C**hronic lymphocytic leukemia: novel prognostic factors and their relevance for risk-adapted therapeutic strategies**

**Background and Objectives.** Many years ago it was established that prompt treatment of early stage chronic lymphocytic leukemia (CLL), the stage at which almost two-thirds of CLL patients present, has no benefit over a management of watching and waiting, then treating progression. However, this fact was based on series treated ineffectually with chlorambucil, which were not stratified according to prognostic markers.

**Design and Methods.** The prognosis and clinical course of CLL are heterogeneous. While some patients may have a normal life expectancy without requiring treatment, others die of drug-resistant disease as early as within two years of presentation. However, unlike the situation in non-Hodgkin's lymphoma, there is no standard Prognostic Index that can be used to group patients with CLL according to likely outcome or to guide treatment.

**Results.** A number of clinical and biological factors of prognostic relevance, which may add to the classical assessment provided by the staging systems, have been identified. These include clinical characteristics, such as age, gender and performance status, and laboratory parameters reflecting the tumor burden or disease activity, such as lymphocyte count, lactate dehydrogenase (LDH) increase, bone marrow infiltration pattern or lymphocyte doubling time. Recently more informative prognostic parameters have been identified: serum markers such as soluble CD23, β2-microglobulin or thymidine kinase and genetic markers of tumor cells, such as genomic aberrations, gene abnormalities (p53, ATM), the mutation status of the variable segments of the immunoglobulin heavy chain genes (IGHV) or surrogate markers for these factors, such as CD38 and ZAP-70.

**Interpretations and Conclusions.** From the clinician’s perspective the importance of this new knowledge is how it affects treatment. It is now possible to produce molecular remissions even in advanced disease using combinations of purine analogs and monoclonal antibodies. Moreover, potentially curative therapeutic modalities such as autologous and allogeneic stem cell transplantation are becoming safer. Clinical trials of effective treatment stratified by more reliable prognostic markers are surely now warranted.

**Key words:** chronic lymphocytic leukemia, prognostic factor, risk-adapted treatment.

Haematologica 2005; 90:391-399
©2005 Ferrata Storti Foundation
Table 1. Correlation of specific chromosome aberrations with clinical characteristics and outcome in patients with B-CLL.

<table>
<thead>
<tr>
<th>Aberrations</th>
<th>Clinical characteristics and outcome</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 12</td>
<td>Atypical morphology</td>
<td>16%</td>
</tr>
<tr>
<td>13q aberrations</td>
<td>Favorable outcome if isolated aberration</td>
<td>55%</td>
</tr>
<tr>
<td>11q aberrations</td>
<td>Extensive lymphadenopathy</td>
<td>18%</td>
</tr>
<tr>
<td>17p aberrations</td>
<td>Shorter treatment free interval</td>
<td>7%</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>Favorable outcome</td>
<td>18%</td>
</tr>
</tbody>
</table>

The aforementioned prognostic impact of cytogenetics is relevant in CLL: the median survival of patients with 15q- is 133 months; that of patients with trisomy 12q is 114 months, in those with no detectable aberration the median survival is 111 months; in patients with 11q- it is 79 months and finally in those with 17p- it is 52 months.4 (Table 1).

Table 2. Serologic indicators of tumor burden in CLL.

<table>
<thead>
<tr>
<th>Serologic markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic dehydrogenase (LDH)</td>
</tr>
<tr>
<td>β2 microglobulin (β2-MG)</td>
</tr>
<tr>
<td>sCD23</td>
</tr>
<tr>
<td>Thymidine kinase (s-TK)</td>
</tr>
</tbody>
</table>

Table 2. Serologic indicators of tumor burden in CLL.

Serologic parameters

A number of serologic staging parameters such as β2-microglobulin (β2-MG), thymidine kinase (TK) and soluble CD23 emerged as being independently discriminatory after accounting for the stage of the disease.5 β2-MG is an extracellular protein that is non-covalently associated with the α-chain of the class I major histocompatibility complex (MHC), which is detectable in the serum. β2-MG is associated with adverse prognostic features at presentation and higher values have been found in CLL patients with a shorter survival.5 Evaluated in the context of some other prognostic parameters, β2-MG appears to maintain an independent prognostic value.6

Serum TK activity (s-TK) in CLL patients is probably related to the number of dividing neoplastic cells, reflecting tumor mass and rate of tumor cell proliferation. The ability of s-TK levels to detect a subgroup of patients with early, non-smoldering CLL at risk of rapid disease progression seems particularly useful. In an interim analysis of the CLL1 trial of the German CLL study group, s-TK levels were among the four parameters best predicting a short progression-free survival.4 CD23 is a functionally relevant surface molecule on B-CLL cells. Higher serum levels of its cleaved form (sCD23) indicate a worse prognosis.6 However, its independent prognostic significance has not been proven. The value of some of these serum markers is currently limited by the lack of a standard assay method, different cut-off points used in various series or the lack of validation in a prospective study. An attractive option is to include different serologic markers that contribute individually to prognosis of CLL into prognostic models under the speculative assumption that their combined use, integrating different biological aspects of CLL, would provide greater prognostic information than that of a single marker4 (Table 2).

Few studies have been published on LDH measurement in CLL. Some authors have demonstrated that the total LDH activity in B-CLL was not significantly different from that of normal B cells.9 Another group proposed a biological score combining LDH and β2-MG values, which seems to be of prognostic interest.10

mitotic index of the neoplastic cells and by sub-optimal quality of metaphases. The introduction of interphase cytogenetics using fluorescent in situ hybridization (FISH) has greatly increased the sensitivity of cytogenetic analyses. FISH has two advantages over conventional cytogenetics: (i) it allows for the detection of specific chromosome lesions in non-dividing cells which would be missed by metaphase analysis and (ii) it is able to detect loss of chromosome material in the order of magnitude of one hundred-kilobases; deletions of this size are far beyond the resolution power of banding analysis. With FISH, abnormalities can be detected in more than 80% of patients using a 4-probe panel for the detection of trisomy 12q13 and deletions 13q14, 17p13 and 11q22-23. An additional 10% of patients can be shown to carry a 6q21 deletion, 14q32 translocation and partial trisomy 3q or 8q. The frequency of each cytogenetic lesion in a large study was as follows: 13q-, 36%, trisomy 12q, 14%; 11q-, 17%; 17p-, 7% other aberrations 8%, no demonstrable lesion, 18%.4 Döhner’s study4 and the latest MRC study (unpublished data), which has similar figures, may have overestimated the frequencies of adverse chromosomal abnormalities because of the inevitable selection bias when studying patients at tertiary referral centers (and in the case of MRC study because patients who required no therapy were excluded). In a Bournemouth survey of unselected local patients, the majority of whom required no therapy, the frequency of 11q and 17p abnormalities was lower (unpublished data).

The aforementioned prognostic impact of cytogenetics is relevant in CLL: the median survival of patients with 15q- is 133 months; that of patients with trisomy 12q is 114 months, in those with no detectable aberration the median survival is 111 months; in patients with 11q- it is 79 months and finally in those with 17p- it is 52 months.4 (Table 1).
genes were much more likely to genes in predicting the time of first mutation status often overlap, albeit in the series by Hamblin + Further studies revealed that sequencing is difficult to perform in a routine (n=274). + which may be because the American study was 50% larger than the two European studies, different antibodies that may give different results, were used and the population in the American study was younger (median age 55 years) than that in the Barcellona study (median age 60 years) or Bournemouth study (median age 67 years). Despite the results of the American study suggesting that ZAP-70 could be a stronger predictor of the need of treatment, it seems that knowing both ZAP-70 level and IgVH mutational status provides more useful prognostic information that knowing only one.

Mutational status of immunoglobulin genes and surrogate markers

In 1999, two groups of investigators demonstrated that patients with a memory cell immunophenotype with mutated immunoglobulin genes (IGVH) had a very favorable outcome and a low probability of developing progressive disease, whereas those with unmutated IGVH genes were much more likely to develop progressive disease and have a shorter survival.13 In the series by Hamblin et al. the median survival for patients without variable gene mutations was 8 years, whereas that of patients with IGVH mutations was 25 years (Figure 1).

Although there is a tendency for adverse karyotypic abnormalities to occur mainly in the subset with unmutated IGVH, the association is not absolute, and immunoglobulin gene mutational status and karyotype are independent prognostic factors. The median survival for patients with unmutated Ig genes and 17p deletions is only about 3 years.14,15 However, IGVH sequencing is difficult to perform in a routine diagnostic laboratory, and thus this assay is currently unavailable for most of the CLL patients.

CD38 is a membrane protein that marks cellular activation and maturation and has signaling activity. CD38 expression is associated with neoplastic cells showing atypical morphology, diffuse bone marrow infiltration, high peripheral blood lymphocytosis and a less favorable overall prognosis.16 Further studies revealed that CD38 and IGVH mutation status often overlap, albeit not always, but CD38 may vary over time. CD38 is now viewed as an independent prognostic marker of outcome, with its own clinical value.17

In a pioneering gene-expression profiling study in CLL, a panel of genes has been identified in which the expression of a small subgroup of genes, including those encoding ZAP-70, IM1286077, and C-type lectin, correlated with the mutational status of IGVH genes.18

ZAP-70 is an enzyme that is normally expressed in T lymphocytes and that is critical for the activation of T cells by antigen. ZAP-70 is an unexpected finding in a B-cell tumor, since the protein has not been reported in normal circulating B cells. Recent data showed that the expression of ZAP-70 protein is limited to CLL cells with unmutated IGVH genes.19 The immunofluorescence method for identifying ZAP-70+ cells in CLL is not fully standardized amongst different laboratories, and it remains to be determined whether this parameter is amenable to the routine clinical workup of patients with CLL.20 An American study comparing a flow-cytometry assay for ZAP-70 and the mutational status of IGVH genes in predicting the time of first treatment in a large series of patients with CLL has recently been published.21 Although the results of the two assays were similar, 23% of the results of the two methods were discordant. This discordance is greater than that reported by European studies22,23 which may be because the American study was 50% larger than the two European studies, different antibodies that may give different results, were used and the population in the American study was younger (median age 55 years) than that in the Barcellona study (median age 60 years) or Bournemouth study (median age 67 years). Despite the results of the American study suggesting that ZAP-70 could be a stronger predictor of the need of treatment, it seems that knowing both ZAP-70 level and IgVH mutational status provides more useful prognostic information that knowing only one.

Use of novel prognostic factors in clinical decision-making: definition of risk groups

CLL is a complex disease with a very heterogeneous outcome. It is generally assumed that not all patients with CLL die of their disease. However, a more recent analysis of data showed that patients who have progression of their CLL die predominantly of complications of the disease, especially infections.24 The development of newer prognostic factors, such as the mutational status of the immunoglobulin heavy-chain variable genes, cytogenetics, CD38 expression, ZAP-70 and some serum markers, has allowed for further discrimination of patients into risk categories. Thus, progressive and smoldering forms of the disease can now be separated more accurately than was previously possible using Rai’s and Binet’s staging systems. Indeed, Binet’s stage A corresponds to a good prognostic group, comprising almost 65% of CLL patients. During the course of the disease, 25% die from CLL-related causes, 40% progress to stages B and C, and 50% ultimately require treatment.25

A recent study examined IGVH mutational status in 145 patients in Binet’s stage A. Median overall survival (OS) and progression-free survival (PFS) were significantly shorter for patients without
mutations than they were for patients with mutations (97 months vs not achieved, \(p=0.0017\); and 42 vs 156 months, \(p<0.0001\)). Thus, wide recognition of patients with unmutated IGVH among those with Binet’s stage A (or Rai’s indolent forms) should provide a means of testing the putative benefits of early treatment, in the frame of prospective randomized trials. Furthermore, in the same study the IGVH mutational profile was able to segregate stage B and C patients into two groups with different survival patterns (median OS, 78 vs 120 months for patients without and with mutations, respectively; \(p=0.002\)). Thus, early recognition of aggressive stage A and indolent stage B and C disease should provide a better rationale for treatment strategies. In the light of these facts how should the prognostic factors of CLL patients be assessed in clinical practice?

The development of effective therapies has transformed many hematologic malignancies (e.g. Hodgkin’s disease, acute myeloid and lymphoid leukemias, diffuse large cell lymphoma) previously considered to be incurable into curable diseases, at least in some cases. The treatment goal for CLL was, for many years, considered to be control of the leukocytosis and the symptoms related to disease expansion. With the introduction of new therapies and novel combination approaches, the therapeutic goal of CLL has shifted to that of achieving a molecular complete remission, especially in younger patients. The elimination of minimal residual disease, as detected by polymerase chain reaction (PCR) technology or by four-color flow cytometry analysis, is going to replace or complement some of the traditional end-points in modern clinical trials. However, the option of palliation still remains an important consideration in elderly patients, given the problems associated with aggressive treatment (Table 4).

**Chlorambucil**

Single-agent chlorambucil has been the most commonly used first-line treatment for CLL. It is given in
a continuous or intermittent schedule. The end-point of treatment is palliation and no standardized criteria for response are applied. Chlorambucil is often administered with prednisone in an intermittent schedule. This regimen was based on data from small studies and, when compared in clinical trials, no differences in response rate or overall survival were reported. Furthermore, the use of prednisone in combination with chlorambucil was associated with an increased incidence of infection. Higher doses of chlorambucil (15 mg/day) seem to be more active but more toxic. This high-dose chlorambucil regimen induced a higher overall response rate and better survival than did the modified CHOP regimen.26

**Combination chemotherapy**

Combination treatment based on alkylating agents, such as cyclophosphamide and combinations including anthracyclines have been extensively studied as initial treatment. These combinations programs, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CAP (cyclophosphamide, doxorubicin and prednisone) and COP (cyclophosphamide, vincristine and prednisone), were explored because of their activity in low grade lymphomas. Several trials have been conducted in order to verify whether combination chemotherapy improves the outcome of patients with CLL if compared with chlorambucil ± prednisone. Results indicated superior response rates for patients treated with combination chemotherapy but without any benefit on survival.26,27 A meta-analysis of 2,022 patients in 10 trials comparing combination therapy, 6 of them including anthracyclines, with chlorambucil ± prednisone showed an identical 5-year survival of 48% in both groups.1

**Purine analogs**

Since chlorambucil became the foundation of CLL therapy, many decades have passed without substantial progress in the treatment of this disease. The discovery of the activity of purine analogs, fludarabine monophosphate, 2-chlorodeoxyadenosine (2-CDA) and pentostatin represented a major breakthrough and has helped to shift the therapeutic goal from palliation to a substantial improvement of response rate (RR) and outcome. The most effective and most extensively studied of these agents is fludarabine. This drug has been shown to give better complete remission (CR) rates and PFS when compared with the CAP regimen (cyclophosphamide, doxorubicin and prednisone) and chlorambucil.28,29 In these studies, myelosuppression and infection were the most common adverse reactions associated with fludarabine. However, so far none of these trials has shown a survival advantage and the disease eventually recurs in all patients. However, the conclusion reached from these randomized studies has been that purine analogs are the most active single agents in CLL and should form the building block of subsequent therapies.

**Fludarabine-based combination regimens**

In order to reduce the relapse rate and increase the number of CR, combinations of fludarabine with other agents have been investigated. Indeed, fludarabine has been shown to exert a biochemical synergy with various agents in vitro, for example with cyclophosphamide, cytarabine, cisplatin and mitoxantrone.30 Thus, combinations of fludarabine and cyclophosphamide and more recently fludarabine, cyclophosphamide and mitoxantrone have been tested. These agents gave high RR in single institution studies and showed higher CR rates than single purine analogs; a longer PFS has also been recorded.31,32 In a small fraction of patients these combinations have been able to achieve minimal residual disease (MRD) negativity. The ability to reach this result in other diseases has translated into longer PFS and an association with long-term survival.33 Patients who become PCR negative after treatment tend to have longer remission than do patients in whom residual disease is detected by the PCR technique.

**Monoclonal antibodies**

Significant advances in the development of monoclonal antibodies (MoAb) have improved targeted killing of leukemic cells with acceptable toxicity. Lymphomas and leukemias are particularly well-suited to MoAb therapies given the identification of multiple tumor cell-specific antigens that are not shared by other tissues. For this reason MoAb-based treatment may be a promising alternative to chemotherapy in refractory CLL. Two antibodies are showing encouraging results: rituximab, a chimeric human-mouse anti-CD20, and alemtuzumab (campath-1H),

### Table 4. Currently available treatments for CLL.

- Alkylating agents ± prednisone (chlorambucil, cyclophosphamide)
- Combination chemotherapy including alkylating agents with or without anthracyclines (COP, CHOP)
- Purine analogs (fludarabine, cladribine, pentostatin)
- Combination regimen including purine analogs (fludarabine + cyclophosphamide, fludarabine + cyclophosphamide + mitoxantrone)
- Monoclonal antibodies (campath-1H, rituximab)
- Chemo-immunotherapy (fludarabine + cyclophosphamide + rituximab, fludarabine + campath-1H)
- Transplantation procedures (Auto, Allo, RIC)
a humanized anti-CD52 antibody.

The pivotal clinical trial with rituximab demonstrated a low level of responsiveness in patients with small lymphocytic lymphoma, the counterpart of CLL. Other studies have confirmed a low RR with conventional doses of rituximab of 375 mg/m² per week for 4 weeks in CLL. Campath-1H targets CD52, an antigen that is present on >95% of human lymphocytes at various stages of differentiation and that is highly expressed in CLL cells. In a pivotal study, campath-1H was evaluated in fludarabine-refractory patients who had previously been treated with alkylating agents and who demonstrated a 33% RR with excellent activity in clearing peripheral blood and bone marrow. When campath-1H was moved into initial treatment administered as a subcutaneous injection, the RR was comparable to that achieved with fludarabine. Cyto megalovirus (CMV) reactivation has been described in most of the reported series and monitoring of CMV reactivation, by analysis of peripheral blood CMV DNA by PCR amplification or by early antigen CMV testing, has become routine. Pre-emptive ganciclovir administered before the onset of clinically overt disease is generally successful.

**Combinations of chemotherapy and immunotherapy**

*In vitro* studies have demonstrated that rituximab sensitizes cell lines to the cytotoxicity of a number of agents, including fludarabine and cyclophosphamide. Fludarabine downregulates CD55 and CD59, which can be considered as complement defence proteins. Based on these observations studies combining rituximab and cyclophosphamide have been designed. The Cancer and Leukemia Group B (CALGB) has compared simultaneous administration of fludarabine with rituximab versus fludarabine followed by rituximab. A higher complete RR was seen in the simultaneous arm of the study than in the sequential arm of the study.

The MD Anderson Cancer Center combined fludarabine, cyclophosphamide and rituximab. The overall RR in 204 previously untreated patients was 95% with a CR rate of 69%. The CR rate and response duration were significantly superior to those obtained with the combination of fludarabine and cyclophosphamide. Furthermore, half the patients became PCR negative for IGVH. Evaluation of the long-term treatment benefit is a very intriguing issue. Concerning the combination of fludarabine with campath-1H, there are data from small series of patients with relapsed or refractory CLL, who showed high overall and complete RR. Another approach to the combination of campath-1H with chemotherapy is based on the concept that this monoclonal antibody may be effective at purging residual disease in patients who achieve a maximal response after fludarabine. A preliminary study in nine patients seems to be very encouraging since all but one patient achieved a CR and 33% became PCR negative for IGVH. These results were recently confirmed in a larger series. However, the still unanswered question is whether this beneficial effect obtained with MoAb translates into a longer survival. Some other issues remain to be resolved concerning the utilization of these MoAb: front-line therapy, combination with chemotherapy (concurrent, sequential), and maintenance treatment.

**Transplantation procedures**

The attainment of a state of minimal disease as a result of treatment with fludarabine or fludarabine-based combinations has provided a basis for examining further status-consolidating therapies. Autografting for patients with CLL has increased significantly over the last years. However, fludarabine, particularly if administered in combination with other drugs, may complicate stem cell harvesting. From a practical point of view, an interval of no less than 3 months should be left between the last dose of fludarabine and the collection attempt because a shorter interval has been associated with poor yields of hematopoietic stem cells. Studies investigating high-dose chemotherapy and autologous stem cell transplantation (ASCT) have demonstrated a low transplant-related mortality (TRM) on the one hand, and the lack of a plateau in the event or relapse-free survival curves on the other hand (Figure 3). Contamination of the reinfused stem cells by leukemic cells is a major concern. In fact the outcome of autologous transplants is strongly correlated with the status of the disease before transplantation. Patients transplanted in CR have a much better outcome than those transplanted with active disease. Persistence of PCR-detectable MRD after autologous transplantation or the switch from a negative to a positive MRD status during the follow-up are highly predictive for clinical relapse. Despite the high relapse rate, survival is improved in some patients. Recently studies investigating the impact of ASCT on patients with unmutated IGVH status have been reported. This adverse prognostic factor remains an indicator of poor outcome even after ASCT if compared to patients with a mutated IGVH status. Nevertheless, the effect of ASCT for this high-risk population appears to be more beneficial than conventional treatment.

As regards the curative potential of ASCT, in a prospective MRC pilot trial assessing the outcome of previously untreated patients with CLL who received fludarabine as debulking followed by ASCT, more than two-thirds of patients achieved a molecular...
remission, as determined by PCR for immunoglobulin heavy chain gene re-arrangements, in the first six months following their transplant. Nevertheless, these molecular remissions are not durable and their loss announces the clinical relapse.

A number of issues still remain open in ASCT: the best conditioning regimen, usefulness of in vitro or in vivo purging, and the optimal timing for transplantation. A reliable evaluation of the impact of ASCT on the prognosis of CLL requires prospective, randomized studies comparing autografting with conventional treatment such as that currently being conducted by the EBMT. Allogeneic stem cell transplantation (alloSCT) is a treatment approach which is fundamentally different from ASCT in the context of indolent diseases such as CLL. Whereas the efficacy and complications of ASCT are based exclusively on the cytotoxic therapy administered, the crucial antileukemic principle of allotransplantation appears to be the graft-versus-leukemia (GVL) effect. There is clear evidence in a number of studies that alloSCT is associated with GVL effects in CLL. This entirely different modality of cellular immune therapy appears to be responsible for the superior antileukemic activity of alloSCT as well as for its considerably higher toxicity. In general, alloSCT is characterized by a high TRM on the one hand and a very low relapse incidence on the other hand. However, young patients with refractory disease, who otherwise have limited treatment options and are better able to tolerate the morbidity of transplantation, should be considered for a standard conditioned allogeneic transplant. Since the GVL effect seems to be crucial for the eradication of the disease, the intensity of the conditioning regimen may not be as important as in other diseases, particularly in patients with a chemosensitive disease. Allogeneic transplantation using a reduced intensity (non-myoeloablative) conditioning (RIC) regimen has been investigated in CLL. In this approach the preparative regimen is not aimed at eradicating the disease, but at providing sufficient immunosuppression to allow engraftment of allogeneic stem cells and the development of a GVL effect. Another line of evidence for the presence of GVL activity and, thus, the curative potential of allografting in CLL comes from the documented efficacy of donor lymphocyte infusions and the fact that CLL cells persisting after dose-reduced conditioning for alloSCT may disappear with the onset of chronic GVL.

Data collected after RIC from 29 European Group for Blood and Marrow Transplantation centers have been recently reported for 77 patients with CLL: complete chimerism was observed in all but two of 73 patients following their transplant. Nevertheless, these molecular remissions are not durable and their loss announces the clinical relapse.

A number of issues still remain open in ASCT: the best conditioning regimen, usefulness of in vitro or in vivo purging, and the optimal timing for transplantation. A reliable evaluation of the impact of ASCT on the prognosis of CLL requires prospective, randomized studies comparing autografting with conventional treatment such as that currently being conducted by the EBMT. Allogeneic stem cell transplantation (alloSCT) is a treatment approach which is fundamentally different from ASCT in the context of indolent diseases such as CLL. Whereas the efficacy and complications of ASCT are based exclusively on the cytotoxic therapy administered, the crucial antileukemic principle of allotransplantation appears to be the graft-versus-leukemia (GVL) effect. There is clear evidence in a number of studies that alloSCT is associated with GVL effects in CLL. This entirely different modality of cellular immune therapy appears to be responsible for the superior antileukemic activity of alloSCT as well as for its considerably higher toxicity. In general, alloSCT is characterized by a high TRM on the one hand and a very low relapse incidence on the other hand. However, young patients with refractory disease, who otherwise have limited treatment options and are better able to tolerate the morbidity of transplantation, should be considered for a standard conditioned allogeneic transplant. Since the GVL effect seems to be crucial for the eradication of the disease, the intensity of the conditioning regimen may not be as important as in other diseases, particularly in patients with a chemosensitive disease. Allogeneic transplantation using a reduced intensity (non-myoeloablative) conditioning (RIC) regimen has been investigated in CLL. In this approach the preparative regimen is not aimed at eradicating the disease, but at providing sufficient immunosuppression to allow engraftment of allogeneic stem cells and the development of a GVL effect. Another line of evidence for the presence of GVL activity and, thus, the curative potential of allografting in CLL comes from the documented efficacy of donor lymphocyte infusions and the fact that CLL cells persisting after dose-reduced conditioning for alloSCT may disappear with the onset of chronic GVL.

Data collected after RIC from 29 European Group for Blood and Marrow Transplantation centers have been recently reported for 77 patients with CLL: complete chimerism was observed in all but two of 73 patients following their transplant. Nevertheless, these molecular remissions are not durable and their loss announces the clinical relapse.

A number of issues still remain open in ASCT: the best conditioning regimen, usefulness of in vitro or in vivo purging, and the optimal timing for transplantation. A reliable evaluation of the impact of ASCT on the prognosis of CLL requires prospective, randomized studies comparing autografting with conventional treatment such as that currently being conducted by the EBMT. Allogeneic stem cell transplantation (alloSCT) is a treatment approach which is fundamentally different from ASCT in the context of indolent diseases such as CLL. Whereas the efficacy and complications of ASCT are based exclusively on the cytotoxic therapy administered, the crucial antileukemic principle of allotransplantation appears to be the graft-versus-leukemia (GVL) effect. There is clear evidence in a number of studies that alloSCT is associated with GVL effects in CLL. This entirely different modality of cellular immune therapy appears to be responsible for the superior antileukemic activity of alloSCT as well as for its considerably higher toxicity. In general, alloSCT is characterized by a high TRM on the one hand and a very low relapse incidence on the other hand. However, young patients with refractory disease, who otherwise have limited treatment options and are better able to tolerate the morbidity of transplantation, should be considered for a standard conditioned allogeneic transplant. Since the GVL effect seems to be crucial for the eradication of the disease, the intensity of the conditioning regimen may not be as important as in other diseases, particularly in patients with a chemosensitive disease. Allogeneic transplantation using a reduced intensity (non-myoeloablative) conditioning (RIC) regimen has been investigated in CLL. In this approach the preparative regimen is not aimed at eradicating the disease, but at providing sufficient immunosuppression to allow engraftment of allogeneic stem cells and the development of a GVL effect. Another line of evidence for the presence of GVL activity and, thus, the curative potential of allografting in CLL comes from the documented efficacy of donor lymphocyte infusions and the fact that CLL cells persisting after dose-reduced conditioning for alloSCT may disappear with the onset of chronic GVL.

Data collected after RIC from 29 European Group for Blood and Marrow Transplantation centers have been recently reported for 77 patients with CLL: complete chimerism was observed in all but two of 73 patients following their transplant. Nevertheless, these molecular remissions are not durable and their loss announces the clinical relapse.

A number of issues still remain open in ASCT: the best conditioning regimen, usefulness of in vitro or in vivo purging, and the optimal timing for transplantation. A reliable evaluation of the impact of ASCT on the prognosis of CLL requires prospective, randomized studies comparing autografting with conventional treatment such as that currently being conducted by the EBMT. Allogeneic stem cell transplantation (alloSCT) is a treatment approach which is fundamentally different from ASCT in the context of indolent diseases such as CLL. Whereas the efficacy and complications of ASCT are based exclusively on the cytotoxic therapy administered, the crucial antileukemic principle of allotransplantation appears to be the graft-versus-leukemia (GVL) effect. There is clear evidence in a number of studies that alloSCT is associated with GVL effects in CLL. This entirely different modality of cellular immune therapy appears to be responsible for the superior antileukemic activity of alloSCT as well as for its considerably higher toxicity. In general, alloSCT is characterized by a high TRM on the one hand and a very low relapse incidence on the other hand. However, young patients with refractory disease, who otherwise have limited treatment options and are better able to tolerate the morbidity of transplantation, should be considered for a standard conditioned allogeneic transplant. Since the GVL effect seems to be crucial for the eradication of the disease, the intensity of the conditioning regimen may not be as important as in other diseases, particularly in patients with a chemosensitive disease. Allogeneic transplantation using a reduced intensity (non-myoeloablative) conditioning (RIC) regimen has been investigated in CLL. In this approach the preparative regimen is not aimed at eradicating the disease, but at providing sufficient immunosuppression to allow engraftment of allogeneic stem cells and the development of a GVL effect. Another line of evidence for the presence of GVL activity and, thus, the curative potential of allografting in CLL comes from the documented efficacy of donor lymphocyte infusions and the fact that CLL cells persisting after dose-reduced conditioning for alloSCT may disappear with the onset of chronic GVL.

Data collected after RIC from 29 European Group for Blood and Marrow Transplantation centers have been recently reported for 77 patients with CLL: complete chimerism was observed in all but two of 73 patients following their transplant. Nevertheless, these molecular remissions are not durable and their loss announces the clinical relapse.
Final remarks

In summary, as a result of all these advances the median survival of patients with CLL has increased from 5-6 years in series reported two decades ago to about 10 years at present. However, being diagnosed with CLL still has a significant impact on life-expectancy, especially for younger patients. The introduction of new and more reliable prognostic factors may facilitate the design of randomized clinical trials to determine whether early intensive treatment of patients with low tumor burden and poor risk factors can prolong survival. Moreover, they may influence the choice of initial treatment and subsequently the need for and the benefit of additional treatments for patients with advanced or progressive disease.

Thus, the following recommendations for a risk-adapted treatment of a CLL patient seem justified by scientific evidence: (i) the prognostic assessment of a patient should no longer rely exclusively on the Binet or Rai stage but include biological and genetic markers at the time of diagnosis in order to make a prediction as accurate as possible; (ii) the treatment recommendation should take into account the patient's performance status; (iii) the therapeutic approach should be inspired by the patient's age as the diagnosis of the disease is increasingly being made in younger individuals with indolent disease and (iv) the concept that patients in early stage should not be treated should be re-challenged and investigated in clinical trials as new and more effective treatments for this disease are now available.

All the authors contributed to the assessment of the data collected by personal experience and review of the literature.

The Meeting “LEUCEMIA LINFATICA CRONICA 2003” held on November 14th, 2003, organized by Enrica Morra and Marco Montillo, at the Niguarda Ca' Granda Hospital in Milan, Italy was an opportunity to point out the impact of new prognostic factors in CLL treatment. This paper updated with new data that appeared in the literature during the 2004, summarizes the main topics discussed during the Meeting. Speakers invited to the Meeting were: Maura Brugnara, Federico Calligaris-Campo, Gianluigi Castoldi, Paolo Corradini, Michael Hallek, Terry Hamblin, Vincenzo Liso, Emili Montserrat, Anna Maria Nosari, Giovanni Pizzolo, Mario Regazzi. The Meeting "LEUCEMIA LINFATICA CRONICA 2003" appeared in the literature during the 2004, summarizes the main topics discussed during the Meeting. Speakers invited to the Meeting were: Maura Brugnara, Federico Calligaris-Campo, Gianluigi Castoldi, Paolo Corradini, Michael Hallek, Terry Hamblin, Vincenzo Liso, Emili Montserrat, Anna Maria Nosari, Giovanni Pizzolo, Mario Regazzi. Manuscript received June 24, 2004. Accepted January 22, 2005.

References


56. Haematologica/the hematology journal | 2005; 90(3) | 399 |