

REVIEW ARTICLE

The use of inexpensive broad spectrum lower toxicity therapeutics in chronic lymphocytic leukemia

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Summary

The use of new and highly efficient targeted therapies for chronic lymphocytic leukemia (CLL) is costly and out of reach for many health care systems. On the other hand, in recent years, few inexpensive, broad-spectrum low-toxicity therapeutics have proven to be effective both in the preclinical and clinical settings. In early-stage CLL, the use of 2000 mg of epigallocatechin-3-gallate (EGCG) from the green tea extract twice a day was able to reduce the absolute leukocyte count. Supplementation of >2000 IU/day of Vitamin D in early low-risk CLL patients is able to delay disease progression and postpone the moment of initiation of the first treatment. The doses of both vitamin D and EGCG were shown to be safe in older patients. Vitamin D, EGCG and Curcumin, either as monotherapy or in combination, have additive and synergistic effects with conventional chemotherapy. Further observations have identified the improvement of response to rituximab-fludarabine-cyclophosphamide (R-FC) therapy with concomitant administration of statin and aspirin combination in relapsed/refractory CLL. Finally, high dose dexamethasone with 40mg/m²/day for 4 days, every 28 days, either alone or with monoclonal antibody, might be used as a salvage therapy or for debulking before transplantation in refractory/resistant cases. Dexamethasone therapy is followed by transient response and high rate of infections, but fluid retention and other toxicities are lower compared to high dose methylprednisolone schedules.

The low cost therapeutics discussed in this review could not be a substitute for the more effective targeted therapies, but their use in every day practice might postpone the need for early implementation of new and costly medications.

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Key words: chronic lymphocytic leukemia, curcumin, epigallocatechin-3-gallate, steroids, vitamin D

Introduction

The recent decade has witnessed major breakthroughs in treatment of CLL. The emergence of inhibitors of crucial signaling pathways from B cell receptors and downwards has changed the treatment strategies and considerably improved outcomes even in patients with resistant disease forms. Nevertheless, the prices of new oral targeted agents have tremendously increased the overall cost of treatment. In the second-line treatment setting, the use of Ibrutinib and Idelalisib in United States led to 70% rise of pharmaceutical costs since their approval by the FDA in 2014 [1]. It was estimated that the approval of Ibrutinib in

the first-line treatment in March 2016 based on the results of the Resonate-2 trial, will cause a cost increase of 350% of the 2013 level [1,2]. The increase in the treatment costs would be accompanied by substantially improved survival and the need for continuous administration of oral therapies [3].

The growing incidence and higher prevalence of CLL has additionally enlarged the financial burden of treatment in many countries [4,5]. The majority of CLL patients are over 70 years old [6]. In many European countries and particularly in the Balkan region, the rise of aged population

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has become striking. The growing aging index in Greece and Slovenia combined with the depopulation of young people in west Balkans and Bulgaria have set the ideal conditions for the increase of incidence of CLL throughout the Balkan peninsula [7,8]. High economic debt and low health care budgets of the Balkan region countries have become the greatest barrier to acquire novel therapies that are expensive even for developed countries. Until economic crises reach their end, medical practitioners could apply less expensive strategies that might be able to improve the response to current treatment modalities or perhaps postpone the need for therapy.

Vitamin D

Population studies have shown that the lower serum concentrations of Vitamin D were more frequent in the age groups typically affected by CLL [9]. This deficiency is common even in regions with high ambient ultraviolet radiation, due to poor mobility of elderly population and poor dietary intake of vitamin D [9].

Besides genes that regulate bone metabolism, Vitamin D regulates the expression of nearly 200 genes critical for differentiation, apoptosis and angiogenesis of healthy and malignant cells [10,11]. These effects lead to a considerable impairment of immunological response in infection and malignancy [12,13]. Having in mind previous data, the association of Vitamin D deficiency with inferior survival of many types of lymphoid neoplasms, including diffuse large B cell lymphoma, follicular lymphomas and CLL, is not surprising [10,13-15]. In diffuse large B cell lymphoma, vitamin D insufficiency causes disruption of immune response, minimizing the effectiveness of Rituximab [16].

Low level of Vitamin D has negative impact on overall survival and is an independent predictor of shorter time to treatment in CLL patients [17]. Further confirmation of the association of shorter time to first treatment with Vitamin D insufficiency came from a study by Molica et al. in 130 previously untreated Binet A stage CLL patients [18]. Many of these clinical data lead to the conclusion that supplementation of Vitamin D might be a logical and useful strategy in CLL [19]. A recent meta-analysis showed that sufficient intake of Vitamin D might prevent the development of CLL [20]. Vitamin D supplementary therapy might be a useful attempt to delay disease progression in early stages of CLL [18]. In rare cases the benefit of this early treatment strategy could

induce complete remission of CLL [21].

The exact dose of Vitamin D supplementation in CLL patients has not been studied extensively. It is believed that serum levels of 30-40ng/ml of 25-OH-D₃ are necessary to obtain normal immune function [22]. Since the therapeutic range is wide, Vitamin D toxicity is rare and occurs only if given as consecutive intramuscular injections at extremely high cholecalciferol doses such as 600,000 IU [23]. It is worth noting that intermittent high dose Vitamin D may not be effective [24]. Oral intake could rarely cause hypervitaminosis and its associated symptoms. In a small study with CLL patients by Kubecko et al. supplementary dose of 2000 IU appeared to be sufficient to increase the serum of 25-OH-D₃ to levels between 20-30ng/ml [25]. According to the Central European guidelines for Vitamin D supplementation in adults and elderly, all patients with 25-OH-D₃ concentration lower than 20ng/ml, should receive 7000-10000 IU of cholecalciferol per day [26]. Generally the daily oral dose of 10,000 IU is accepted as the safe upper limit for Vitamin D supplementation [27].

While waiting for the formal guidelines and recommendations, clinicians should be encouraged to apply Vitamin D supplementation in their everyday treatment practice in CLL patients.

Curcumin

Recent literature contains extensive data on the efficacy of curcumin in the preclinical setting. Curcumin induces apoptosis of B-CLL cells in a dose-dependent manner [28]. This effect is a result of both activation of programmed cell poly(ADP-ribose) polymerase cleavage and inhibition of prosurvival pathways including STAT3, Akt and NFκB [28,29]. Moreover, curcumin suppresses the antiapoptotic MCL-1 and X-linked inhibitor of apoptosis proteins and upregulates the proapoptotic protein BIM [28]. When transferred into the clinic, the effectiveness of curcumin is limited by its reduced solubility and bioavailability in patients. Small clinical benefit was observed in a cohort of 21 patients in stage 0/I CLL, after a 6-month treatment with curcumin. In this group, only few patients had decreased absolute lymphocyte count [30]. Modest effect, if any, was described by the same authors in a pilot study in 2016, with only 10 CLL patients in stage 0/1, treated with a combination of curcumin and rice bran arabinoxylan [31]. These results were in concordance with a statement of Laura et al. that curcumin alone would not be effective, but it may

enhance the effect of a variety of compounds [32]. In this manner, curcumin may potentiate the effects of Vincristine [33]. In the meantime, various curcumin combinations with specific adjuvants, nano-formulations, hybrid molecules or curcumin analogues are under development in order to improve its bioavailability and effectiveness [34].

Epigallocatechin-3-gallate

Another promising approach came from use of oral green tea extracts, particularly its major constituent, epigallocatechin-3-gallate (EGCG), in CLL patients. The rationale for clinical studies came from *in vitro* observations of anti-proliferative and proapoptotic effects and suppression of activation of NF κ B mediated by EGCG in tumor cell cultures [35]. This compound strongly inhibited growth factor mediated pathways, mitogen activated protein kinase dependent pathways and ubiquitin/proteasome degradation pathways in tumor cells [36].

The half maximal inhibitory concentration of EGCG (IC₅₀) that measures its effectiveness to inhibit biological functions in CLL cell cultures is 4 μ M [37]. This value is much lower for CLL compared to other cancers [37]. Having in mind that after normal green tea consumption IC₅₀ plasma levels of EGCG stay below 1 μ M, the value of 4 μ M is not unreachable [38]. The combination index calculated *in vitro*, using combinations of Chlorambucil or Fludarabine with EGCG, found that EGCG concentration of 4 μ M, was able to reduce viability of B-CLL cell in culture to below 10%. This means that there is an additive and synergistic effect of EGCG with chemotherapy drugs in CLL [37].

In phase I and II studies, Shanafelt et al. demonstrated that EGCG is effective and safe for clinical use [39,40]. First, a phase I study with 33 patients in Rai stage 0-II identified the dose of 2,000 mg of EGCG per os twice a day as low toxic and effective. Inclusion criteria in this study were previously EGCG naive asymptomatic CLL patients that were not candidates for treatment according to National Cancer Institute Working group criteria for initiation of therapy [41]. In the phase II trial with 42 low risk CLL patients in Rai I-II stage, EGCG showed significant clinical activity. Criteria for biological response were considered fulfilled in case of sustained decrease of absolute leukocyte count \geq 20% and/or at least 30% reduction in the sum of all nodal areas during a 6-month period of active EGCG treatment. Reduction of absolute leukocyte count was registered in

13 (31%) patients, while reduction of lymphadenopathy had 20/29 (69%) of the cases [40].

The limitation of this treatment approach is the poor oral bioavailability of EGCG, patient compliance (the need to take many pills) and lack of differentiation between many green tea extracts on the market [37]. Numerous EGCG derivatives, prodrugs and micellar nanocomplex combinations have been designed to improve stability and bioavailability. While the search for the most effective derivative is ongoing, clinicians should not be discouraged to use EGCG and related polyphenols in CLL. It is worth mentioning that in clinical trials with advanced cancers, EGCG doses as high as 1g/m² three times a day could be tolerated up to 6 months [42]. Until commercially stable and reliable therapeutics appear, the clinical use of EGCG in combination with other low toxic broad spectrum substances in CLL will be limited to successful induction of remission in sporadic case reports [43].

Statins and CLL

Statins, 3-hydroxy-3 methylglutaryl-coenzyme A reductase inhibitors (HMG-CoA) are widely used in the treatment of cardiovascular diseases and dyslipidemia. Except their initial therapeutic use, it was found that HMG-CoA significantly reduced cancer-related mortality from 27 various cancer types [44]. Furthermore, recent large studies have found a strong association between statins and reduced risk for development of non Hodgkin lymphomas [45,46]. Other studies with follicular and diffuse large B cell lymphomas have failed to prove interference of Rituximab efficacy caused by statins [47]. Also, HMG-CoA has no influence on survival in these lymphoma subgroups [47,48]. However, a recent study has demonstrated reduced mortality in multiple myeloma patients that concomitantly receive statins [44]. This effect could be partially explained by blockade of the mevalonate pathway, which has critical function in myeloma pathogenesis [49].

Preclinical studies in CLL have made several discoveries that provided the rationale for clinical trials with statins. It was found that the mevalonate pathway cascade and RAS/ERK1-2 and RhoA/RhoA kinases are more active in IGVH unmutated CLL [50].

CLL cells utilize free fatty acids to produce chemical energy. This is mediated by STAT 3 pathway which is constitutively activated in CLL [51]. Therefore, CLL cells have impaired lipid metabolism and increased mitochondrial activity, that

could explain the frequent occurrence of hypercholesterolemia in CLL patients [52,53]. Taken together, the presented data have postulated that lowering cholesterol and interfering with the lipid metabolic pathways may be beneficial for CLL patients.

The initial hypothesis that use of statins and aspirin may induce survival benefit in CLL patients could not be confirmed in a study published by Shanafelt et al. In this observational cohort study with 686 newly diagnosed stage 0 CLL patients, neither statin or aspirin monotherapy, nor their concomitant use had any influence on the delay of the time to first treatment [54]. On the contrary, concomitant statin and aspirin treatment in advanced relapsed/refractory CLL seemed to have some benefit [55]. In the paper of Chae et al [55], 58 patients receiving salvage R-FC protocol concomitantly with aspirin and statins had superior response rate in comparison to the group that received R-FC alone. Overall response rate (ORR) reached 100% for statin and aspirin users either alone or in combination, while patients who took neither drugs had ORR of 72%. Significant prolongation of overall (OS) and progression free survival (PFS) was superior in the statin and aspirin group reaching 9.2 and 6.1 years, respectively. OS and PFS in non users was 1.6 and 3.7 years, respectively. Interestingly, multivariate analysis has shown that neither of single-agent statin or aspirin had any influence on PFS in patients with CLL. Taken together, it seems that the benefit from the use of statins in CLL is limited.

Corticosteroids

Despite the widespread use in numerous B cell malignancies and autoimmune diseases mediated by B cells, steroids were not considered essential in the treatment of CLL. When given in standard doses, steroids don't show any significant activity given alone and they don't improve the effectiveness in combination with purine analogs [56-58].

Monotherapy with high dose methylprednisolone (HDMP), on the contrary, has shown activity in relapsed/refractory CLL [59]. The usual dose of HDMP is 1g/m², days 1-5 repeated every 4 weeks. This schedule demonstrated efficacy in high-risk refractory CLL, including cases with p53 gene mutation or deletion [60]. Short duration of response led to development of numerous combinations of HDMP with monoclonal antibodies Alentuzumab and the less toxic Rituximab [61]. Rituximab-HDMP combination showed increased efficacy, especially in p53 affected groups but high

levels of steroid toxicity remained unchanged [62]. Many relapsed/refractory CLL patients besides profound immunodeficiency developed steroid diabetes, fluid retention and increased rate of infections with almost 50% early deaths after HDMP [63]. As a result of an attempt to reduce treatment-related complications, a recent combination of high-dose Dexamethasone combined with Rituximab in relapsed disease emerged. High-dose Dexamethasone (40mg on days 1-4 repeated every 28 days) with Rituximab in this treatment schedule had 6-fold lower cumulative dose of steroids with regard to relative glucocorticoid activity compared to R-HDMP protocol [64]. This approach could not ameliorate the development of infection. Nevertheless, it has proved to be successful in debulking before allogeneic stem cell transplantation, with overall response in 75% but low complete remissions in 3% of cases [64]. Rituximab-Dexamethasone protocol (R-Dex) had short median PFS of 8 months with median time to next treatment of 12.9 months and median survival of 25.5 months [64].

Although response in CLL is transient and complicated with immunosuppression, clinicians should not give up easily from steroids. The main reason lays in the fact that steroids affect many aspects of biology of normal and malignant B cells. Low-dose steroids induce redistribution of CLL cells [65]. They also interfere with the activity of proinflammatory genes through inhibition of NFκB and AP-1 transcription factors in normal B cells and affect signaling through the T cell receptor and downstream kinases in healthy T cells [65]. All of the above effects might be important for the malignant B cell development and interactions with its microenvironment. Their use could be explored in future CLL therapies in a different setting and therapeutic combinations.

In conclusion, ≥2000 IU/day of Vitamin D as well as 2000 mg/twice a day of EGCG from the green tea extract, showed to be effective and safe in older patients in early-stage CLL. Supplementation of Vitamin D in early low-risk CLL patients is able to delay disease progression. Vitamin D, EGCG and Curcumin either as a monotherapy or in combination, have additive and synergistic effects with conventional chemotherapy. In relapsed/refractory CLL, response to R-FC therapy could be improved with concomitant administration of statin and aspirin combination. Finally, high-dose Dexamethasone with 40mg/m²/day for 4 days, every 28 days, either alone or with monoclonal antibody, showed equal rate of infections, but lower rate of other

steroid-related toxicities than HDMP schedule.

The low-cost therapeutics discussed in this review could not be a substitute for the more effective targeted therapy, but their use in every day practice might postpone the need for early imple-

mentation of new and costly medications.

Conflict of interests

The authors declare no conflict of interests.

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