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Use of selected purine analogs in neoplastic and autoimmune diseases

Zastosowanie analogów nukleozydów purynowych w chorobach nowotworowych i autoimmunologicznych

INTRODUCTION

Synthetic Purine Nucleoside Analogs (PNAs) are derivatives of purines and their nucleotides in which the structure of the heterocyclic ring or the sugar molecule is modified in order to obtain the specific therapeutic action. PNAs are a group of cytotoxic compounds with strong action used in the treatment of neoplastic and autoimmune diseases. After intravenous introduction of PNAs to the body, these compounds diffuse into the cells through the cell membrane and they are phosphorylated to the mono-, di- and triphosphate active forms. There are two enzymes which are involved in phosphorylation: deoxycytidine kinase (cDK) and mitochondrial deoxyguanosine kinase (dGK) [46,53,68]. The purine analogs show high affinity for lymphoid cells, which are characterized as presenting high activity of cDK and low concentration of 5'-nucleotidase (5'-NT), the enzyme which is responsible for their dephosphorylation [53]. They work both on proliferating and resting cells, therefore the cytotoxic effect is multidirectional. In dividing cells, the action of PNAs is based mainly on inhibition in synthesis of the deoxynucleotides which play a significant role in DNA replication and repair. Besides the aforementioned, they inhibit the activity of rybonuleotide reductase (RR). RR is an enzyme vital to the speed of the synthesis of diphosphodeoxyribonucleotides (dNDP). Preventing dNDP production interferes with the balance of the nucleotidotriphosphates (dNTP) pool, which activate endonuclease release. Endonucleases lead to cracking in one or both strands of DNA. Such DNA breaks set in motion poly (ADP-ribose) polymerase (PARP-I). When the damage in the structure of the DNA is small, PARP-I participates in their repair and the cell stays alive. Conversely, if extensive DNA damage occurs, intensified remedial mechanisms lead to the exhaustion of the intracellular nicotinamide adenine dinucleoside (NAD) and adenosine triphosphate (ATP) resources. This may lead to cell death by necrosis [68]. Moreover, the synthetic nucleosides during DNA replication can embed to the polynucleotide chain, and this may lead to the interruption of its increase

during DNA synthesis. In this case, the best action is induced by nucleoside analogs which in the rest of the heterocyclic ring do not contain hydroxyl groups (-OH). Compounds presenting such action are used mainly to treat viral infections. Cytotoxicity of PNAs is also connected with breaking the activity of DNA polymerases. This action has a significant impact on the conduct of the replication and DNA repair, as well as the rapidity of genetic information transfer. The action of purine analogs is also based on the induction of apoptosis in target cells. Studies show that programmed cell death may take place both through the activation of the death receptors Fas/CD95 on the extrinsic pathway, but also along the intrinsic pathway involving the mitochondria [67].

In this work, the authors will discuss the selected purine nucleoside analogs: fludarabine (FA, 2-fluoro-9-β-D-arabinozylo-2-fluoroadenine, F-ara-A), cladribine (2-CdA, 2-chloro-2'-deoxyadenosine), pentostatin (DCF, 2'-deoxyformycin) and clofarabine (CAFdA, 2-chloro-9-2'-fluoro-2'-deoxyarabinofuranozyloadenine) and their application in the treatment of neoplastic and autoimmune diseases.

All purine analogs are similar in chemical structure, but fludarabine, cladribine, and clofarabine, in order to obtain biological activity, must be intracellularly phosphorylated, and cytotoxicity depends on the level of their cellular triphosphate form. The presence of a halogen atom, instead of the hydrogen atom, in the adenine ring makes these compounds resistant to hydrolysis by adenosine deaminase (ADA), the enzyme which metabolises purines. Change in the construction of the ring provides increased accumulation of the drug in target cells [53].

FA, 2-CdA and DCF, in the 1990s, were approved by the US Food and Drug Administration (FDA) as a chemotherapeutics used in the therapy of neoplastic diseases within the lymphatic system. They demonstrate a relatively low toxicity in relation to nonlymphatic tissue. PNAs can be used in monotherapy, as well as in conjunction with other cytostatic drugs or together with monoclonal antibodies. Immuno-suppressive properties and reports in the last few years have shown that PNAs may be effective in the therapy of multiple sclerosis, anaemia, rheumatoid arthritis, psoriasis, lupus, refractory autoimmune disorders and after transplantation [53,56,68]. However, despite the continuous progress of knowledge, there are still not enough references and studies carried out as for PNAs in autoimmune diseases [68].

In view of the cytotoxic effects of purine nucleoside analogs, the more frequent adverse reactions in patients using this group of drugs are bone marrow depression and associated implications that extend the thrombocytopenia, neutropenia and anaemia. Besides the previously mentioned effects, PNAs induces a reduction of the level of lymphocytes CD4+ and CD8+, which can persist up to 24 months. The effect of intensified neutropenia and a reduction in the number of T lymphocytes brings about opportunistic infections and infection with pathogens such as Listeria monocytogenes, Pneumocystic carinii, Cytomegalovirus (CMV) and herpes (HSV), mycobacteria and the zoster virus (VZV). In addition, frequently occurring adverse reactions include nausea, vomiting, headache, fever, pruritus, dermatitis and symptomatic hyponatremia via an unknown mechanism [11]. There is also undesirable effect involving the cardiovascular system and the digestive system related to the liver and bile ducts, as well as the urinary system (particularly the kidney and urinary tract) [86]. Therefore, in most cases, during PNAs therapy, it is recommended that doctors use additional drugs in combined therapy, such as antibacterial antiviral, antifungal, analgesics, emetics and painkillers.

Moreover, doctors should also prescribe drugs which protect the stomach, liver and kidney, as well as recommend irrigation and electrolyte replacement [11,68].

In addition, cases have been described in regard to CNS toxicity that reveal rapid vision loss in patients with metastatic melanoma who have been prescribed fludarabine at up 25mg/m^2, as well as at dosages of 30mg/m^2 in patients with lupus erythematosus [7]. Neurotoxicity also is evident if the pentostatin is used in a dosage higher than 4mg/m^2 [79]. Not proven so far explicitly, if fludarabine has induced histologic transformation or therapy-related MDS/AML [52,65].

The cancers of the lymphatic system, in which the purine nucleoside analogs have their application, are mainly leukemias and lymphoma. In these diseases, vesicles are induced due to the uncontrolled expansion of lymphocytes of different stages of maturity. This is often found in the hematic tract and forces out other disordered maturing haematopoietic cells [17]. During the treatment of lymphatic diseases, a variety of substances are used, including cytostatic drugs, monoclonal antibodies, immunotoxins, radiation therapy, as well bone marrow transplant. Currently, most tumor therapy is based on the use of the relevant protocols of treatment, with successive different combination schemes of medicine prescription.

Autoimmune diseases are the result of a specific organism producing an abnormal immune response that is directed against its own host of antigens. The fatal reactions of the organism's own cells occurs within both the cellular and humoral immune response mechanisms. This invalid response may be brought about by autoreactive B or T lymphocytes, which have not been eliminated by the organism's immune tolerance or which have acquired the characteristics of being autoreactive as a result of the interruption of this tolerance, i.e by infection [33]. Currently, there are many treatments for autoimmune diseases, however, in most cases, the first line of therapy are the immunosuppressive drugs. These inactivate the autoreactive lymphocytes or counteract the antibodies already produced. One such mechanism is the induction of lymphocytes apoptosis, through the use of purin nucleoside analogs.

Characteristics of selected purin analogs

Fludarabine

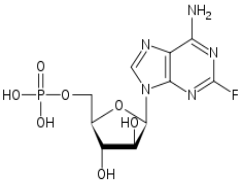

Figure1. Fludarabine (FA, 2-fluoroβ-9-D-arabinozylo-2-fluoroadenine)

Fludarabine (FA) is an analog of adenosine. A change in the construction with substitution of fluorine at 2' position adenine ring makes FA resistant to the action of ADA. Moreover, the limited solubility of FA led to the synthesis of the pro-drug, fludarabine 5'-monophosphate (FA-MP). Fludarabine gets to the destination cells by the way of the participation of the relevant NT, which binds only the dephosphorylated form, so before entering the cells, in plasma, FA-MP is dephosphorylated to the FA [68]. Furthermore, as 2-CdA and CaFdA, FA undergoes intracellular phosphorylation with

the participation of the cDK and becomes the active form of active 2-fluoro-ara-ATP. This active form inhibits DNA polymerases, ribonucleotide reductase, DNA ligases and consequently, the synthesis of DNA. Besides the aforementioned, they inhibit the synthesis of RNA and the synthesis of proteins. As a consequence of this multifaceted action, cellular division is inhibited, and apoptosis in leukemia cells is induced [39,80].

FA-MP is mostly administered in a 30 min infusion or injections, at a dose 25-40mg/m^2 for 3-5 consecutive days, with a 3-5 week rest period. There are other modes of supply of the substance in doses of approximately 90mg/m^2 for 5 to 7 days. However, a dose of approximately 96mg/m^2 induces strong toxicity in the central nervous system [7]. Fludarabine is also available in the form of tablets and by way of this route of administration, the bioavailability is around 50-75%, and its effectiveness remains unchanged [28]. The oral form is easier to use, especially by home-bound patients. Studies show that FA is removed by the kidneys, approximately 60% of the drug is present in the urine after 24 hours of last dose of the substance [68].

Fludarabine as an analog of monophosphate deoxyadenosine is most effective in the treatment of chronic lymphocytic leukemia (CLL), low-grade B-cell lymphoma and non-Hodkin's lymphoma (NHL). It is also used in acute lymphoblastic leukemia of high-risk lymphoplasmacytic lymphoma, and in the conditioning prior to bone marrow transplants. Moreover, Fludarabine is used in monotherapy or in combination with other cytostatic drugs [39,68]. Application of fludarabine with mitoxantrone, cyclophosphamide, Thiotepa, or with cytarabine raises the effect of chemotherapy due to inhibition by FA of DNA repair mechanisms damaged by other medicines [14].

Since the mid 1990s, PNAs have been used in the treatment of CLL with good results [34,67]. Research has shown that the use of fludarabine, like cladribine, in the treatment of CLL, gives better results, compared with the chlorambucil that was in use in earlier years: the total percentage of the response (OR, overall response) being 62% vs. 37%, and the duration of remission is increased from 14 to 25 months. In addition, according to randomized III phase research, fluarabine with cyclophosphamid achieves 95% OR, compared to 84% in the case of PAN monotherapy and complete remission (CR) is at 20.3% vs. 8.6% for patients with CLL in first treatment [83].

In view of the increasing advances made in the application of monoclonal antibodies in the treatment of lymphoid malignancies, numerous evaluation studies have been carried out in regard to the effectiveness of the use of rituximab (anti CD20) in conjunction with PNAs in the treatment of CLL and NHL. A randomized III phase trial comparing the use of fludarabine with cyclophosphamide (FC) and cyclophosphamide, fludarabine with rituximab (FCR) for CLL demonstrates significant improvements in median progression-free survival (PFS) in treatments associated with rituximab (51.8 months vs 32.8 months for FC, and 3-year overall survival (OS) 87% vs. 83% respectively) [35]. Similar effects (90% 2-year overall survival) were obtained in patients with CLL and small lymphocytic lymphoma (SSL) treated with oral fludarabine combined with rituximab. A large randomized trial comparing the use of fludarabine, cyclophosphamide, and rituximab together (FCR) and fludarabine with rituximab (FR) is ongoing and may help to further clarify the role of alkylating agents (that work synergistically with PNAs) in chemoimmunotherapy combinations in CLL [28].

A study to assess the treatment of fludarabine NHL, including Low-Grade NHL, follicular NHL, mantle cell lymphoma and indolent lymphomas, has demonstrated the high effectiveness of this

medication [21,57,71]. One of the accepted medical treatments of lymphoid neoplasms is the use of schemas based on fludarabine: fludarabine, mitoxantrone, and dexamethasone (FND), fludarabine and cyclophosphamide (FC) or fludarabine, cyclophosphamide and mitoxantrone (FCM) [15,41].

Also in regard to NHL, ongoing studies are done on the combining of PNAs with monoclonal antibodies. Furthermore, studies comparing the effectiveness of the FCM scheme (fludarabine, cyclophosphamide, mitoxantrone) with R-FCM (FCM with rituximab) in treating relapsed follicular lymphoma (FL) or other lymphoma subtypes have shown a significantly better treatment schema R-FCM; the overall response being 79% vs. 58% and CR being 33% vs. 13%, while PFS being 16 vs. 10 months. Similar results were achieved in the treatment of recurrent FL with R-FCM (OR 62% vs. 20%) [34].

Relapsed in mantle cell lymphoma, the addition of rituximab improves the overall response rate (65% vs. 33% without rituximab), and the complete response rate being 35% with rituximab, versus 0% without rituximab [41].

Ongoing studies are also occurring on the combining of purin nucleoside analogs for treatment of NHL with yttrium-90 (^{90}Y)-labelled ibritumomab tiuxetan (Zevalin, a murine monoclonal immunoglobulins G1 kappa antibody is conjugated to the CD 20 metal chelator tiuxetan for retention of the beta emitter 90 Y) [74,88]. Research has shown that at stage III or IV, untreated follicular NHL indolent treated with oral fludarabine (40 mg/^{2} on m-days 1 to 3) and intravenous mitoxantrone (10 mg/^{2} on m, day 1), and then if at least a partial response occurs and good blood parameters of morphology are demonstrated, treatment occurs with rituximab and Yttrium-90, this regime results in 96.5% CR (55 of 57 total), a 76% 3-year progression-free survival and a 100% 3-year overall survival rate [88].

In addition, fludarabine is used in the treatment of poor prognostic acute lymphoma, both in adults and in children. Research shows that the application of fludarabine with cytarabine, idarubicin and granulocyte colony-stimulating factor (G-CSF) by FLAGS-IDA schema in patients with regression or with bad prognosis acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML), produces better results than accepted treatment in use today. In a study by Tavil et al., complete remission is obtained in 60% of the tested children with AML who received treated according to this schema, while the OS amounted to 28.6 +/-17.7 months [80].

Researchers have expressed hope in the therapy of AML patients by way of treatments using fludarabine-based medical gemtuzumam-ozogamicin (GO, a humanized anti-CD33 antibody conjugated with cytotoxic and antitumor antibiotic, calicheamicin). A study done by Candoni et al. shows that FLAI-GO schema (cytarabine, idarubicin, fludarabine and GO) is significantly more effective than without the connection to GO in induction therapy in CD-33 positive AML (CR rate 90% vs.74%) and is safe for use with patients younger than 65 years [14].

Fludarabine is also used in combination with other medicines in conditioning before allogeneic hematopoietic stem cell tranplants (HSCT) in patients with AML and myelodysplastic syndrome (MDS), or with severe aplastic anaemia (SAA), Fanconi anaemia (FA), mantle cell lymphoma, primary myelofibrosis (PMF) and neuroblastoma [3,16,63,78,87].

Nemecek et al., in treating MDS/AML, conditioned their clinical subjects for HSCT with a treosulfan and fludarabine combination, inducing a 2-years relapse-free survival (RFS) of 58% and 88% without high-risk cytogenetics [63]. In conditioning before the HSCT, patients with SAA were

effectively treated using a combination of fludarabine with cyclophosphamide [2,49]. However, in patients with AML or FA, a combination of fludarabine with busulfan proved more effective [3,78,87]. Research is still on-going on trying to reduce the incidence of graft versus host disease (GVHD) in these patients. What seems to be promising is the application of antithymocyte globulin (ATG, Thymoglobuline), tacrolimus, mycophenolate mofetil, methotrexate or pentostatin as GVHD prophylaxis as in conditioning before the HSCT, along with other cytostatic drugs [3,49,78].

In addition, the action of busulfan was strengthened by a combination of clofarabine in different doses and/or fludarabine in pre-transplant conditioning therapy for AML and MDS. An investigation has shown that clofarabine support allo-HSCT is sufficiently immunosuppressive in myeloid leukemia and a combination of clofarabine +/- fludarabine with busulfan is safe in high-risk myeloid leukemia. However, the establishment of an adequate dose of individual substances requires further research [3].

Moreover, in patients undergoing total body irradiation (TBI) before the HSCT, fludarabine is used as a radiosensitizer and allows dose reduction for TBI (for 12 Gy 9 Gy) and in pediatric HSCT [52]. Use of fludarabine in association with the ATG has made it possible to achieve 93% success with more than 80% of donor chimerism, along with a modest incidence of GVHD in 42% of MDS/AML patients [31].

For myelofibrosis, using a conditioning regimen before allo-HSCT that contained fludarabine, resulted a 2-year overall survival of 87% [16].

Fludarabine has beneficial effects in combination with other drugs in cases of Waldenström macroglobulinemia (WM, lymphopsmacytic lymphoma with monoclonal immunoglobulins M (IgM) paraprotein in the serum). In a study, Peinert et al. demonstrated the excellent efficacy of fludarabine in the treatment of WM, both in patients not treated previously and in patients with regression; the overall response rate (ORR) being up to 90%, while the major response rate being 83%. In this test, the effectiveness of WM treatment was comparable in both fludarabine combined with rituximab and without it, in conjunction with only the cyclophospamide or mitoxantrone ($p = 0.7$ for PFS, and $p = 0.1$ for OS) [65]. Another study has shown that the addition of rituximab to fludarabine and cyclophosphamide can reduce the dose of fludarabine, and thus reduce the adverse reactions after FA [43].

Studies are ongoing in regard to the application of bortezomib (the proteasome inhibitor), thalidomide, perifosine and everolimus in association with other cytostatic drugs, including PNAs used in WM [70,82].

The treatment of WM with fludarabine-based combinations is well tolerated. PFS in this study was 43 months, which also ensured a good patient quality of life with any given treatment. These studies confirmed earlier reports emphasizing the advantages of treatments using most WM-based fludarabine, in comparison with other schemes as DRC, CHOP, CVP [10,37,40]. However, present research has so far not established a standard of care in WM and epicycle centers treat the disease with different combinations of drugs [70].

This situation also describes the application of fludarabine in the treatment of pure red cell aplasia that does not respond to standard treatment with other immunosuppressive drugs, and administration of fludarabine in dose 30mg/m^2 in combination with cyclosporine, resulted in a rapid and lasting improvement in the condition of the test patient [38].

Data concerning the application of fludarabine in autoimmune diseases are limited. There were reports on the application of FA for systemic lupus erythematosus (LSE) patients, but this study has not been confirmed by controlled trials, so these agents cannot be recommended for LSE [6].

Besides the above, fludarabine-based therapy has been carried out in patients with rheumatoid arthritis, the test individuals receiving 2 different doses of the drug: 20 mg/m^2 and 30mg/m^2. After 6 months of therapy, in both groups of patients, a reduction in sensitivity and swelling of joints has been observed. Moreover, in all treated patients, the level of lymphocytes T and B was reduced [68].

What is more, with Systemic sclerosis (SSc) patients, fludarabine is used with low-dose total-body irradiation as conditioning before allo-HSCT [47,75].

Cladribine

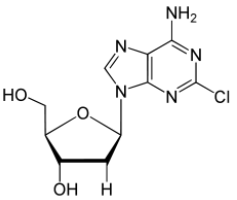

Figure 2. Cladribine (2-CdA, 2-chloro-2-deoxyadenosine)

Cladribine is a deoxyadenosine analog and like FA, DCF and CAFdA, cladribine belongs to the group of antymetabolites which are characterized by having a toxic effect on lymphocytes and monocytes. The 2-CdA was synthesized at the Scripps Research Institute in 1970s. The substitution of a hydrogen atom by a chlorine atom at position 2 of the deoxyadenosine ring makes it resistant to the action of ADA (ADA being an enzyme which metabolizes purines). This drug was accepted by the FDA in the 1980's for hairy cell leukemia therapy [56,77].

The mechanism of action of cladribine is similar to other nucleoside analogs, and like other PNAs, 2-CdA works on the dividing and resting cells [36,56,77].The 2-CdA permeates through the blood-brain barrier (BBB), and therefore beyond the peripheral cells. Thus, it also interacts with the central nervous system cells. Cladribine permanently reduces the level of the CD4+, CD8+ and B lymphocytes, and has minor effects on NK cells, while the effect when applied to monocytes and neutrophils is transient. In addition to its direct influence on the number of lymphocytes, cladribine also acts on the proinflammatory cytokine, modifying their level [36,37,56].

After administration, cladribine is present in the urine and in the plasma. Its main formed metabolite is 2-chloroadenine. The maximum concentration in the plasma after oral administration is reached after 30-50 minutes. About 20% of this involves a protein serum. Its average half-life is 5.6-7.6 hours and 18.4-19.7 hours, depending on the phase of elimination. Oral bioavailability is around 40% [56].

Cladribine shows complex effects on the lymphatic system and the best results are observed during the treatment of haematological diseases, especially in hairy cell leukemia therapy (HCL) [36]. For about 30 years, it has been used, like pentostatin, in the treatment of HCL, resulting in 80-90% of the CR. The median disease-free survival is 16 years [19,30]. In some studies, cladribine showed more potent activity of 2-CdA than pentostatin in HCL, but also greater myelosuppression,

so treatment must be individually tailored for each patient with HCL [46]. A small percentage of patients who achieve a partial response (PR) and who have had relapsed or refractory HCL treatments after the purine analogs, may be then treated with rituximabem. In this case, high effectiveness was demonstrated [19]. In addition, currently, cladribine is prescribed for the hairy cell leukemia variant (HCL-V), which in comparison with the classic HCL (HCL-C), gives patients a worse prognosis, and is more resistant to PAN treatment. However, some reports indicate that rituximab and alemtuzumab are active in HCL-V. Promising data has also come from conducted trials of anti-CD22 immunotoxin for HCL-V [69]. Cladribine like fludarabine, is also used in the treatment of CLL, as already mentioned in the description of the FA action [83].

Much research has been devoted to assessing the effectiveness of the treatment of NHL by way of using cladribine [77]. The results indicate a high effectiveness of 2-CdA among this group of patients. The study of Blum et al., showed an overall response rate at 100% of patients with indolent non-Hodgkin lymphoma when treated with cladribine [9]. Moreover, a high (75%) response was obtained in a test done by Laurencet et al., but the treatment involved a strong toxicity and fatalities resulting from infections in pretreated patients [55]. Kalinka-Warzocha et al. compared the action of cladribine alone, with cyclophosphamide and with another therapy (CVP) in lymphoplasmacytic lymphoma treatment, SSL, marginal-zone lymphoma, follicular lymphoma and not otherwise specified B-cell LGNHL. The study revealed that the highest effectiveness of treatment occurred with cladribine and cyclophosphamid therapy (CC), the overall response being 85% for CC, 75% for 2-CdA alone and 51% for CVP therapy [48]. Cladribine treatment was equally effective for patients with mantle cell lymphoma. In this case, the ORR being 81%, with 42% of CRs in a previously untreated group, and the ORR being 46%, with a 21% CR rate in those treated for recurrent disease. In this test, 29 eligible patients with a median age of 70 years, received 2-CdA with rituximab. The ORR in these cases was 66% and the CR rate was 52%. This indicates that the addition of rituximab in 2-CdA may increase the efficiency of cladribine in NHL [42].

Good results have been obtained among pediatric patients when using cladribine during AML treatment [77]. In adults, administration of cladribine with other cytostatic drugs such as mitoxantrone, cytosine arabinoside, and G-CSF (CLAG-M scheme), CR at 58% has been achieved in patients with primary resistant or relapsed AML [85]. In addition, this therapy has proven to be safe for patients up to 60 years of age [40].

The high efficiency of cladribine has been demonstrated in the treatment of Langerhans' cell histiocytosis (LCH) in children. So effective is this drug that 100% remission is common [61]. The effectiveness of cladribine was also demonstrated in the treatment of LCG 2-CdA, as tested by Biswas et al. in children with relapsed or refractory LCH. When cladribine was administered, 33% of the patients achieved PR and 33% patients had SD on imaging, but are clinically better [8]. In the study done by Weitzman et al., 2-CdA produced a high response rate in children with low-risk multisystem LCH (62% patients responded) and 2-year survival of 97% is predicted for these patients. Among the patients with organ infection, the response rate was 22%, and 2-year predicted survival is 48%. Children who fail to respond to 2-CdA have a high mortality [84]. However, reports about LCH are based on limited observations, and therefore must be validated by prospective clinical trials. Hence, The Histiocyte Society recommends that 2-CdA be used only in specific cases as salvage therapy [59].

Besides the aforementioned, there have been attempts to treat autoimmune diseases with cladribine. Among these diseases are multiple sclerosis, rheumatoid arthritis, systemic lupus and erythematosus associated glomerulonephritis [36,56].

The efficiency, safety and tolerance of cladribine during SM therapy have been assessed in multiple trials. There were 3 randomized studies and placebo II and III phases in the treatment of relapsing forms of MS. In these, the effectiveness of the therapy has been confirmed by way of clinical and magnetic resonance image [56]. The first study used cladribine in intravenous and subcutaneous injections, yet the oral form proved to be better tolerated by patients, particularly in cases of prolonged dosage [37,56]. Cladribine doses were different in various tests (cumulative doses of 0.7mg/kg to 5.25mg/kg), with no significant difference in toxicity [37,56,77]. So far, unequivocally recommended dosages to treat SM have not been established [27]. The most up-to-date study from the phase III showed the comparable efficacy of CLARITY-treatment of MS when using cladribine in cumulative dosages of 3.5mg/kg and 5.25mg/kg. Such dosages showed similar system toxicity [29]. However, according to some authors, chronic treatment with cladribine is too toxic therefore it should be applied only in worsening and/or first-line therapy [76].

Pentostatin

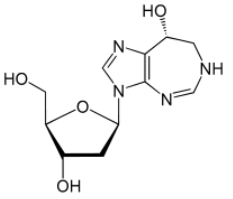

Figure 3. Pentostatin (DCF, 2'-deoxyformycin)

Pentostatin (DCF) had been accepted in Europe before 1990, for use in rare malignancy therapy, mainly in HCL treatment. Unlike the FA, 2-CdA and CaFdA, DCF was isolated from Streptomyces antibiticus. The chemical structure of pentostatin is a tetrahydroimidazol ring, which has a deoxyribose tail [20,68]. The main action of the drug is based on the inhibition activity of ADA, the enzyme which is highly concentrated in the lymphatic cells. ADA prevents the accumulation of 5-triphosphate deoxyadenosine (dATP), which exhibits toxicity in high concentrations (as evidenced in in vitro studies). The activity of ADA in resting lymphocytes is blocked by pentostatin. This action proved to be the key to the DCF therapeutic use potential in malignancies, as in research, in vivo pentostatin reduced T lymphocyte numbers (more CD4+ than CD8+), both in patients with HCL and in patients with refractory solid tumors. At the end of therapy, as shown in this research, circulating B lymphocyte numbers and IgG levels were also reduced, while NK cell numbers and IgA and IgM levels were spared. What is more, after inducing remission, it was found that pentostatin treatment often increased NK cell activity [72].

During rare malignancy therapy, pentostatin is usually administered at a dose of 4mg/m^2 in tablet form or by 20-30 minute intravenous. Pentostatin can cross the BBB, reaching 10-12% concentration in serum. At a dose of 10-30mg/m^2, half-life amounted to 4.9-6.2 hours, however, in the course of the use of high doses, high toxicity was revealed. DCF is discharged unchanged mainly by the kidneys [68,72].

In clinical trials, response to treatment was evident in approximately 25% of CLL cases. However, a sustained response in the majority of the patients was short-lived. It was also noted that mielotoxic effect of pentostatin is weaker than cladrybine or fludarabine treatments [68]. As reported by Dillman, in regard to patients with relapsing CLL, after administration of pentostatin in conjunction with chlorambucile or cyclophosphamide, a high response was demonstrated [20]. Moreover, pentostatin used with cyclophosphamide (PC) for heavily pretreated patients with CLL gave an overall response frequency of 74%; with CR, the figure was 17% [72].

Pentostatin, when combined with rituximabem, has an enhanced effectiveness, and combined treatment of pentostatin, cyclophosphamide and rituximab (PCR) is safe and has clinical activity in CLL therapy, as well as SSL, increasing the CR frequency to 25%. Studies comparing the rehabilitative FCR with PCR for CLL patients show that in pentostatin-based treatment, grade ¾ infections, neutropenia, anaemia and trombocytopenia rarely occur. Moreover, there is no difference in incidence of CR or OR [20,72]. However, the treatment proved to be too risky for patients over the age of 65 or who have high-risk disease. This forced the authors to early closure of their trial [20]. Other research has shown that the application of PCR is equally effective as FCR is in the treatment of CLL patients, but so far, the impact of this regimen on survival has not been determined [12].

Numerous studies have evaluated the use of pentostatin in other lymphoid malignancies, like T-cell acute lymphoblastic leukemia (TALL), mature leukemias such as T-cell prolymphocytic leukemia (T-PLL) and T-cell large granular lymphocytic leukemia (T-LGL), extranodal mycosis fungoides tumors such as hepatosplenic T-cell and lymphoma (HSTCL), nodal disorders such as peripheral T-cell lymphoma (PTCL), as well as neoplasms with mixed patterns such as adult T-cell leukemia/lymphoma (ATLL). It was also reported that pentostatin with alemtuzumab is relatively safe and feasible with manageable toxicity in treating these lymphoid malignancies. In addition, with patients who have T-PLL, the response rates and duration seem to be superior to single-agent [66,72]. In the study done by Ravandi et al., 54% of the test subjects with T-PLL, ATLL, HSTCL or T-LGL showed a response, while, unfortunately, none of the T-ALL and PTCL patients achieved any response [66].

As already described earlier, pentostatin, as with cladribine, has been used for many years in the treatment of HCL patients, and has shown very good results [19,30,46,69,72]. In many studies, a similar efficacy was evident when either substance was used. However, pentostatin, when used in HCL, is cost-effective when compared with cladribine [32].

Bajwa et al., describes the effectiveness of pentostatin application in the treatment of autoimmune lymphoproliferative syndrome (ALPS) patients. In severe cases, refractory to multiple agents, an ALPS with the defect in the pathways for apoptosis bone marrow transplantation is recommended. In their study, Bajwa et al. used pentostatin to achieve remission before the HSCT. This treatment showed very good effectiveness and tolerance [5].

In addition, immunosuppressive properties of pentostatin have been utilized in prophylaxis and treatment of both acute and chronic GVHD in the setting of allo-HSCT. This treatment revealed documented efficacy even when steroid-resistance was evident [44,51,64,72,73]. In their study, Klein et al., describe the effects of pentostatin in the treatment of steroid-refractory acute intestinal graft versus host disease. An analysis of their experimental results shows that 83% of patients responded to pentostatin, with 70% achieving CR and 13% achieving PR. Moreover, the 2-year survival rate

was 43% [64]. In experiments of Schmitt et al., CR or very good PR was observed in 38% of the patients and the 2-year survival rate was found to be at 17% [73]. What is more, in a preliminary (unconfirmed) study conducted by Parmar et al., the use of pentostatin in different doses was compared for treatment of GVHD. Their results showed that pentostatin increased the likelihood of success when used at a dose of 1.5mg/m^2 [64]. Confirmation, however, is also needed for research on the application of pentostatin in steroid-refractory chronic GVHD in children, although preliminary experiments provide promising data [44].

The application of DCF in a manner similar to FA use for allo-HSCT conditioning, was examined in experimental animals. The results of this work show that the use of synergistic actin of pentostatin with cyclophosphamide leads to the depletion of the host's CD4+ and CD8+ T cells. Hence, it is thought that a PC-based regime can improve engraftment when undertaken prior to allo-HSCT [58]. What is more, pentostatin has been shown to be effective in the treatment of severe colitis in IL-10 deficient mice. This is because it impairs T cell expansion and reduces pro-inflammatory cytokine production [10]. Furthermore, animal testing has been carried out which demonstrates that the application of pentostatin with cyclophosphamide (PC) can increase the efficiency of immunotoxin therapy of cancer. This is because chemotherapy using anti-PC safely prevented immunotoxin antibody formation with uniform efficacy [60].

Clofarabine

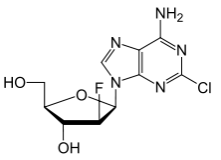

Figure 4. Clofarabine (CAFdA, 2-chloro-9-2-fluoro-2'-deoxyarabinofuranozyloadenine)

Chemically, clofarabine is 2-chloro-9-2-fluoro-2'deoxyarabinofuranozyloadenine. It is also known under the name CAFdA or CFA. This drug belongs to a new generation of purin nucleoside analogs. These were found to combine the best features and pharmacokinetic properties of cladrybine and fludarabine. Similarly to FA and 2-CdA, the substitution of the halogen atom instead of the hydrogen atom in the 2nd position of the adenine ring makes CFA resistant to ADA. However, in order to obtain a better stability to the acidity of the gastro tract and reduce the biodegradability by microbial enzymes, at the 2nd position of the deoxyribose ring, the hydrogen atom has been replaced by a fluorine atom. The result of this structural change is an increase in bioavailability after oral administration. However, the effectiveness of oral forms is under investigation [50,53,81]. Still, a study done by Faderl et al. has shown high effectiveness of oral clofarabine in the treatment of MDS, (an overall response rate of 43%, with 25% CR) [23].

The metabolism of clofarabine is similar to other PNAs, and combining the features of both FA and 2-CdA, ensures that clofarabine triphosphate persists longer in leukemic cells. Its half-life is 24 hours. This differentiates it to other PNAs and makes it more efficient [50]. In vitro studies show that its breaking action is similar to cladrybine, and reveals that it is ten times stronger than fludarabine [26]. Moreover, the multidirectional effects of the drug have been found to be based on the induction

of apoptosis. Furthermore, studies show that a large dose of clofarabine in CLL can lead to a loss of integrity of mitochondrial membranes, and consequently, to releasing proapoptotic factors and to forming the complex structure called an 'apoptosome'. This formed complex activates a cascade of caspases and leads to programmed cell death. Clofarbine differs to other PNAs in that in resting cells, it follows the intrinsic [50,53].

In the USA and Canada, CFA is registered under the name Cloral®, while in Europe, Australia and New Zealand, the commercial name is Evoltra®. It was approved by the FDA in December 2004, and by 2006, the European Medical Council had approved it for therapy for children with ALL that did not show a response to the the previously discussed chemotherapies or who exhibited a relapse [26,50]. What is more, clorofarabine and nelarabine have also been approved for treating individuals showing a lack of response to the previous two existing schemes of treatment for T-ALL, or T-LBL patients in HSCT. The recommended dose of clofarabine for children and youth is 52mg/m^2 in intravenous injection, administered for 2 hours for 5 days, with 2-6 weeks break between cycles [86].

In June 2008, clofarabine was accepted in Europe for therapeutic use in AML for elderly people (over 70 years of age) who have shown a secondary AML, as well as a contraindication to the application of intensive chemotherapy [53]. The effectiveness of clofarabine is demonstrated in the treatment of pediatric clofarabine patients with multiple relapsed or refractory AML. In this study, the response rate was 26% and the treatment was well tolerated [45].

In a randomized study, different doses of the intravenous form of clofarabine were compared (15mg/m^2 vs. 30mg/m^2 daily for 5 days) in the treatment of high-risk MDS. This experiment revealed the good effect of clofarabine in MDS patients (ORR 36%, with CR 26%) regardless of the applied dose. Lower doses, however, appeared less toxic [23]. This study has confirmed earlier reports that when treated with clofarabine, patients with MDS showed an overall response rate of 31% to 43% [81].

Furthermore, high efficiency of clofarabine was shown in treating relapsed and/or refractory NHL, even in failed stem cell transplantation or rituximab-refractory disease. In this study, 42% of the treated patients achieved ORR, with 23% CR and 19% PR. Moreover, treatment was well tolerated, the major toxicity being the myelosuppression [62]. A phase I trial also demonstrated that the use of high-dose clofarabine (60mg/m^2) with busulfan as a myeloablative regime for allogeneisc SCT is effective and well tolerated for high-risk acute leukemia patients [24]. Moreover, in one further study, in vitro clofarabine has demonstrated effectiveness in multiple human cell line therapy and in tumor models of human cancers of the colon, lung, breast and stomach [26].

Clofarabine is also thought justified for use with other cytostatic drugs due to the synergistic operation of the CFA. Moreover, measures such as cytarabine or oxiplatin on DNA damage and inhibition of DNA repair, and induction of apoptosis [50] show that the association of clofarabine with cytarabine exhibits a high efficiency (CR 47%). This is accompanied by good tolerance in adult patients with relapsed or refractory AML, in patients with high-risk MDS and in elderly patients with untreated AML and heart disease who also exhibit high risk for anthracycline toxicity [1,23].

CONCLUSION

As shown in this work, purine nucleoside analogs are widely used in medicine, both in treating neoplastic and autoimmune diseases. Futhermore, attempts are made to connect PNAs with other cytostatic medicines

or with monoclonal antibodies. PNAs, FA, 2-CdA and DFC are widely used in the treatment of many cancers emanating from the lymph system. However, the best therapeutic effects are obtained in CLL and HCL therapy. In addition to the current multifaceted application, more research is being undertaken and more purine-based drugs are being developed. At present, approved purine analogs include clofarabine, nelarabine, forodesine and 8-chloroadenosine. Coming onto the market is a unique cytotoxic agent, Bendamustine, which has a combination of alkylating and antimetabolite properties [54]. The chemical structure of newer analogs is based on substances which already exist. The structure of clofarabine for example, is based on FA and 2-CdA, and allows better and more efficient use of the drug during therapy [53]. Clofarabine has been accepted for treatment of relapsing and resistance in the treatment of ALL, while Nelarabine demonstrates activity in monotherapy for patients with T-cell ALL [25].

At present, with new PNAs, research has expressed enthusiasm in providing greater therapeutic success for both adults and children patients with difficult to treat neoplastic diseases or with autoimmune diseases.

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SUMMARY

Purine Nucleoside Analogs (PNAs) are classified as cytostatic drugs. These are used in therapy of tumours and in therapy of autoimmune diseases. In the 80s and 90s, cladribine, fludarabine and pentostatin had been accepted by the US Food and Drug Administration (FDA) for use in hematological cancer therapy [68]. The chemical structure of all PNAs is based on the nucleoside ring. The mechanism of action is multidirectional and it consists principally in the inhibition of replication and DNA repair, the inhibition of activity of DNA polymerases, as well as induction of accumulation of DNA strand breaks and apoptosis in target cells. These drugs have cytotoxic effects on both proliferating and quiescent cells. Numerous studies confirm that PNAs used in monotherapy and in combination with other cytostatic drugs or with antibodies, show good results and are relatively non-toxic.

Keywords: purine nucleoside analogs, cladribine, clofarabine, fludarabine, pentostatin

STRESZCZENIE

Analogi nukleozydów purynowych (PAN) zaliczane są do cytostatyków, które wykorzystywane są w terapii nowotworów i chorób autoimmunologicznych. W latach 80 i 90 kladrybina, fludarabina i pentostatyna zostały zaakceptowane przez US Food and Drug Administration (FDA) w terapii nowotworów hematologicznych [68]. Struktura chemiczna wszystkich PAN opiera się na pierścieniu nukleozydowym. Mechanizm działania jest wielokierunkowy i polega głównie na hamowaniu replikacji i naprawy DNA, hamowaniu aktywności polimeraz DNA, kumulacji pęknięć nici DNA i indukowaniu apoptozy w komórkach docelowych. Leki wywierają efekt cytotoksyczny zarówno na komórki proliferujące jak i w stanie spoczynku. Liczne badania potwierdzają, że PAN użyte w monoterapii oraz w połączeniu z innymi cytostatykami lub przeciwciałami monoklonalnymi wykazują dobre efekty i są stosunkowo mało toksyczne.

Słowa kluczowe: analogi nukleozydów purynowych, kladrybina, klofarabina, fludarabina, pentostatyna