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Second line treatment for relapsed chronic lymphocytic leukemia



Introduction

In spite of the remarkable therapeutic achievements obtained with purine analogues and monoclonal antibodies, chronic lymphatic leukaemia (CLL) has still to be considered an incurable disease. Indeed, in the vast majority of patients, the natural history of the disease is characterized by multiple relapses and by multiple remissions, induced by the potential treatments available.

Accordingly, overall survival and quality of life should be the most important endpoints of the clinical management of patients, while the achievement of a clinical or molecular complete response (CR) should be considered major endpoints in the context of controlled clinical trials, aiming to demonstrate that CLL may be a curable disease.

The choice of the best treatment for the single patient at any time during the course of his disease is dependent on a number of factors which include age, performance status, comorbidities, type and effectiveness of the previous treatment received. Obviously, the ultimate goal of treatment, which can be in many cases only palliation, should also be considered.

Herein available data on second-line therapy in CLL will be briefly reviewed, with particular emphasis to standard-dose chemotherapy, since further options, like the use of monoclonal antibodies and of hematopoietic stem cell (HSC) transplantation, as well as the treatment of truly refractory patients will be covered by other contributors

Specifically, when considering the choice of second-line treatment in patients refractory or relapsed after primary treatment, the type of first-line treatment administered, the level of the response achieved and its duration are to be considered. Moreover one should also try to foresee the future treatment options which will be still available for the patient, when he will fail the second-line treatment chosen, as he most probably will do.

Informations regarding the previous history of patients treated, as well as the outcome of patients after subsequent lines of treatment are lacking in many of the large number of trials performed in CLL, making an evidence-based choice often difficult. Herein, the second-line treatment options available are discussed according to the type of first-line treatment received by the patient.

Chlorambucil pretreated patients

Wait and see

The concept that first-line treatment should be reserved to patients with symptoms, evidence of marrow failure or rapid disease progression is supported by controlled studies and has therefore gained general acceptance in CLL at diagnosis.¹ While not supported by formal studies, the same concept may also be used in the setting of pretreated patients, particularly in those with indolent relapses and in the absence of adverse prognostic factors. Such strategy may be most useful in patients receiving non aggressive first-line treatment, such as single agent chlorambucil, because of age or poor performance status.

Retreatment with chlorambucil

Chlorambucil is still first choice upfront treatment for many CLL patients, particularly for the elderly and for those with significant comorbidities. Retreatment with chlorambucil or other alkylating agents can achieve response rates ranging between 22% and 62%, with very few complete responses.² However the response rate is lower and the responses are often of shorter duration compared to first-line therapy. Therefore the strategy of retreating patients with the same agent can be recommended only when the duration of the first response has been longer than 6 months,³ according to the opinion of experts.

Single agent fludarabine

Purine analogues obtain higher response rates and responses of longer duration than chlorambucil. In the Intergroup randomized study, at crossover, fludarabine obtained an overall response rate of 46% in chlorambucil-pretreated patients whereas only 7% of fludarabine-pretreated patients responded to second-line chlorambucil.⁴ There are a number of studies in which single-agent fludarabine, at

the dose of 25 mg/sqm/iv daily for 5 days have been tested as second-line therapy. The overall response rates range from 32 to 59% with as much as 23% of patients achieving a complete response. The median duration of response was longer than with alkylating agents, ranging from 11 to 21 months,^{5,6} but no long-term cure was achieved.

Attempts to improve the results with minor modifications of the dose and duration of fludarabine, the addition of prednisone, as well as the use of other purine analogues⁷ did not obtain a significantly different outcome.

Combination therapy

Since combination of alkylating agents with anthracyclines, vincristine or other cytostatic agents, excluding nucleoside analogues, did never prove superior to chlorambucil in patients at diagnosis, their use as second-line therapy after chlorambucil failure has a very weak rationale and should be reserved to the lack of any other possibility.^{8,9}

On the other hand, the combination of fludarabine with cytostatic agents, in primis cyclophosphamide, has both a sound biological rationale and documented efficacy. Fludarabine and cyclophosphamide lack significant overlapping toxicity, except for myelotoxicity, and show antileukemic synergy which appears to be related to induction of DNA damage by cyclophosphamide followed by inhibition of DNA repair by fludarabine.

The combination of the two drugs (Flu-Cy) can achieve response rates as high as 85%, with 15% CRs in fludarabine-naïve patients.¹⁰ Similar results have been reported in phase 2 studies using other nucleoside analogues, and somewhat better CR rates with the addition of mitoxantrone to Flu-Cy.¹¹

Autoimmune hemolytic anemia is a well-known complication of fludarabine. However in the randomized MRC trial its frequency did not differ between patients receiving fludara-

bine or chlorambucil as first-line agent and it was lowest in the arm treated with Flu-Cy, which may be therefore considered the first option in patients with a positivity of the direct antiglobulin test.

Immunochemotherapy

The combined use of monoclonal antibodies and cytostatics, including alkylating agents and purine analogues, is a very promising treatment approach for CLL patients. The addition of rituximab to Flu-Cy (FCR) achieved an overall response rate of 76% and a CR rate of 28% in a small group of 25 fludarabine-naïve patients.¹² Results in this setting did not differ significantly from those achieved with Flu-Cy but the limited number of patients treated and the lack of controlled trials does not allow definite conclusions. Obviously, given that since single-agent chlorambucil as first line treatment is currently reserved to elderly patients, only selected cases among them may benefit from aggressive second-line protocols, as well as transplant options.

Fludarabine pretreated patients

Patients with CLL receiving fludarabine as their first-line treatment are generally younger and in better general conditions than patients receiving first-line chlorambucil. Their life expectancy is often longer and therefore, even in the presence of an indolent disease course, a conservative management with the aim of limiting the risks and side effects of treatment, may not be appropriate.

Chlorambucil

As already mentioned the use of chlorambucil, which can obtain a response in less than 10% of patients, as well as combination chemotherapy programs not including nucleoside analogues, should be reserved as pallia-

tive treatment for patients unfit for more aggressive programs.

Retreatment with fludarabine-containing regimens

Single-agent fludarabine induced a second response in approximately two thirds of patients receiving fludarabine as first-line agent. The frequency and duration of responses were apparently not affected by the duration of the first response, but were better in patients relapsing after a CR than after a partial response. Indeed a CR was obtained in 20% of patients overall, but only among those who had already achieved a CR after first-line fludarabine.¹³

The quality of remission is important since it may correlate with the efficacy of further therapeutic procedures, particularly stem cell transplantation. In a series of phase II trials, the CR rate was lower in patients retreated with fludarabine alone compared to combinations of fludarabine with cyclophosphamide ± other cytostatic agents¹⁴ and, more recently, by further adding monoclonal antibodies like rituximab or alemtuzumab^{12,15,16} or innovative biological agents like antisense oligonucleotides.¹⁷

Unfortunately, the scarcity of comparative trials precludes any firm conclusion on what may be the best fludarabine-containing combination regimen for fludarabine-relapsed patients. Moreover the type of first line fludarabine-containing regimen, whether single-agent vs Flu-Cy vs immunochemotherapy is likely to impact on the frequency and quality of responses to retreatment, adding further complexity to the choice of second-line treatment. Once again, prospective trials would be needed to assess not only the best regimen but also the best sequence of regimens to be used and it is therefore of paramount importance that relapsing patients be always treated in the context of controlled trials (guide lines).

Alemtuzumab

Alemtuzumab has been approved for treatment of fludarabine-refractory patients based upon a response rate of 33% obtained in heavily pretreated CLL patients. Its elective efficacy on disease localized in blood and bone marrow supports its use in patients without significant lymphnode and liver or spleen involvement. However given the modest CR rate of 2% and the median time to progression of 9.5 months,¹⁷ it may be more useful and is actively investigated in combination regimens with cytostatic agents¹⁶ or other biological agents.

A specific indication for alemtuzumab derives from its elective activity in patients carrying a P53 gene mutation, which causes refractoriness to both cytostatic agents and purine analogues.¹⁷

Refractory patients

While patients refractory to first-line chlorambucil can be effectively rescued by purine analogues, significant long-term lasting responses are not to be expected in patients primarily refractory to first-line fludarabine. In these patients combination of fludarabine with cyclophosphamide and monoclonal antibodies seems justified.^{12,19} Purine analogues other than fludarabine can be effective in relapsed patients, but there is no convincing evidence of their efficacy in fludarabine-refractory patients.¹⁹ Occasional respond to anthracycline-containing combination chemotherapy ± monoclonal antibodies have been reported.¹³

Fludarabine refractoriness is a dismal condition, with a median survival of less than one year,²⁰ for which high-dose treatment modalities, new agents, as well as innovative treatment strategies, like consolidation or maintenance therapy to prevent its development, are being actively tested.^{21,22} They will be discussed in detail elsewhere.

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