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PRACA POGLĄDOWA – Review Article

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Treatment of rofractory and relapsed chronic lymphocytic leukemia

Leczenie nawrotowych i opornych postaci przewlekłej białaczki limfocytowej

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SUMMARY

For many years alkylating agents especially have been considered the drugs of choice for first-line treatment of progressive and symptomatic chronic lymphocytic leukemia (CLL). However, this agent is not effective in early relapsed and refractory patients. More recently treatment approaches have included purine nucleoside analogs (PNA), fludarabine (FA), cladribine, (2-CdA) and pentostatin and monoclonal antibodies (MoAb). PNA are highly active in CLL patients, both previously treated and untreated and are frequently effective in patients refractory to alkylating agents. The MoAbs directed against CD52 antigen (alemtuzumab) and CD20 antigen (rituximab) demonstrate also significant activity in CLL and should be used in patients refractory to PNA. Combination therapies with PNA and CY and especially with rituximab are more active than monotherapy with PNA in regards to response rate and possible survival. Alemtuzumab may be an effective treatment for patients refractory to PNA. Recently a number of novel agents and therapies are being evaluated especially in patients refractory to PNA, including those targeting the antiapoptotic bcl-2 family of proteins and receptors, vaccines and stem cell transplantation.

KEY WORDS: Chronic lymphocytic leukemia – Purine nucleoside analogs – Fludarabine – Cladribine – Rituximab – Alemtuzumab – Chemoimmunotherapy – Monoclonal antibodies – Stem Cell transplantation.

STRESZCZENIE

Przewlekła białaczka limfocytowa (CLL) jest klonalną chorobą charakteryzującą się proliferacją i akumulacją małych limfocytów B z ekspresją CD5. Chlorambucyl jest stosowany w leczeniu CLL od ponad 40 lat i jest wciąż przydatny, zwłaszcza u chorych starszych i w złym stanie ogólnym. Jednakże lek ten nie jest skuteczny u pacjentów opornych na analogi puryn i przeciwciała monoklonalne. Analogi nukleozydów purynowych, fludarabina i kladrybina, są stosowane u większości chorych na CLL, zarówno w pierwszej linii jak i w przypadku oporności na leki alkilujące. W randomizowanych badaniach potwierdzono większą skuteczność analogów puryn skojarzonych z cyklofosfamidem lub z cyklofosfamidem i ritukasmabem w porównaniu z monoterapią. Alemtuzumab może być skutecznym lekiem u chorych opornych na analogi puryn. Ponadto w badaniach klinicznych znajduje się wiele nowych leków, które w przyszłości mogą się przyczynić do dalszej poprawy wyników leczenia chorych na CLL.

SŁOWA KLUCZOWE: Przewlekła białaczka limfocytowa – Analogi nukleozydów purynowych – Fludarabina – Kladrybina – Rituksimab – Chemioimmunoterapia – Przeciwciała monoklonalne – Przeszczepianie komórek krwiotwórczych

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a clonal lymphoid disease characterized by proliferation and accumulation of small CD5/CD19-positive lymphocytes in the blood, lymph nodes, spleen, liver and bone [1]. CLL is the most common indolent lymphoid leukemia, accounting for approximately 30% of all leukemias in Europe and North America with an estimated annual age–adjusted incidence of 3–5 per 100 000 persons [2]. In the Western world an estimated incidence is nearly 96,000 with an estimated 15,100 new cases and 4,390 deaths in the US, in 2008 [3] The disease is diagnozed most commonly in the elderly and the median age at diagnosis is 65–70 years with 80% of patients diagnozed more than 60 years of age.

The natural clinical course of CLL is highly variable and chemotherapy is usually not indicated in early and stable disease [4, 5]. However, patients with symptomatic and/or progressive disease should be immediately treated [6]. Widely accepted guidelines for the initiation of chemotherapy in CLL patients have been proposed by the National Cancer Institute Sponsored Working Group (NCISWG) [6]. According to these guidelines the criteria for the initiation of therapy may not be identical for routine clinical practice and for patients included in clinical trials. Therapy should not be initiated in patients who have smoldering CLL, including those with Rai stage 0 or Binet A until disease progression or unless disease-related symptoms. Laboratory results supporting deferred therapy include non-diffuse pattern of bone marrow involvement, serum Hb concentration >13g/dl, peripheral blood lymphocytes less than 30×10^9/l and lymphocytes doubling time longer than 12 months. The criteria for treatment initation include disease related symptoms, especially fever, body weight loss and extreme fatigue, increasing bone marrow failure, autoimmune anemia and/or thrombocytopenia responding poorly to corticosteroid treatment, massive or progressive splenomegaly and/or lymphadenopathy, progressive lymphocytosis and recurrent infections.

Indications for the 2nd and subsequent therapies are basicly the same as for initial treatment – advanced or progressive disease. According to the recent updated guidelines indications for treatment are different in clinical trials and general practice [7, 8]. Patients who have resistant disease, a short time to progression after the first treatment, and/or leukemia cells with del(17p) often do not respond to standard chemotherapy and have a relatively short survival. Therefore, such patients should be offered investigative clinical protocols, including allogeneic hematopoietic stem cell transplantation. The response to second or subsequent line treatment depends on a variety of factors especially, clinical stage, adverse biological prognostic factors and numbers of prior therapies. However, the most important is refractoriness to the last treatment.

Criteria for response evaluation

Updating standardized criteria of the National Cancer Institute and Working Group for diagnosis and response assessment in CLL has been recently published in Blood [8]. According to this criteria only three possibilities are identified in the evaluation of response – Complete response (CR), partial response (PR) and treatment failure, which includes stable disease, non-response, progressive disease and death from any cause.

Assessment of response should include a careful physical examination and evaluation of the blood and marrow. Imaging studies in particular CT scans, generally are not required, except to monitor the response to therapy in clinical trials. CR is approved if the following criteria as assessed at least 2 months after completion of therapy are fulfill:

1. Peripheral blood lymphocytes below 4×10^9/L (4000/μL),
2. Absence of significant lymphadenopathy (eg, lymph nodes >1.5 cm in diameter) by physical examination. In clinical trials, a CT scan of the abdomen, pelvis, and thorax is recommended,
3. No hepatomegaly or splenomegaly by physical examination,
4. Absence of constitutional symptoms,
5. Neutrophils should be higher than 1.5×10^9/L, platelets more than 100×10^9/L and hemoglobin more than 11.0 g/dL,
6. For patients in clinical trial, a marrow aspirate and biopsy should be performed at least 2 months after the last treatment if clinical and laboratory demonstrate that a CR has been achieved. To confirme a CR, the marrow sample must be at least normocellular , with less than 30% of nucleated cells being lymphocytes and lymphoid nodules should be absent. In general practice, the use of a marrow biopsy for evaluating a CR is not necessary,
7. In clinical trials the quality of the CR should be assessed for MRD by flow cytometry or by immunohistochemistry.

PR is defined by the following criteria:

1. A decrease in the number of blood lymphocytes by 50% or more from the value before therapy,
2. A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy,
3. A reduction in the enlargement of the spleen or liver by 50% or more,
4. In the blood count neutrophils should show more than 1.5×10^9/L, platelet counts greater than 100×10^9/L or 50% improvement over baseline and hemoglobin greater than 11.0 g/dL or 50% improvement over baseline.

Progressive disease is characterized by at least the one of the following parameters:

1. Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates or an increase by 50% or more in greatest determined diameter of any previous site,

2. Increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly,
3. An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter,
4. Transformation to a more aggressive histology (eg, Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy,
5. Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) not attributable to treatment.

Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease are defined as a stable disease.

Duration response should be measured from the last treatment until evidence of progressive disease. Relapse of CLL is defined as a patient who has previously achieved the CR or PR but after a period of 6 months or more demonstrated evidence of disease progression. Refractory disease is defined as treatment failure or disease progression within 6 months to the last antileukemic therapy.

Available strategies for refractory or relapsed disease

Several drugs and therapeutic strategies have been developed in the last 50 years. These include alkylating agents, purine analogs (PNA) and combination chemotherapies [9–11]. This agents are used both as initial treatment, and in the treatment of refractory or relapsed disease. However, alkylating agents, especially chlorambucil are usually not active in the treatment of PNA refractory disease. More recently the introduction of monoclonal antibodies (mAb), especially rituximab directed against CD20 and alemtuzumab directed against CD52, has renewed interest in CLL therapy [11]. Combination therapies with PNAs and cyclophosphamide and especially with PNA, cyclophosphamide and rituximab are more active than monotherapy in terms of overall response (OR), CR and progression free survival (PFS). In randomized trials the combination of rituximab with fludarabine and cyclophosphamide (R-FC regimen) demonstrated higher rates of overall response, CR and PFS in previously untreated and relapsed/refractory CLL [12, 13]. In our center the management of relapsed CLL patients is in line with the recent ESMO recommendations [7]. The first line treatment may be repeated, if the relapse or progression occured 12 months or longer after initial therapy. According to the ESMO recommendations the treatment of patients with no response or relapsed within 12 months should depend on the method of 1st therapy [7].

Recently, several new agents have been explored and have shown promise in treating CLL [15–18]. These treatments include new mAbs, agents targeting the antiapoptotic bcl-2 family of proteins, receptors involved in mediating survival signals from the microenvironment, antisense oligonucleotides and other agents. The most promising are new mAbs targeted CD20 molecule, lumiliximab, epratuzumab, apolizumab, galiximab and anti-CD40 mAbs [16, 17]. Oblimersen, flavopiridol and lenalidomide are also being evaluated both in pre-clinical studies and in early clinical trials [17, 18].

Purine nucleoside analogs in refractory/relapsed CLL

Purine nucleoside analogs, fludarabine (FA), cladribine (2-CdA) and pentostatin used as single agents inpreviously untreated or relapsed/refractory patients have been evaluated in several clinical trials [19–23]. The OR rates ranged from 20 to 80% in a case of fludarabine and cladribine. Pentostatin was rather less active in pretreated patients.

Several authors indicate that use of the same agents which were effective in the first treatment is an attractive option. In the study performed by Thomas et al. [24] 142 previously FA sensitive patients were re-treated with this agent used alone. The response rate was 85% including 11% of CR and 63% of PR.

Cladribine seems to by similarly active to FA in previously treated patients in several clinical trials [25–27]. Responses rates ranged from 31 to 68%. The important observations have been made in our randomized study comparing 2-CdA with chlorambucil [21–22]. In this study patients relapsed after at least 12 months were re-treated with the same regimen as initially and the patients refractory to or relapsed within 12 months were, switched to an alternative treatment. We found that re-treatment with 2-CdA or chlorambucil leads to response in about half of the patients in both 2-CdA and chlorambucil arm. Moreover, the duration of response was shorter in re-treatment than 1st line treatment and myelotoxicity was more pronunced. However 2-CdA was active when applied as second – line treatment in chlorambucil refractory patients than vice versa.

The existence of cross-resistance of PNAs is a matter of debate. The majority of clinical studies suggest that there is cross-resistance between 2-CdA and FA in CLL patients. Juliusson et al. [28] obtained response to 2-CdA in four patients previously non-responsive to FA. Similarly, Byrd et al. [29] reported lack of clinical cross-resistance between FA and 2-CdA. They treated with 2-CdA 28 patients with FA refractory CLL without severe thrombocytopenia or granulocytopenia. No patient had a CR, but nine (32%) attained a PR. The median progression free survival (PFS) was 9 months and the median OS was 2.2 years. However, myelotoxicity of 2-CdA was significant, including grade 3–5 neutropenia in 75%, thrombocytopenia in 68%, and infections in 45% of the patients. In contrast, O'Brien et al. found cross-resistance between these two agents in a similar group of patients. Our studies also indicated cross-resistance when 2-CdA was used as first line therapy and FA as a second-line therapy [30]. There were only two partial responses to FA therapy in 10 CLL patients refractory to 2-CdA and eight patients were non-responding. Taking into account the above observations, other agents including anti-CD20 monoclonal antibody rituximab and anti-CD52 antibody alemtuzumab should be rather used in PNA refractory patients.

Among cytotoxic agents alkylating drugs and anthracyclines were the most frequently combined with PNA [31, 32]. Several studies have shown that PNA and cyclophosphamide has high efficacy in pretreated patients with CLL and a significant advantage over single agent fludarabine in previously untreated and relapsed/refractory patients [33–36]. In the study of O'Brien et al pretreated patients not refractory to

fludarabine and/or alkylating agents can achieve an OR rate of ≥ 80% [36]. Patients refractory to FA have a response rate of 38%. The median time to progression in responding patients who have previously received FA and alkylating agents was 20 m and in patients who had only received alkylating agents a median PFS was 33 m. Prior therapy also affects median survival. Estimated PFS was 21 m for those treated with alkylating agents and 12 m for those who were FA refractory.

Monoclonal antibodies

The most important clinical value in the patients with CLL have at present rituximab and alemtuzumab [37, 38]. Unfortunately, rituximab in conventional doses of 375 mg/m^2 weekly for four doses has rather low activity in CLL. However, some studies suggest that higher doses are more effective than standard doses used rutinely in other lymphoid malignancies [39]. The results of recent clinical studies suggest that in patients with CLL rituximab in combination with PNA can increase the response rate including the CR, compared with PNA alone [40–43]. Investigators at the MD Anderson conducted a single- arm study of rituximab combined with FC (R-FC) in 177 patients with previously treated CLL [41]. CR was achieved in 25% and OR rate in 73% of the patients. The above study indicate that R-FC regimen has extraordinary clinical activity in pretreated patients with CLL.

We investigated the efficacy and toxicity of combined therapy consisting of rituximab and 2-CdA (RC protocol) or 2-CdA, CY and rituximab (RCC protocol) in patients with refractory or relapsed CLL [42, 43]. The RC regimen consisted of a 6-hour infusion of rituximab 375 mg/m^2 on day 1 and hour infusion of 2-CdA 0.12 mg/kg on days 2–6. The RCC protocol consisted of rituximab at a dose of 375 mg/m^2 on day 1, 2-CdA at a dose of 0.12 mg/m^2 on days 2 through 4, and intravenous CY at a dose of 250 mg/m^2 per day on days 2 to 4. The RC/RCC courses were repeated at 4-week intervals. Fourty six patients entered the study. Three patients (6.5%) achieved a CR and 31 (67%) patients achieved a PR.

Subsequently, multicenter, randomized phase III study has been initiated to evaluate the efficacy and tolerability R-FC vs FC regimens in relapsed or refractory patients with CD20 positive CLL (REACH study). In this trial 552 relapsed or refractory patients from 17 countries were randomized (1:1) to receive either R-FC or FC [44]. A median of one prior treatment had been administered, consisting of single-agent alkylator therapy (66%), PNA (16%), or combination treatments (CHOP, COP, FA-containing, 18%). Patients with prior FC combination treatment or prior rituximab were not eligible. Median observation time was 25 months. The primary endpoint PFS was significantly prolonged by median 10 months in the R-FC arm (30.6 months) compared to FC (20.6 months, p =0.0002). Secondary endpoints showed similar results. Overall response rate was higher for R-FC vs. FC (70% vs. 58%, p=0.0034), due to superior CR rates (24% vs. 13%, p=0.0007). Grade 3/4 adverse events were higher in the R-FC arm (80%) vs. FC (74%), but serious adverse events were similar (50% vs. 48%, respectively). Grade 3/4 neutropenia and febrile neutropenia were only margin-

ally increased for R-FC (42% and 15%) vs. FC (40% and 12%, respectively), the same was seen for thrombocytopenia (R-FC 11% vs. FC 9%). Grade 3/4 infections (R-FC 18%, FC 19%) were similar, and there was no difference in bacterial, viral, or fungal infections between the two arms. Grade 3/4 anemia was slightly increased in the FC arm (R-FC 2%, FC 5%) [44].

Alemtuzumab, an anti CD52 humanized mAb is an active drug in previously treated patients with CLL, refractory to alkylating agents and PNA [38]. The effectiveness of alemtuzumab in CLL patients was first reported in 1997 by Osterborg et al. [45]. The drug was administered at a dose 30 mg in 2-h intravenous infusion, three times weekly for a maximum period of 12 weeks. They found an OR rate of 43% in 29 patients and a CR in 4% with relapsed or refractory CLL. The median duration of response was 12 months. However, resolution of lymphadernopathy was only observed in 7% of the patients. Several reports have confirmed significant activity of alemtuzumab in relapsed or refractory CLL. Keating et al. [46] investigated the efficacy and safety of alemtuzumab in 93 patients with relapsed or refractory CLL exposed to alkylating agents and having failed previous FA therapy. The OR rate was 33% including CR of 2% and PR of 31%. The median response duration was 8.7 months. Overall median survival was 16 months and median survival for responders was 32 months. The results of other studies in smaller groups of previously treated CLL patients have also been published. In different studies, the OR rate ranged from 31% to 60% and the CR rate from 0% to 31% [47–50]. In the majority of studies, antitumor effects of alemtuzumab were more significant in blood and bone marrow than in lymph nodes.

Recent studies have shown that alemtuzumab can be combined with FA or rituximab with a significant responsiveness and acceptable toxicity [51, 52]. A preliminary reports suggest that alemtuzumab in combination with FA (FluCAM) can increase the response rate in comparison with FA or alemtuzumab alone including CR, with acceptable toxicity. The rationale for combining alemtuzumab with cytotoxic agents or other mAbs is to improve efficacy against bulky disease and better effectiveness in elimination of MRD. Moreover, MoAbs and PNAs have non-overlapping mechanism of action and in consequence, lack of cross resistance. CLL has demonstrated a significant responsiveness to alemtuzumab used in combination with FA or rituximab in several studies [51, 52]. Toxicity of this combined therapy was acceptable. Elter et al. [52] used a reduced intensity FluCam regimen in which FA was administered at a standard dosage of 30 mg/m^2/day for 3 consecutive-days immediately before the alemtuzumab infusion at a dose of 30mg and repeated on day 28 for a total of four cycles. A total of 36 patients were treated in this phase II study. The overall response rate was 83% including 11 CR and 19 PR. The major toxicity in 140 assessable cycles was myelotoxicity with 44% grade 3/4 thrombocytopenia leukopenia, 26% grade 3/4 neutropenia and 30% grade 3/4. These results indicate that FluCam regimen is effective and feasible in CLL patients with relapsed and refractory CLL. On the other side the combination of alemtuzumab with rituximab has rather no advantage over alemtuzumab monotherapy [51].

High dose methyl prednisolone

The results of high dose methyl prednisolone (HDMP) alone or combination with rituximab in advanced CLL resistant to FA has been recently reported by several groups [53–58]. Thornton et al. [53] treated 11 patients with advanced, resistant CLL with HDMP alone. HDMP was given at a dose of 1 g/m^2 for five days, at monthly intervals for one to seven courses depending on the response. H2 antagonists and antimicrobial prophylaxis were given concurrently. Acyclovir prophylaxis was given if there was a recent history of herpes infection. Six patients had a PR as defined by the NCI guidelines and no patient had a CR. The mean duration of PR was 19.6 months with a median of 8 months (range 6–78). Seven patients have died including the 5 non-responders. Previous treatments included chlorambucil, FA, pentostatin, anthracycline containing regimens such as CHOP and alemtuzumab. HDMP was generally well tolerated. Side effects included fluid retention, hyperglycaemia, bradycardia, herpes simplex, and pneumonia in a patient with a previous history of recurrent chest infection and pneumonia. These results suggest that HDMP may be beneficial in the treatment of refractory CLL. Subsequently, the same group used HDMP to treat 25 patients with advanced refractory CLL of whom 45% had p53 abnormalities (54). Fifteen were resistant to FA and 16 were non-responders to their most recent therapy. HDMP was given alone or in combination with other drugs including vincristine, CCNU, Ara-C, doxorubicin, mitoxantrone and chlorambucil, according to the results of *in vitro* sensitivity. The overall response rate was 77% with a median duration of 12 months (range 7 –23+). Responders included 5/10 with abnormal p53, of which two achieved nodular PR. There were no differences in response according to whether HDMP was used alone or in combination. Main toxicity was infection observed in seven patients. This study demonstrates that HDMP alone or in combination with other agents is a useful treatment strategy in refractory CLL including patients with p53 abnormalities.

Castro et al. [56] examined the clinical response of FA-refractory CLL patients treated with HDMP and rituximab. Fourteen patients were treated with three cycles of rituximab (375 mg/m^2 weekly for 4 weeks) in combination with HDMP (1 gm/m^2 daily for 5 days). All patients were refractory to FA. The overall response rate was 93% and the CR rate was 36%. The median time-to-progression was 15 months and the median time-to-next treatment was 22 months. Median survival has not been reached after a median follow up of 40 months. Patients tolerated the treatment well and serious adverse events were rare. All but one patient responded to treatment and the overall survival and time-to-progression were superior to those of other published salvage regimens.

Bowen et al. [55] treated with the HDMP-rituximab 37 patients with with relapsed, refractory, and cytogenetically high-risk CLL. After a median of one cycle of HDMP-rituximab, 29 (78%) patients had an objective response including five of nine patients with deletion of 17p13.1. Eight (22%) patients had a complete clinical response. Although well tolerated, 11 (29%) patients developed infectious complications before completing one month of therapy.

Recently, Dungerwalla et al. [57] described 14 heavily pre-treated CLL patients treated with a combination of HDMP and rituximab. All patients were heavily pre-treated (2–5 prior therapies), with a median disease duration of 54 months. Thirteen patients (93%) had previously received fludarabine and 5 patients had prior exposure to rituximab. HDMP was given intravenously at a dose of 1 gm/m^2 daily for 5 days in combination with 375 mg/m^2 of rituximab on day 1 of a 28 day cycle. Patients received a maximum of 6 cycles of treatment. All patients were given a proton pump inhibitor, cotrimoxazole and low dose oral antifungal prophylaxis with fluconazole. Acyclovir was used in those with a previous history of herpetic infection. The results were compared with a similar historical control group treated with HDMP alone. The combination of HDMP and rituximab induced superior overall (93%) and complete (14%) response rates compared to HDMP alone (overall 43%, complete remission 0%). Responses were seen in all 5 patients with del 11q. However, the single patient with 17p – did not respond. Median PFS was 7 m and median survival 20 m. Despite its efficacy the combination was not easily manageable because of the high rate of opportunistic infections. Three patients developed fungal infections during or soon after treatment, and a further 2 patients went on to develop fungal infections while in remission or after further treatment. Two patients developed opportunistic viral infections.

Quinn et al. [58] reported recently 12 patients with advanced/refractory CLL treated with a combination of rituximab and high-dose steroids. However, 50% of these patients received 40 mg of dexamethasone (HDD) orally for 4 days in 28 day cycles in place of HDMP. The overall response rate was 75%) with one CR and eight PR which included one patient with deleted 17p13.1 who had relapsed after allogeneic stem-cell transplant. The patient who achieved a complete response was treated with HDMP whilst the eight patients who achieved PR included four who received HDD and four who received HDMP. Median duration of response is 14 months (6–35). Twenty-five percent of the patients developed infectious complications. However, there were no patient deaths during treatment. This study suggests that rituximab combined with HDD, with lower doses ogf glucocorticoids, might produce less toxicity than rituximab combined with HDMP without a reduction in efficacy.

New agents

Recently several new agents have been explored and have shown promis in treating CLL. Novel therapies are being evaluated in preclinical studies and early clinical trials. This treatments include bendamustin, new monoclonal antibodies and other agents.

Bendamustin

Bendamustin was designed in the 1960s with the aim of creating bifunctional anticancer agent possessing an alkylating group and also antimetabolite properties [59–61]. In CLL phase I/II trials bendamustin showed response rates of 56–60% in heavily

pretreated patients. Bergman et al. [59] performed a phase I/II study of this agent in pretreated CLL patients. Sixteen patients with relapsed or refractory disease was treated with bendamustine at a shutting dose 100 mg/m^2 on day 1 and 2, repeated every 3–4 weeks. Nine (56%) patients responded to therapy and two (12.5%) of them achieved a CR. Early death within 3 months occured in three (19%) patients. The median duration of response was 42.7 months and after a follow-up period of 53.2 months five patients (31%) were still in remission. Major toxicities were grade 3–4 leukpenia in 8(50%) patients and grade 3–4 infections in seven patients. This study confirms the excellent efficacy of bendamustin even in patients with pre-treated and fludarabine or chlorambucil resistant CLL. Lissitchkow et al. [60] conducted a phase I/II study to determine the maximum tolerated dose (MTD) and dose limiting toxicity of bendamustine. The drug was given at a starting dose of 100 mg/m^2 on days 1 and 2 every 2 weeks. The level of 110 mg/m^2 was established as MTD and the dose of 100 mg/m^2 was recommended for further investigations. Moreover, the treatment intervals of 21 days as defined in the protocol were prolonged to 28 days to allow for sufficient recovery. After the end of therapy nine of 15 patients responded including four CR two PR, and three patients had a stable disease. After a follow-up period of 15 months, the four patients with CR were still in remission. However, it should be noted that all patients included to the study were fludarabine naive. The most common grade 3/4 toxicities were in general haematological, mainly granulocytopenia and thrombocytopenia. Bendamustin was also investigated in combination with rituximab in phase II study.

Novel monoclonal antibodies

Over the last few years, several new mAbs directed against lymphoid cells have been developed and investigated in preclinical studies and clinical trials. Some of them are highly active in CLL [62, 63]. New mAbs directed against CD20 include human mAb ofatumumab, IMMU-106 – which has a > 90% humanized framework and GA-101, a novel third – generation fully humanized and optimized mAb . These agents are highly cytotoxic against B-cell lymphoid cells and are evaluated in CLL.

Ofatumumab is the first fully human anti CD-20 mAb, targets a novel epitope of the CD20 molecule on B-cells and releases very slowly from the target compared with rituximab [63]. Compared with rituximab ofatumumab has similar ADCC but stronger CDC activity. Safety and toxicity of ofatumumab was investigated in a multicenter dose-escalating study including 33 patients with relapsed or refractory CLL [64]. Three cohorts of patients received 4 once weekly infusions of ofatuzumab at the doses of 500, 1000 and 2000 mg. The response rate of cohort C was 50%. Seventeen (51%) of 33 patients experienced infections, 88% of them of grade 1–2.

Recently, the results from the planned interim analysis of an international pivotal trial of ofatumumab in patients with CLL refractory to fludarabine and alemtuzumab (double refractory, DR) or refractory to fludarabine with bulky lymphadenopathy (>5cm) (FBR) has been reported (Hx-CD20-406 phase III study) [65]. Prior rituximab-containing regimen obtained 59% of the patients from DR group and 54% in FBR

group. Patients received 2000 mg of ofatumumab in 8 weekly infusions followed by 4 monthly infusions. The ORR was 51% for the DR group and 44% for the BFR group. These results demonstrate the high effectiveness of atumumab in CLL patients with very poor prognosis, which is double-refractory or bulky fludarabine-refractory disease, who have exhausted standard treatment options.

GA-101 is a novel third generation mAb differed from rituximab. It has high affinity binding to CD20 type II epitope. *In vitro* study GA-101 mediated 5–50 fold enhanced induction of ADCC in comparison with rituximab. However, reduction in CDC upon binding to CD20 was observed [66].

Lumiliximab is an anti-CD23 mAb that is being investigated for the treatment of relapsed CLL. In phase I study reduction of lymphocytes in peripheral blood of CLL patients was observed [67].

Bcl-2 family antagonists

BCL-2 is an apoptosis regulating protein which over expression is associated with chemotherapy resistant disease, oggressive clinical course and poor survival. Therapeutic modulation of the Bcl-2 pathway may represent a new treatment option in CLL.

Oblimersen (Genasense, Bcl-2 antisense, G3139) is a synthetic, 18-base, single strand phosphorothioate DNA oligonucleotide designed to down-regulate Bcl-2 mRNA expression [68]. Oblimersen reduces levels of Bcl-2 expression, reduces cell viability, increases activity of pro-apoptotic mechanisms, reduces tumor size and enhances anticancer drug activity. The agent recognizes the first six codons of Bcl-2, forming a DNA/RNA complex that inhibits translation of the protein [68]. In a phase I-II study, 40 patients with relapsed or refractory CLL previously treated with FA received oblimersen administered at doses ranging from 3 to 7 mg/kg/d as a 5-day continuous intravenous infusion every 3 weeks [69]. Dose limiting reactions in phase I included hypotension and fever. The maximum tolerated dose determined in phase I was 3 mg/kg/d. Two (8%) of 26 evaluable patients achieved a PR. The most common adverse events were pyrexia (33% of patients), fatigue (30%), cough (20%) and hypotension (20%). In a phase III study, O'Brian et al. [70] showed that the addition of oblimersen to chemotherapy with FA and CY produced a significant increase in the number of durable remissions in patients with relapsed or refractory CLL. The results of these studies indicate that oblimersen is a promising agent in refractory or relapsed patients with CLL.

Obatoclax is a hydrophobic molecule developed as a Bcl-2 family antagonist. Recently O'Brien et al. (71) reported the results of a phase I trial of obatoclax in CLL patients. The drug was administered to patients with advanced CLL both as a 1-hr infusion at doses ranging from 3.5 to 14 mg/m^2, and as a 3-hr infusion at doses between 20 to 40 mg/m^2 every 3 weeks. Twenty six patients received a total of 74 cycles. The most frequent adverse event was somnolence and euphoria occurring during the infusion or shortly afterwards. The MTD was 28 mg/m^2 over 3 hours every 3 weeks. One (4%) of 26 patients achieved a partial response. Patients with anemia (3/11) or throm-

bocytopenia (4/14) experienced improvements in hemoglobin and platelet counts. Circulating lymphocyte counts were reduced in 18/26 patients with a median reduction of 24%. Reported the results of a phase I trial in patients with CLL. PR was noted in 1 and stable disease in 7 even of 15 patients.

Flavopiridol is a synthetic flavonoid that is under development by Sanofi Aventis and NCI. It was originally described as a cyclin dependent kinase and other protein kinase inhibitor. Studies in vitro shoved that flavopiridol promote apoptosis of CLL cells independently of p53 function [72]. This agent has no clinical activity in relapsed, FA refractory CLL when administered as a 24-h or 72-h continuous infusion [73]. However, flavopiridol seems to be more active when used in 30 min loading dose followed by have infusion administered weekly for 4 or 6 weeks [74]. Of the 42 patients with refractory CLL 19 (45%) achieved a PR including patients with 11q and 17p.

Thalidomide and its derivative lenalidomide are immunomodulating agents with antiangiogenic properties [75]. Lonalidomide was investigated in relapsed and refractory patients and showed significant activity [76]. However, the toxicity of this drug seems to be an important problem and the optimal dosing schedule needs to be defined in future trials.

Recently three novel PNA, clofarabine, nelarabine and forodesine, have been synthesized and introduced into clinical trials [77]. These agents showed clinical activity in lymphoid tumors, especially T-cell malignancies. Forodesine seems to be the most promising agent in CLL. Recently first studies concerning its efficacy in the treatment of patients with refractory, relapsed CLL has been initiated.

Haematopoietic stem cell transplantation

In recent years significant improvement in hematopoietic cell transplantation procedures has been observed [78–81]. However, the exact role of this therapy in the standard management of CLL patients is still undefined. HSCT has been utilized mainly for patients with high risk CLL or for those who failed standard therapies.

Autologous HCT have the potential for achieving molecular remission in 60–70% of the patients. However relapses are frequent and there is no evidence of plateau for overall and event free survival. Allogenic HCT is the only curative therapy of CLL. Unfortunately, this therapy is associated with high treatment related mortality.

Development of reduced intensity conditioning regimens has improved the tolerability of allogenic HCT in CLL with preserving graft versus leukemia effect [80]. Recently, the EBMT transplant consesus regarding indications for allogenic stem cell transplantation in CLL has been reported by an international expert panel [81]. The EBMT experts indicate that allogenic HCT is a reasonable treatment option for yonger patients with non-response or early relapse after heaving achieved a response with PNA based combination or autologous transplantation and patients with P53 abnormalities requiring treatment. However, the optimum transplant strategies may vary according to dictinct clinical situation.

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