 30 months (range, 7 to 80 months). Furthermore, minimal residual HCL can be identified in the marrow of patients in apparent CR. Thaler et al identified minimal residual hairy cells by immunostains in four patients, of whom two were in apparent marrow remission after treatment with 2-DCF. Similarly, studies of marrows from patients have suggested that nonspecific immunostains can detect occult disease in some patients after 2-CdA. The analysis of the degree of minimal residual disease after 2-DCF has not been as extensive as that undertaken for patients after 2-CdA. Recently, Fillleul et al showed that each of seven evaluable patients in CR by conventional morphology showed evidence of minimal residual disease by polymerase chain reaction (PCR) and clonogenic probes derived from the hypervariable region of the Ig heavy chain genes. Although there are insufficient data at present to determine whether residual HCL identified by any of these techniques will predict relapse, a preliminary study suggests that detection of residual disease by immunostaining may, in fact, correlate with morphologic relapse. However, because HCL is often particularly indolent, the clinical relapse rate will remain the most important measure of the impact of both 2-DCF and 2-CdA.

Fludarabine. Fludarabine also has activity in patients with HCL. In two brief reports, three of four patients treated achieved PRs with multiple cycles of therapy. Despite its activity in this disease, fludarabine is unlikely to have any role, given the success of both 2-CdA and 2-DCF.

CLL

Fludarabine. Although all three of the nucleoside analogs have activity in patients with advanced, previously treated CLL, the largest experience has been with fludarabine (Table 3). Grever et al treated 21 heavily pretreated patients with 20 mg/m² daily for 5 days at monthly intervals.
A single patient attained CR, and 3 (14%) achieved PR. Myelosuppression was the major toxicity. In the largest published series, the overall response rate in previously treated patients given a more standard dose of 25 to 30 mg/m² daily for 5 days is 58%, with 30 of 78 patients (38%) attaining CR. In previously untreated patients in this same series, the overall response rate was 80%, with 40 of 50 patients (80%) attaining CR. In this study, 4% of patients who had either failed or had progressive disease after an initial response to alkylating agents achieved a CR and 40% achieved a PR. However, the median duration of response was only 4 months. Of the 50 patients who were categorized as nonresponders, 27 (54%) showed a sustained reduction of greater than 50% in the absolute lymphocyte count despite the lack of improvement in the hemoglobin concentration or the platelet count.

Puccio et al administered fludarabine as a single bolus infusion of 20 mg/m² on day 1, followed by a daily dose of 30 mg/m² as a continuous infusion for 48 hours at 4-week intervals. The response rate was considerably lower; however, such results are difficult to interpret given the alternative schedule and the lower dose intensity of the drug.

The major toxicity in all studies has been infection related to both myelosuppression and immunosuppression. In Keating’s study, pneumonia and fever of unknown origin were the most frequent cause of febrile episodes. Sepsis occurred in four patients, dermatomal herpes zoster in five patients, and minor infections involving the oropharynx, sinuses, urinary tract, and soft tissues also were seen.

2-CdA. Four series of patients with previously treated CLL have been reported with variable response rates. The largest series has been the experience of Saven et al. In this study, 4% of patients who had either failed or had progressive disease after an initial response to alkylating agents achieved a CR and 40% achieved a PR. However, the median duration of response was only 4 months. Of the 50 patients who were categorized as nonresponders, 27 (54%) showed a sustained reduction of greater than 50% in the absolute lymphocyte count despite the lack of improvement in the hemoglobin concentration or the platelet count.
overall response rate of 67%. The differences in response rates between the latter study and that of Saven et al may be explained by several factors, including the small size of the study, the administration of more cycles of drug, and a less heavily pretreated population.

At Northwestern University (Chicago, IL), response rates are similar to those reported by Saven et al. Twenty-six patients with refractory and relapsed B-cell CLL were treated and, although none achieved CR, eight (31%) achieved PR. The actuarial median time to progression was 16 months. Patients who received multiple prior regimens, including fludarabine, were less likely to respond, and there was significant morbidity and mortality in this population of heavily pretreated patients.

Recently, O’Brien et al reported a series of 28 patients, all of whom had previously received alkylating agents and were subsequently refractory to fludarabine. These investigators found that such patients are unlikely to benefit from 2-CdA because only 2 patients (7%) achieved PRs and no CRs were attained. Furthermore, 8 patients died within 60 days due to infections.

Because 2-CdA has activity in patients with advanced disease, it is anticipated that significantly better response rates will occur in previously untreated patients. Indeed, three preliminary studies have reported markedly higher response rates of 2-CdA in this patient population.

2-DCF. Although 2-DCF has activity in patients with CLL, the response rates appear to be less than those seen with fludarabine. In the largest study, 36 evaluable patients were treated with 2-DCF at a dose of 4 mg/m² three times a week and then every other week. Among a group of 26 patients who had received prior therapy, only 1 achieved a CR and 3 achieved a PR. These results are particularly disappointing in view of the fact that eligibility required exposure to only one prior regimen. There were two infectious deaths during the first 8 weeks of therapy. Among a group of 13 previously untreated patients, no patients achieved a CR and 6 patients achieved a PR. The overall response rate was 46%. Dearden and Catovsky treated 17 previously treated patients with advanced disease and observed no CRs and 6 PRs (35%).

Given the results of these phase II studies, fludarabine appears to be the most active agent in CLL; however, there has been no prospective comparison between the nucleoside analogs. Furthermore, few studies have been performed with 2-CdA, and most studies to date have included heavily pretreated patients. Large prospective clinical trials with purine nucleoside analogs given earlier in the natural history of the disease and in previously untreated patients are underway and will help define the role of these agents in the treatment of patients with this common leukemia.

Low-Grade NHL

Fludarabine. In the largest series of patients, Hochster et al treated 27 patients (Table 4). The response rate was 52%, with 5 patients achieving CR and 8 patients achieving PR. The best responses were observed in patients with follicular small cleaved histology. Patients in this study were limited to no more than two prior regimens and therefore may have been less heavily pretreated. Whelan et al reported that among 34 patients with advanced, previously treated NHL, CR was achieved in 6 patients and PR in 7 patients for an overall response rate of 38%. In a smaller study of 13 previously treated patients, no patient achieved CR, and 8 patients (62%) achieved PR. Among 8 previously untreated patients, there were 3 PRs (38%) and 3 CRs (38%). All patients had stage IV disease, and the 3 patients achieving CR remain in remission at 13, 15, and 17 months from treatment. The principal toxicities in these series are hematologic and infectious. The largest series of patients with previously treated lymphoma was reported by Redman et al. Five of 40 patients (13%) achieved CR, and 18 (45%) achieved PR. Infection or fever of undetermined cause were the most common toxicities. No significant neurologic toxicity was observed. In general, no significant nonhematologic toxicity was reported except in the series by Hochster et al in which a 10% incidence of neurologic toxicity was observed.

2-CdA. 2-CdA appears to have similar efficacy to fludarabine in patients with previously treated NHL. There have been four small series of patients reported. The largest series has been reported by Kay et al, in which 40 patients were studied. Eight patients (20%) achieved CR and 9 (23%) achieved PR, for an overall response rate of 43%. The patient population was heavily pretreated with a median of three prior treatment regimens (range one to six). The duration of responses ranged from 1 to 33+ months, with a median duration of 5 months. Toxicity was limited to myelosuppression, with 18% of patients developing neutropenia and 30% developing thrombocytopenia. In a series of 21 relapsed or refractory patients, 9 (43%) responded, with 3 (13%) achieving CR and 6 (29%) achieving PR. Thirty-two percent of patients experienced at least one episode of neutropenic fever and 6 patients (29%) died of infection. Two patients developed Pneumocystis carinii pneumonia; however, both were treated with 2-CdA immediately after failing to respond to another nucleoside analog. Finally, Betticher et al reported the results of 16 patients who had either refractory disease (6 patients) or relapsed disease (10 patients) and found that 3 patients achieved CR and 9 patients achieved PR, for an overall response rate of 75%.

In a preliminary study, Emanuele et al reported the results of 2-CdA in 26 evaluable patients with previously untreated indolent NHL and observed CR in 9 (35%) and PR in 14 (54%). The median duration of remission was 9 months (range, 2+ to 36 months), and the major toxicity was myelosuppression.

2-DCF. Studies of 2-DCF in indolent NHLs are limited. Duggan et al reported that 7 of 24 patients with relapsed or refractory disease responded, for an overall response rate of 29%. Three of five patients with small lymphocytic cell lymphoma responded. Toxicity was generally mild and included leukopenia or thrombocytopenia and some serious infections, but there were no treatment-related deaths. The Eastern Cooperative Oncology Group reported 2 CRs (8%) and 2 PRs (8%) among 12 patients with low-grade lymphoma.

Waldenström’s Macroglobulinemia

Fludarabine. Only a single report exploring the activity of fludarabine in patients with Waldenström’s macroglobu-
linemia has been published (Table 5). In this study, 5 of 11 patients (45%) responded, with a greater than 50% reduction in the IgM, with a projected median duration of response of longer than 1 year. The tempo of response was slow, as evidenced by a median of 5.2 months for a 50% reduction in IgM. Toxicity was mild and reversible, including infections in only 3 patients.

2-CdA. Recent reports evaluating 2-CdA in patients with Waldenström’s macroglobulinemia suggest that limited exposure may be important to prevent protracted pancytopenia. Investigators at The M.D. Anderson Cancer Center (Houston, TX) described their initial experience with only two cycles of 2-CdA in 20 patients resistant to alkylating agent-based combination chemotherapy. Forty percent of patients responded, including 3 of 4 patients (75%) who relapsed off therapy, 4 of 9 patients (44%) who were primarily refractory, and 1 of 7 patients (14%) whose disease was refractory at relapse. Subsequently, 26 previously untreated patients were treated. Twenty-two of the 26 patients (85%) responded, including 3 with CRs and 19 with PRs. Responses were rapid and continued even after therapy was stopped.

The median time for 50% reduction in the IgM paraprotein was 1.2 months. Despite the limited exposure, CD4 lymphocyte counts were markedly depressed for a sustained period of time. Delannoy et al treated 18 patients, of whom 13 had been previously treated (9 refractory, 4 untreated relapse), and 5 were previously untreated. PR was achieved in 7 patients (39%), 2 previously untreated and 5 previously treated. No CRs were observed. Hematologic toxicity was more severe than that reported in the series by Dimopoulos et al. The median nadir neutrophil and platelet counts were $0.6 \times 10^9/L$ and $65.5 \times 10^9/L$, respectively in the report by Delannoy et al, compared with $1.5 \times 10^9/L$ and $170 \times 10^9/L$ in the report by Dimopoulos et al.

In this particular disease responses occur slowly and continue to occur long after use of the drug is stopped. Therefore, strategies similar to the approach in HCL, with a limited number of cycles, possibly at longer intervals, may yield the best results with the least toxicity.

2-DCF. Only a single patient with Waldenström’s macroglobulinemia has been reported, and a CR was achieved.

### Table 4. Activity of Nucleoside Analogs in Low-Grade NHL

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<tr>
<th>Reference</th>
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<th>Partial</th>
<th>None</th>
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<td>9 (75)</td>
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<td>Duggan et al</td>
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<td>17 (43)</td>
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</table>

Abbreviation: NA, not available.
* At least 2 patients achieved CR, but complete details of responses not provided.
† Includes 4 patients who died (2 of progressive disease, 1 pulmonary embolus, 1 infection).
‡ Includes 3 patients with minor response.

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Table 6. Activity of Nucleoside Analogs in CTCL

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Prior Therapy</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td>Complete</td>
</tr>
<tr>
<td>DCF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cummings et al.</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Grever et al.</td>
<td>4</td>
<td>4</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Dang-Vu et al.</td>
<td>3</td>
<td>3</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Mercieca et al.</td>
<td>29</td>
<td>NA</td>
<td>3 (10)</td>
</tr>
<tr>
<td>2-CdA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Saven et al.</td>
<td>15</td>
<td>16</td>
<td>3 (20)</td>
</tr>
<tr>
<td>O’Brien et al.</td>
<td>11</td>
<td>11</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Kuzel et al.</td>
<td>21</td>
<td>21</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Fludarabine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Von Hoff et al.</td>
<td>31</td>
<td>31</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.
* Includes 10 patients with clinical improvement, 2 with stable disease, 9 with progressive disease, 2 inadequate evaluation, and 2 early death.

CTCL

2-DCF. The earliest experience with purine analogs in CTCL was with 2-DCF (Table 6). Several studies with small numbers of patients treated at doses ranging from 4 to 10 mg/m²/d for 3 days have been conducted in advanced mycosis fungoides or Sezary syndrome.18,22-26 Overall response rates of 33% to 67% have been reported with CR rates of 10% to 50%. Several CRs of 7 to 9 months have been reported. Toxicities have included renal failure, myelosuppression, and neurotoxicity. In the largest series published, Mercieca et al. reported 3 (19%) CRs and 7 (44%) PRs among 16 patients with Sezary syndrome, with a median duration of response of 9 months (range, 3 to 66), but no responses among 5 patients with mycosis fungoides.

2-DCF (4 mg/m² for 3 days) has been combined with intermittent high-dose IFN in 41 patients with advanced or refractory mycosis fungoides or Sezary syndrome. A response rate of 41% (2 CR, 15 PR) was reported with a median time to progression of 13.1 months.26 Seven patients had reversible grade 3 mentation changes.

Fludarabine. Von Hoff et al. treated 33 patients, both with prior systemic therapy (poor risk) and without prior systemic therapy (good risk), with fludarabine at doses of 25 mg/m²/d for 5 days (good risk) or 18 mg/m²/d for 5 days (poor risk) and observed 1 CR and 5 PRs. Myelosuppression was the major toxicity.

Fludarabine also has been combined with IFN (5 million units/m² three times per week) in a single phase II trial of 35 patients, and a response rate of 51% was observed with 4 (11%) CRs and 14 (40%) PRs.44 In this study, the median time to progression was 5 to 8 months; however, 3 of the 4 CRs were of considerable duration (18+, 20+, and 35+ months). One episode of reversible neurotoxicity occurred, manifested by seizures and hemiparesis attributable to a diffuse demyelinating process.

2-CdA. Three trials of patients with CTCL treated with 2-CdA have been reported, with promising results.33,35,36,37 Saven et al. treated 15 patients with previously treated CTCL and observed a 47% response rate. Three of the eight patients (38%) with mycosis fungoides or Sezary syndrome responded. O’Brien et al. treated 11 patients classified as mycosis fungoides or Sezary syndrome, and only 2 (18%) responded. At Northwestern University, 19 patients with previously treated CTCL have been reported.97 Three CRs (16%) and three PRs (16%) were observed with a median duration of response of 4 months. The major toxicity was myelosuppression, particularly thrombocytopenia, which was pronounced in patients with extensive prior therapy and among those receiving multiple cycles.

Multiple Myeloma

2-DcF. Two small studies exploring the activity of 2-DcF in patients with advanced myeloma have been published.98,99 Four of seven patients (57%) had an objective response in a study by Belch et al.98 Two patients had a greater than 50% decrease in the level of monoclonal protein of 7 and 10 months’ duration and improvement in bone pain, and two other patients showed reduction in soft tissue masses, but no reduction in the monoclonal protein. In contrast, Grever et al. observed no responses among 14 patients with previously treated myeloma.

2-CdA. Several reports, including small numbers of patients, indicate that the experience with 2-CdA in myeloma has been disappointing.100 Further study will be required to determine whether or not activity of the drug is shown when larger numbers of previously untreated patients are treated, when high doses are administered, or when combinations with other active agents are explored.

Fludarabine. Fludarabine has also shown no activity in patients with previously treated myeloma.102

IMMUNOSUPPRESSION

The degree of immunosuppression induced by the purine nucleoside analogs has important implications with respect to both opportunistic infections and potential secondary malignancies. The CD4 and CD8 lymphocyte counts decrease significantly after 2-DCF and 2-CdA and often for a prolonged period of time.45,86,103,104 Recovery of CD4+ T cells is slow, and the count remains significantly lower than baseline at a median of 23 months after a single cycle of 2-CdA for HCL.45 The median time for the CD4+ lymphocyte count to recover to normal in this population is 40 months. In contrast, natural killer (NK) cell activity may increase after treatment.106 Patients receiving fludarabine also have prolonged decreased CD4+ and CD8+ cells.57 Depletion of these cells likely contributes to a variety of opportunistic infections that have been reported, particularly when the nucleoside analogs are administered with prednisone or after another nucleoside analog.42,43,46,107 However, no direct correlation has been reported between the CD4 level and the incidence of infection.
CROSS-RESISTANCE

Because the structures of the nucleoside analogs are similar and they are all active in patients with lymphoproliferative disorders, it is important to determine the degree, if any, of cross-resistance between them. This is particularly important for patients with CLL who have received fludarabine and are being considered for treatment with 2-CdA.

Few data have been published regarding the issue of cross-resistance. Among 5 patients with HCL who were either resistant to (3 patients) or were intolerant of (2 patients) 2-DCF, 4 patients achieved a CR with 2-CdA with a median follow-up of more than 11 months. Larger numbers of patients with HCL who are truly refractory to therapy with 2-DCF will be needed to determine if they will respond to 2-CdA. Because the durable CR rate with 2-CdA or 2-DCF is so high, this issue may never be resolved.

In a recent report of only four patients, Jüliusson et al. suggested that patients who fail fludarabine may respond to 2-CdA. However, the aggregate experience reported suggests otherwise. Investigators at the Scripps Clinic (La Jolla, CA) reported that none of 14 such patients responded. Similarly, investigators at The M.D. Anderson Cancer Center reported only 2 responses among 28 patients who had failed to respond to fludarabine. Among a total of 52 patients in the United States previously treated with fludarabine, only 3 (6%) have responded. However, it is unclear whether fludarabine failure itself predicts cross-resistance to 2-CdA. Because fludarabine has generally been reserved for treatment of refractory patients, the lack of response to 2-CdA may be attributable to the extensive prior drug exposure and refractory status of this population rather than to prior fludarabine exposure. This issue can only be clarified by assessing the response of 2-CdA in patients who have been previously treated only with fludarabine. This may be possible because more patients now receive fludarabine as their first treatment.

NEUROLOGIC TOXICITY

The neurologic toxicity of the purine nucleoside analogs has recently been extensively reviewed. Neurologic toxicity with all three purine analogs has been reported at higher-than-usual doses. However, at the doses of 2-CdA and 2-DCF currently used, neurologic toxicity has been uncommon. Reports of neurotoxicity with fludarabine appear to be slightly more common but usually mild and reversible. Fludarabine has been more extensively evaluated than 2-CdA or 2-DCF. It is possible that a similar incidence of neurotoxicity may emerge as 2-CdA is more commonly used.

FUTURE DIRECTIONS

The purine analogs represent a major opportunity to improve the lives of patients with incurable malignancies. Despite their structural similarity, one or another of these agents appears to be more active in a particular disease. Cross-resistance, an issue of particular interest in CLL and HCL, has not been definitively established and will require further study. Opportunistic infections due to immunosuppression are emerging as an important toxicity that warrants further attention and evaluation. In addition, neurotoxicity appears to be a unique extramedullary toxicity that is generally mild and reversible. As these agents are more commonly used, the significance of these toxicities will be better defined.

FUTURE DIRECTIONS

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ACKNOWLEDGMENT

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REFERENCES

2-CDA in LYMPHOPROLIFERATIVE DISORDERS


Purine nucleoside analogs: emerging roles in indolent lymphoproliferative disorders [published erratum appears in Blood 1996 Mar 1;87(5):2093]

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