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Advances in the treatment of indolent lymphomas

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Summary

Non-Hodgkin's lymphomas (nHL) are a heterogenous group of lymphoid malignancies with a different pattern of behaviour and response to treatment. In Europe and North America mainly B-cell lymphomas (86%) are observed. Indolent lymphomas are lymphoproliferative diseases with a relatively good prognosis and long natural history. They usually affect elderly people and more than 90% of cases are diagnosed in advanced stages of the disease. Forty percent all cases of nHL are indolent lymphomas. Indolent lymphomas are curable only in their early stages when radiotherapy is the treatment of choice. In advanced stages chemotherapy is used. However, up till now aggressive chemotherapy does not improve the overall survival rate and it leads to serious adverse events. This article presents current options of management of indolent nHL, especially using purine analogues and monoclonal antibodies.

Purine analogues (fludarabine, 2-chloro-2'desoxyadenosine- 2CdA) are thought to be very promising agents as they induce apoptosis and have cytotoxic activity against noncycling lymphocytes which dominate in indolent lymphomas histology. In recent years monoclonal antibodies against antigens present on the lymphoma cells such as rituximab (Mabthera) antiCD20 or alemtuzumab (MabCampath) antiCD52 have been widely used.

Key words: non-Hodgkin's lymphomas, treatment, purine analogues, monoclonal antibodies.

Postępy w leczeniu chłoniaków o przebiegu powolnym

Streszczenie

Chłoniaki złośliwe nieziarnicze (lymphoma malignum, non Hodgkin's lymphoma) jest to heterogenna grupa nowotworów wywodzących się z układu chłonnego o zróżnicowanym przebiegu klinicznym i odpowiedzi na leczenie. W Europie i Ameryce Północnej 86% przypadków stanowią chłoniaki B komórkowe. Chłoniaki o przebiegu powolnym należą do schorzeń limfoproliferacyjnych o stosunkowo dobrym rokowaniu i wieloletnim przebiegu naturalnym. Zazwyczaj występują u ludzi starszych i w ponad 90% przypadków rozpoznanie jest ustalane w zaawansowanym stadium klinicznym choroby. Stanowią ok. 40% wszystkich chłoniaków. Chłoniaki o przebiegu powolnym są wyleczalne jedynie we wczesnych stadiach. Leczeniem z wyboru jest wówczas radioterapia. U chorych w stadiach zaawansowanych stosuje się chemioterapię. W tej grupie chłoniaków agresywna chemioterapia nie poprawia wyników odległych, a naraża chorych na wystąpienie poważnych objawów niepożądanych. Artykuł omawia współczesne możliwości leczenia chłoniaków o przebiegu powolnym ze szczególnym uwzględnieniem analogów purynowych i przeciwcial monoklonalnych.

Analogi purynowe (fludarabina, 2-chloro-2'dezoksyadenozyna- 2CdA) są bardzo obiecującymi preparatami ze względu na indukowanie apoptozy i działanie cytotoksyczne wobec limfocytów spoczynkowych (nieaktywnych w cyklu komórkowym), które dominują w populacji komórek chłoniaka o mniejszej złośliwości. W ciągu ostatnich kilku lat coraz szersze zastosowanie w leczeniu chłoniaków nieziarniczych znajdują przeciwciała monoklonalne przeciwko antygenom obecnym na powierzchni komórek chłoniakowych np. anty CD20 (rituximab, Mabthera) lub anty CD52 (alemtuzumab, MabCampath).

Słowa kluczowe: chłoniaki nieziarnicze, leczenie, analogi purynowe, przeciwciała monoklonalne.

Non-Hodgkin's lymphomas (nHl) forms a heterogenous group of carcinomas originating from lymphocytes, their precursors or cells which are formed as a result of differentiation or transformation of B or T lymphocytes and, in rarer cases, of histiocytes. At Poland's latitude, 86% of all cases are those of the B-cell type. Clinically, i.e depending

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on the course of the disease and the response to treatment, lymphomas can be classified into aggressive lymphomas and indolent lymphomas.

Following the REAL classification indolent lymphomas include:

- small-lymphocyte lymphomas/ chronic lymphatic leukaemia,
- limphoplasmocytoidal lymphoma / Waldenstrom's macroglobulinemia,
- hairy cell leukemia lymphoma,
- splenic marginal zone B-cell lymphoma,
- marginal zone B-cell lymphoma:
- extranodal marginal zone B-cell lymphoma of MALT type,
- nodal marginal zone B-cell lymphoma.

Stage I and II follicular lymphoma is the most often encountered type of indolent lymphoma. Mycosis fungoides is an example of indolent lymphoma originating from T lymphocytes [1].

Chromosomal mutations (eg. translocations, deletions) lead to the activation of oncogens or loss of suppressor genes, which, as a consequence, results in the disturbances in proliferation, differentiation and cell death (apoptosis). In indolent lymphomas the dominant process is thought to be that of the impairment of the apoptosis , which more often than not, involves bcl2 overexpression. Modern techniques of molecular biology (FISH, PCR) make it possible to detect cytogenetical disorders in 80-90% of lymphomas, eg. (14,18) translocation with Bc12 oncogene activation observed in follicular lymphomas. These disturbances rarely involve only one clonal aberration, they are mostly of a complex nature. In the course of the disease new changes appear [2].

Indolent lymphomas, which made up about 40% of all lymphomas, belong to lymphoproliferative disorders with relatively good prognosis and natural course lasting many years. They are usually found in elderly people, whereas in 90% of all cases the diagnosis is established in the advanced clinical stage of the disease (stages III and IV according to Ann Arbor). Indolent lymphomas are curable only in early stages, when radiotherapy is the treatment of choice. In stages I and II 30 Gy target irradiation allows us to obtain a 10-year disease free survival (DFS) in some 50% of all patients. Attempts at a combined modality therapy of early stages of lymphomas, eg. radiotherapy + COP-Bleo /CHOP-Bleo, do not lead to unequivocal results. Early combined treatment seems to prolong DFS, it does not, however, have much effect on the overall survival (OS) [3,4].

In patients in advanced stages of the disease chemotherapy is administered. In the case of indolent lymphomas aggressive chemotherapy exposes patients to serious adverse effects rather than improves long-term results. Since this treatment is palliative in nature, in cases when the disease is stable, the onset of the therapeutic process can be postponed, according to the approach of "wait and watch", until the disease progresses to a more advance stage.

In order to determine the aim of the prognosis, and thus treatment planning procedures, an International Prognostic Index (IPI) is employed, which takes into account the following parameters: age, general condition, number of extranodal locations, clinical stage according to Ann Arbor, and the activity of lactate dehydrogenase. The IPI was originally designed to be used in aggressive lymphomas. Thus this index is generally regarded as one that does not make possible predict the clinical course of indolent lymphomas Therefore, in 2002 a new prognostic index for follicular lymphomas was proposed [5,6]. See *Table 1*.

Table 1. The Follicular Lymphoma International Prognostic Index (FLIPI).

Risk group	No of factors	OS	
		5 years %	10 years %
low	0 - 1	91	71
medium	2	78	51
high	> 2	53	36

OS - overall survival

Age 60 years
Haemoglobine 12 g/dL
LDH > normal
Stage (according to Ann Arbor) III - IV
Number of involved nodal groups 5

The indications for chemotherapy for indolent lymphomas are as follows: haematopoetic insufficiency (anaemia, leukopenia, thrombocytopenia), occurence of B signs (fever, night sweats, weight loss), fast progression of the disease, large tumor mass, and patient's wish. In most cases a positive clinical outcome can be obtained by administering alkylating drugs such as cyclophosphamide and/or chlorambucil, sometimes in combination with steroids or by applying polychemotherapy, eg. COP (cyclophosphamide + vincristine + prednisone). Treatment of this type makes it possible to obtain a mean overall survival of between 5.6 and 10 years [3].

Purine analogues (fludarabine, 2-chloro-2'desoxyadenosine-2CdA) are very promising as they induce apoptosis and have cytotoxic activity against noncycling lymphocytes (non-active in the cell cycle), which are dominant in the population of less malignant lymphoma cells. Fludarabine used in monotherapy as next line treatment makes it possible to obtain about 50% of positive clinical responses. This figure rises to 70% in patients who have not been treated earlier, 38% of them having registered complete remission. Similar results have been obtained with the use of 2CdA [7]. Despite the high percentage of total and partial

remissions a relapse of lymphoma occurs in most patients. High hopes for improved results are linked with the use of purine analogues combined with other anticancer drugs. The theoretical rationale for using fludarabine combined with mitoxantrone or cyclophosphamide is based on the inhibitory effect of fludarabine in the repair mechanism of DNA impaired by alkylating drugs or mitoxantrone. The efficacy of fludarabine combined with, among other drugs, cyclophosphamide; mitoxantrope and dexamethasone (FND); cyclophosphamide and mitoxantrone (FMC); and cisplatine (FLUDAP) has been studied. The administration of FND in relapsed NHL resulted in 94% responses, 46% of which led to complete remission with the mean survival of 21 months [8]. The present opinion holds that the combination of fludarabine with steroids enhances the immunosuppresive effect without significantly increasing the anticancer effect. That is why the Southwest Oncology Group has suggested applying the FM (fludarabine + mitoxantrone) protocol in the first line treatment of indolent lymphomas, which resulted in 44% of complete remissions and 50% of partial remissions. Despite this high efficacy of FM combination the comparison with historical groups treated using CHOP, PROMACE-MOPP protocols did not show any improvement in the progression free survival (PFS) and overall survival (OS) in the group treated with fludarabine and mitoxantrong [9].

In the last few years monoclonal antibodies against antigens presented on the lymphoma cells, eg. rituximab (Mabthera) antiCD20 or antiCD52 (alemtuzumab, MabCampath) have become becoming widely used. Rituximab is a chimera-type (mouse-human) monoclonal antibody selectively bound to CD20 antigen present on preB cells and mature B lymphocytes. The CD20 antigen is found in 95% of all line B lymphomas. This antigen is not internalised when combined with an antibody, it is not released from the surface of the cell, and does not exist in a free form in the plasma. Rituximab molecule, which activates the mechanism of cell lysis as a result of antibody dependent cell cytotoxicity (ADCC) and the complement dependent cell cytotoxicity (CMCC), also has a direct antiproliferative effect on cancer cells. Multicentre studies have demonstrated 40% to 60% of positive responses in monotherapy of relapsed and resistant lymphomas using rituximab, which as a drug targeted at lymphoma cells does not enhance myelotoxicity involved in chemotherapy. The reports published so far claim that the adverse effects related to the haematopoietic system are rare, moderate and transient. Severe thrombocytopenia and neutropenia have been found in 1.8% of patients, whereas severe anaemia was observed in 1.4% of cases. *In vitro* studies have shown that rituximab increases the anticancer drugs' sensitivity of human cell lines obtained from B limphocytes resistant to chemotherapy. As a result a rationale for introducing combined rituximab + chemotherapy has been established. At present rituximab is used both in monotherapy and in other modalities of combined treatment with anticancer drugs such as CHOP, CVP or fludarabine or immunomodulating drugs, eg. interferons [10,11,12]. In the first-line treatment Czuczman et al. administered rituximab combined with CHOP, and thus they were able to obtain 100% of positive clinical responses including 66% of total remissions. Similarly, over 90% of positive outcomes was achieved using rituximab in combination with fluradabine [13]. What is worth noting is that almost half of the patients undergoing combined treatment were found to respond by molecular remission in the form of eradication of bcl-2 positive cancer cells from the peripheral blood and bone marrow.

At present attempts are being made to increase the antibody activity by combining them with a radioisotope, eg. ibritumobab (Zevalin) or tositumobab (Bexxar) or immunotoxin. The administration of ibritumobab (antibody against CD20 conjugated with Yttrium ^{90}Y) in a group of patients with follicular lymphoma made it possible to obtain a clinical response in 74% of patients. In relapsed or resistant indolent lymphomas ibritumomab provides statistically a greater number of positive responses than ritiximab (80% vs. 56%) [14].

Interferon alpha in combination with cytotoxic agents improves the clinical outcome in patients with follicular lymphoma. On ECOG study the administration of interferon alpha resulted in longer progression free survival. However, on SWOG study these observations were not validated [7].

Megachemotherapy supported by autologic peripheral stem cell transplantation used in relapsed or progression lymphomas makes it possible to obtain more than 90% positive responses, albeit most patients have recurrences of the disease. The effectiveness of megachemotherapy in combination with auto or allotransplantation of the bone marrow or stem cells from the peripheral blood has been subjected to clinical investigations. In a similar way, the efficacy of new anticancer drugs such as rapamycin analogues, bcl-2 antisense oligonucleotides, antiidiotypic or DNA vaccines has been determined. Proteasome inhibitor (bortezomid) inhibits proliferation and induces lymphoma cell apoptosis. Phase II studies have shown that bortezomid is effective in many types of relapsed non-Hodgkin's lymphomas, including those of the indolent course, and the percentage of clinical responses ranges between 40% and 53% [15,16,17].

Despite high susceptibility of indolent non-Hodgkin's lymphomas to chemo or radiotherapy and the relatively long survival, the available methods do not afford permanent cure except for the cases in early clinical stages. Most patients suffer from subsequent, even late, relapses, progression of histologic malignancy (Richter's syndrome), as well as progressive resistance to treatment. The full use of the latest advances in molecular biology and immunology has also brought with them significant advancement in the diagnosis of the pathogenesis of non-Hodgkin's lymphomas. The introduction of new drugs and attempts

at individualised therapy dependent on the type of lymphoma and risk factors raise hopes for better results in the treatment of lymphomas.

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