

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## Frontline Therapy for Chronic Lymphocytic Leukemia Patients

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### **H&O** What is the recommended current frontline therapy for chronic lymphocytic leukemia (CLL)?

**BE** CLL is a chronic disease that is not curable with conventional chemotherapy. Because the disease cannot be eradicated in early Rai stage 0 and I, treatment is currently indicated only in the advanced stages. However, recently published retrospective data show that new chemoimmunotherapy regimens prolong the overall survival in CLL, similar to the data in follicular lymphoma.<sup>1</sup>

The current standard frontline therapy for physically fit patients is therefore the chemoimmunotherapy regimen FCR: fludarabine, cyclophosphamide, and rituximab (Rituxan, Genentech). This regimen was first evaluated within a large phase II trial performed by the M.D. Anderson Cancer Center.<sup>2</sup> The FCR regimen resulted in a very high complete remission (CR) rate of 70%, with more than 90% overall response (OR). The CLL8 trial of the German CLL Study Group was the first randomized trial comparing fludarabine plus cyclophosphamide alone (FC) versus FCR prospectively in first-line therapy of physically fit patients. The first data were presented at last year's American Society of Hematology meeting<sup>3</sup> and showed significantly higher OR rates (93% vs 85%), higher CR rates (44% vs 23%), and longer progression-free survival (PFS; nearly 1 year difference between FCR and FC). Although the FCR regimen was associated with a significantly higher proportion of severe, CTC grade 3–5 neutropenias (35% vs 21% of all patients), this regimen did not result in a higher rate of severe infections (19% vs 15%). Rituximab was approved for first-line therapy

of CLL in combination with chemotherapy in February 2009. Due to the promising results of the aforementioned trials, FCR is now recommended for frontline therapy of physically fit CLL patients.

### **H&O** Are there patient groups with different benefits from the current therapy?

**BE** A separate analysis of patients aged 70 years or older treated within the aforementioned randomized phase III trial (CLL8 trial) showed that the FCR regimen was well tolerated in these elderly patients as well, and that similar response and PFS rates were reached.<sup>3</sup> However, this trial only included physically fit patients with a low burden of comorbidity and normal renal function. Therefore, the optimal treatment for comorbid patients still has to be defined, and randomized trials have to be initiated to define the value of less toxic chemoimmunotherapies in this patient population. Subgroup analyses of the aforementioned CLL8 trial showed that FCR is also very effective in patients with high-risk CLL, defined by the unmutated status of genes coding for the heavy chains of immunoglobulins (unmutated immunoglobulin heavy chain variable region [IgVH] status) as well as patients with a deletion at chromosome 11 (del(11q)).<sup>4</sup> Both of these poor risk groups had better response rates and longer PFS when FCR was administered in comparison to FC alone. However, the patient group with the poorest prognostic marker—those whose CLL cells have a deletion at the chromosome 17 (del(17p))—did not benefit from FCR treatment.

Although CR rates were also higher with FCR therapy, a small but significant difference was noted in PFS in this very high-risk patient group, overall survival was very poor in both treatment arms, with a median time to death of only 2–3 years. In conclusion, these data show that treatment with FC or FCR is not satisfactory in patients with del(17p).

### H&O What do we know about identifying prognostic subgroups to optimize treatment management?

**BE** As outlined above, there are mainly 3 different prognostic groups in advanced CLL. First, the group of very high-risk CLL is defined by the presence of del(17p), which is detected in about 7–10% of CLL cases.<sup>5</sup> These patients have a short relapse-free survival time, although responses to various regimens such as FCR, alemtuzumab (Campath, Genzyme) or fludarabine plus alemtuzumab (FluCam), or FCR plus alemtuzumab (CFAR) were quite remarkable.<sup>6–8</sup>

Overall survival also remains poor after administration of antibody-based regimens. Patients with clinical refractory disease or very early relapse within 6 months after the end of purine analog-containing treatment have a similar dismal prognosis. The option of allogeneic stem cell transplantation is the only treatment strategy that allows to induce longer lasting remissions and survival time in these 2 patient groups with very poor prognosis.<sup>9</sup>

The group of high risk patients is defined by the detection of del(11q) in 18–20% of the patients<sup>5</sup> and/or unmutated IgVH status in more than 50% of the patients with advanced stage.<sup>10</sup> Data from several trials show that these high-risk patients benefit from first-line therapy with rituximab-based chemoimmunotherapy.<sup>4,11</sup>

All other patients, including those with del(13q), trisomy 12, mutated IgVH status, or other aberrations, belong to the good risk group. Although these patient subgroups benefit from chemoimmunotherapy in first-line therapy, further studies will investigate the optimal treatment in these patients.

### H&O What is the current role of stem cell transplants in current treatment strategies for CLL?

**BE** With the introduction of chemoimmunotherapies, the role of autologous stem cell transplantation has decreased in past years. A few years ago, high-dose chemotherapy and autologous stem cell transplantation were thought to overcome the inferior prognosis of patients with poor prognostic factors. However, newer analyses have shown that the relapse-free survival of

patients with unmutated IgVH status, for example, remains short even after high-dose therapy.<sup>12</sup> As mentioned above, these patients benefit from the FCR regimen, which is associated with less acute toxicity and probably also less late toxicity with regard to the incidence of secondary neoplasia.

Nowadays, in a relapse situation, these patients should rather be considered for allogeneic stem cell transplantation because the graft-versus-leukemia activity may also overcome the therapeutic resistance and poor prognosis in CLL.<sup>13–16</sup> With the introduction of reduced intensity conditioning (RIC) regimen prior to allogeneic stem cell transplantation, the treatment-associated mortality rate was reduced to approximately 20%.<sup>17,18</sup>

### H&O Which patients should undergo transplantation?

**BE** Allogeneic stem cell transplantation is a reasonable treatment option in patients with refractory CLL or early relapse (within 12 months) to first-line therapy with purine analogs.<sup>19</sup> Also, patients with relapse between 6 and 24 months after purine analog-based combination therapy or a regimen of similar efficacy (FC, FCR, BR or autologous stem cell transplantation) belong to the high-risk group of patients and should therefore be considered for allogeneic stem transplantation. The only subgroup of patients in which allogeneic stem cell transplantation is indicated for first-line therapy are those with very high-risk rapid disease progression: patients with del(17p).<sup>19</sup> However, if possible, allogeneic transplantation should be performed within a disease-specific prospective clinical trial protocol.

### H&O What novel agents are being incorporated to improve existing therapies? What activity have they shown?

**BE** Besides the available standard treatment options for CLL such as fludarabine, FC, chlorambucil (Leukeran, GlaxoSmithKline), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or the antibody alemtuzumab, there are currently several other agents that have been recently approved or will be approved in the near future. Due to the aforementioned data from the CLL8 trial, as well as data from another large randomized trial between FC and FCR in the relapse situation (REACH trial<sup>20</sup>), the anti-CD20 antibody rituximab was approved for first-line and relapse therapy of CLL in combination with any cytostatic agent.

Besides rituximab, there are 2 other anti-CD20 antibodies that are currently under investigation. First,

the antibody ofatumumab has been shown to have significant activity as monotherapy in patients with double refractory or refractory and bulky CLL.<sup>21</sup> Response rates for both patient groups were 51% and 44%, respectively, but median time to the next chemotherapy was short (9 and 8 months, respectively).<sup>21</sup> Ofatumumab is currently investigated in 2 large randomized trials in combination with chlorambucil or FC. The other anti-CD20 antibody, named GA101, was administered in a phase I study in pretreated patients with follicular lymphoma and CLL and showed remarkable activity.<sup>22</sup> Besides these CD20 antibodies, there are several other antibodies which are currently investigated, such as the anti-CD23 antibody lumiliximab (Biogen Idec).<sup>23</sup>

The agent bendamustine (Treanda, Cephalon Oncology) was invented and approved in Germany decades ago and has now recently been approved by the U.S. Food and Drug Administration because data from a randomized trial showed a significant benefit with its use in comparison to chlorambucil in first-line therapy of patients with advanced CLL.<sup>24</sup> Bendamustine showed significantly higher response rates (68% vs 31%) and longer PFS (22 vs. 8 months) in comparison to chlorambucil. Another recently presented trial evaluated bendamustine in combination with rituximab in patients with relapsed CLL.<sup>25</sup> The OR rate was 77%; 14% of the patients had a CR. Although the median number of pretreatments in this trial was 2, myelotoxicity was mild.

Another very promising agent in CLL is the immunomodulatory drug lenalidomide (Revlimid, Celgene). This agent has been shown to induce response rates between 31% and 47% in refractory and relapsed patients.<sup>26,27</sup> Slow dose escalations of the drug, starting at 5 mg or 10 mg and escalating up to up to 25 mg, were tolerated very well and prevented the occurrence of severe tumor lysis syndrome. Currently, several trials are evaluating the tolerability and efficacy of the combination treatment of lenalidomide and rituximab.

Flavopiridol is a cyclin-dependent kinase inhibitor and was investigated within several clinical trials in different dosing regimens.<sup>28,29</sup> Hyperacute tumor lysis syndrome was the dose-limiting toxicity in several dosing regimens, but it was well controlled when the drug was administered as an intravenous bolus, followed by a 4-hour infusion. Patients with bulky disease and high-risk genetic features achieved durable responses with this dosing regimen. The efficacy of this drug is currently investigated in a multicentered, international clinical trial.

Besides these drugs, there are several other agents that are currently under investigation, such as the purine nucleoside phosphorylase inhibitor forodesine or the bcl2-inhibitor ABT263.

## H&O What are some questions to be addressed in future clinical research of CLL?

**BE** There is no indication for early treatment initiation in asymptomatic patients in Binet stage A or B outside of clinical trials. However, unpublished data from prospective clinical trials show that in this patient population, a high-risk group of patients can be defined by using high-risk genetic features, serum parameters, and lymphocyte doubling time. The question of whether these patients benefit from early treatment initiation with chemoimmunotherapy is open.

Another important question is the issue of maintenance therapy in CLL. Previous trials have shown that alemtuzumab maintenance therapy is not well tolerated, although it showed a clinical benefit.<sup>30,31</sup> So far, the only available data are from a phase II trial showing good clinical outcome with rituximab maintenance therapy.<sup>32</sup> However, data from randomized trials evaluating the role of anti-CD20 antibodies in maintenance are pending. Moreover, it is also not clear which patients (high-risk and/or patients positive for minimal residual disease) benefit from maintenance therapy with anti-CD20 antibodies. Therefore, in the future, several clinical trials are needed to elucidate these questions.

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