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Current therapeutic options for subgroups of chronic lymphocytic leukemia. Planning risk-adapted treatment according to recognized prognostic factors

Chronic lymphocytic leukemia (CLL) is the most common of all adult leukemias and is not a homogeneous disorder.[1,2] Although some have argued that this may not be a single entity[3] it is probably one disease with different subgroups displaying different biological behavior patterns, manifesting as different clinical courses and varying responses to treatment.[4] Most recently physicians have acquired more confidence in their approach and have dared to ask the once feared question: is CLL is a curable disease?[5] This change in approach is basically due to the fact that much has changed in our thinking about CLL in the last decade because of the knowledge and data which have accumulated regarding the biology, molecular genetics and prognostic factors, coupled with the development of novel drugs, new concepts of immunochemotherapy and the newer techniques for stem cell transplantation now available.[5] All the latter have allowed us to entertain new ideas for therapy and the concepts of complete (CR) and molecular remission (MR) have now readily been incorporated into our new mode of thinking on how best to treat CLL. Concepts of possible clinical cure have been entertained and questions are asked such as whether very early disease in younger patients should be treated without necessarily waiting for the classical indications of progressive disease before treatment is given. In the light of all the above it is indeed difficult to outline rigid guidelines for what is best for CLL patients and many of these basic questions are the subjects of ongoing clinical trials.[6,7] However it does seem that the correct questions are now being addressed and it is possible that in 5-10 years from now more answers will be available which may well alter the current concepts of therapy for many patients.

Importance of prognostic indicators for treatment selection

Before therapy can be discussed it has to be understood that the clinical presentation and course in CLL is far from uniform and disease progression and individual response to treatment are unpredictable, differing from patient to patient. Nowadays it seems evident that a proportion of patients have a long survival without major progression while an equal number (about one third) have more aggressive disease with progressive clin-

ical features, a shorter survival and require therapy earlier.[3,4] A similar proportion of patients have an indolent clinical course which will eventually progress and require treatment. Thus, it is obvious that is not possible or even wise to plan treatment for all categories of disease without taking into consideration the above variables. In this respect prognostic factors are important and can help to predict who should receive therapy and may also play a role in deciding what approach to use for different subgroups of patients with CLL, thereby helping to establish therapeutic guidelines for these patients.

In the past, prognostic factors and categories were always well defined, starting from the clinical staging systems (Rai and Binet) which were the classical guidelines used for so long. These also included classical clinical and laboratory findings indicative of more rapid progression and shortened survival, such as lymphocytic doubling time, bone marrow pattern of involvement, lymphocyte morphology, serum β2 microglobulin and lactate dehydrogenase (LDH) levels, as well as thymidine kinase and sCD23 levels.[4,8-12] All the above were important in decision-making and in choosing appropriate treatment. However, the surface immunophenotype, particularly CD38 expression, cytogenetics (17p del, trisomy 12 and 11q del), the detection of the unmutated status of the VH Ig genes and more recently the significant expression of ZAP 70 protein have all been found to be of the utmost importance as poor prognostic indicators which will eventually determine survival.[13-16] These can be used as surrogate markers for prognosis and possibly drug resistance and their presence provides an indication of who may have a more aggressive subtype of CLL requiring more effective and earlier therapy. In the light of the above data, decision-making may soon become easier for the treating physician than in the past and should also help to make the design of future clinical trials more logical and simpler.

Treatment choices in individual patients

Elderly patients (> 65 years). Basically it seems that who to treat and which drug therapy to give will always remain the central issues. However it is clearly evident that elderly patients who have truly indolent disease will have a life expectancy well above 10 years and their chances of responding to therapy afterwards are not compromised by delaying/ deferring therapy. This group are probably best treated with a watch-and-wait approach unless we can identify clear-cut evidence of progression by the classic criteria or utilizing the novel surrogate markers - mutational status, $CD38^+$ expression or ZAP 70 positivity-to predict who in this group is likely to have a stormier course and require treatment.[15-18] In the subgroup with poor risk factors treatment up front could be considered earlier in the course of the disease and because of their age one could, indeed, first consider therapy with a single oral agent (such a chlorambucil or fludarabine). The alternative issue of combination chemotherapy in this age group could be left open for further consideration depending on the initial response or whether the patients have progressive disease on therapy.

In this elderly age group another obvious and important issue remains the quality of life (QOL) of the patients with CLL. Thus if these patients are not entered into clinical trials, in day to day practice, most physicians will take QOL into consideration as a guideline for when to start treatment. This will obviously affect the clinician's decision on what regimen to use in the elderly, particularly if QOL and performance status are poor. Thus, in essence QOL, surrogate genetic markers and gene profiling with ZAP 70 expression will remain key indicators for deciding treatment.

Younger patients (<65 years). Should the concept of achieving CR or molecular remission (MR) influence decision-making in this subgroup of patients with CLL? In recent years CLL patients have been able to achieve CR and even MR after receiving combination chemo/immunotherapy. Earlier therapies were rarely able to achieve this status.[19-26] As a result of the concept of meaningful clinical CR and MR, possible clinical cure with prolonged disease-free periods and freedom from progression for a relatively large number of patients has slowly penetrated into our thinking, for the first time in the history of CLL, enabling physicians to consider this as a goal for their patients. However it is still unclear whether achieving CR/MR translates into a meaningful increase in life expectancy and whether the concept of clinical cure is applicable as it is for other lymphoproliferative disorders such as lymphomas and lymphoblastic leukemias. Can we in fact consider this as our optimal goal in younger CLL patients when there is still inadequate long-term follow-up of the recent encouraging data?

Until the era of purine analogs, monoclonal antibody therapy and autologous and reduced intensity (RIC) allogeneic stem cell transplantation (SCT), there was no real debate about whether we could cure a meaningful proportion of younger CLL patients. Because of this, achieving clinical remissions with oral alkylating agents or CHOP - like regimens was not considered so significant a goal, as we never really thought that CLL could be eradicated or controlled by these regimens for prolonged periods of time. Now that we can achieve CR/MR and have other alternatives for therapy, choices of treatment become more important and correct decision-making at an earlier stage seems to be more crucial, particularly in younger patients.

This makes it more difficult for the treating physician who now has to explain this to CLL patients who are aware of this information which is so readily available in the electronic media today. In fact, if patients are not included in clinical trials, the clinician must nowadays decide for himself whether more aggressive combined modality treatment, including chemo-immunotherapy followed by a curative SCT approach, should be adopted as primary therapy in individual cases.

It seems that careful selection of the appropriate subgroup of patients to receive primary therapy with a combination of a purine analog (fludarabine/cladribine), cyclophosphamide and possibly mitoxantrone together with or followed by rituximab or even another monoclonal antibody such as alemtuzumab (Campath 1H) may be the correct approach, in the light of recent reported data.[23-26] These combinations are indeed synergistic for patients with more advanced disease or for those who have predictable poor prognostic features. Side effects of the newer antibodies are mostly seen at the time of infusion and are not really more than would be expected for single chemotherapeutic agents, particularly in previously untreated patients who are not immunosuppressed after multiple prior cycles of combination chemotherapy. The future will no doubt provide us with other additional strategies, perhaps even more effective antibodies, DNA vaccinations and antisense anti-Bcl2 therapy,[27,28] which can be added to the regimens concerned. So, for the first time we really have some effective therapeutic options to apply in the relatively near future. These may translate into increased life expectancy and a proportion of clinical cures with prolonged disease-free periods for some patients with CLL.

Concept of consolidation of remission and stem cell transplants after initial response

Whether achieving CR/MR status has a real impact on the long-term outcome of CLL as in other lymphomas and leukemias remains to be proven but in principle this should become evident in the future. Basically this is so for almost all hemato-oncological disorders and we aspire to achieve CR/MR in most cases because without this we are unable to offer patients meaningful prolonged survival and possible cure. This of course may not be true for all chronic lymphoid neoplasias but if a good PR /CR/MR is not obtained, meaningful prolonged survival and cure is probably not possible. Obviously patients who have responded will require a long future follow-up as median survival has not yet been reached as in most of the reported studies and trials. Despite some early impressions that this cure may indeed be possible, it is still too early to predict. This raises the possibility and feasibility of consolidation/maintenance of the CR/MR status using monoclonal antibodies such as rituximab, mabCampath, others or their combinations.[19-26] This could indeed be appropriate maintenance and could be considered in future trials.

Furthermore, stem cell transplant (SCT) is a possible curative option for CLL patients, particularly those who have achieved remission using fludarabine/2Cda - rituximab regimens and who show early signs of relapse.[29-36] In this respect it seems logical to harvest stem cells from all patients in CR/MR so as to be able to use them for autologous SCT. Whether this approach should be used early on as part of the initial therapy, as consolidation or only when younger patients relapse will obviously need to be tested in the framework of randomized controlled trials. Autotransplantion could theoretically be used at an earlier stage as there is minimal morbidity/mortality associated with the procedure but it lacks a plateau effect in terms of response, although this may improve in the future. In contrast the RIC - mini allogeneic transplants are the only currently curative modality in CLL but are associated with more initial morbidity and mortality. Nevertheless, because they are curative and in the light of improving techniques one could consider using such transplants as consolidation for younger patients, but probably only for those who show evidence of relapsing disease.

Thus, many of the present crucial issues in CLL will have to be tested and analyzed in controlled studies with adequate periods of follow-up as currently proposed.[6,7] Risk- and age-adjusted management of early disease as well as advanced disease and proposals for high-dose therapy with SCT as first and second line treatment will have to be tested for CLL patients in this setting.[6,7] The only logical way to achieve this and to advance towards the desired goals will be through large co-operative, randomized trials with maximal international participation and collaboration.

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Thrombophilias and adverse pregnancy outcome

In this issue of the journal, Facchinetti *et al.*[1] investigated the incidence of inherited thrombophilias, namely factor V Leiden and prothrombin A20210 mutation in women who presented with acute placental abruption. Not surprisingly, they show an increased incidence of both thrombophilias in women with abruptio placentae.

Pre-eclampsia, *abruptio placentae*, intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) greatly contribute to maternal and fetal morbidity and mortality. Their causes are unknown, but all of them may be associated with abnormal placental vasculature and disturbances of hemostasis leading to inadequate maternal-fetal circulation.[2-8]

The subsequent vasculopathy and secondary