## References

1. Trainor KJ, Brisco MJ, Wan JH, Neoh S, Grist S, Morley AA. Gene rearrangement in B and T lymphoproliferative diseases detected by polymerase chain reaction. Blood 1991;78:192-6.
2. Nawroz H, Koch W, Anker P, Stroun M, Sidransky D. Microsatellite alterations in serum DNA of head and neck cancer patients. Nat Med 1996;2:1035-7.
3. Chen XQ, Stroun M, Magnenat JL, Nicod LP, Kurt AM, Lyautey J, et al. Microsatellite alterations in plasma DNA of small cell lung cancer patients. Nat Med 1996;2:1033-5.
4. Mulcahy HE, Croke DT, Farthing MJ. Cancer and mutant DNA in blood plasma. Lancet 1996;348:628.
5. Frickhofen N, Muller E, Sandherr M, Binder T, Bangerter M, Wiest C, et al. Rearranged Ig heavy chain DNA is detectable in cell-free blood samples of patients with B-cell neoplasia. Blood 1997;90:4953-60.
6. Tohda S, Murakami N, Nara N. Polymerase reaction of rearranged immunoglobulin heavy chain DNA in plasma samples is useful in the diagnosis of B-cell lymphoma. Int J Hematol 2000;72:74-8.
7. Muller E. Detection of clone specific immunoglobulin heavy chain CDR3 PCR products in serum and plasma of patients with B cell malignancies. Ann NY Acad Sci 2000;906:106-9.
8. Deane M, Norton JD. Immunoglobulin gene fingerprinting: an approach to the analysis of B lymphoid clonality in lymphoproliferative disorders. Br J Haematol 1991;77:274-81.
9. Lee TH, Montalvo L, Chrebtow V, Busch MP. Quantification of genomic DNA in plasma and serum samples: higher concentrations of genomic DNA found in serum than in plasma. Transfusion 2001;41:276-82.


*Lymphoproliferative Disorders*

## The effect of subsequent therapies in patients with chronic lymphocytic leukemia previously treated with prednisone and either cladribine or chlorambucil


**We present the long-term follow-up and results of subsequent treatments in patients with chronic lymphocytic leukemia treated initially with cladribine + prednisone or chlorambucil + prednisone in a randomized, cross-over study. We found higher complete and overall responses rates in patients who received cladribine + prednisone as first and second-line treatment but no significant differences in survival.**



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Previously, we presented a report of a randomized multicenter trial comparing cladribine + prednisone with chlorambucil + prednisone in untreated patients with progressive or symptomatic chronic lymphocytic leukemia.[1] Here, we present the long-term follow-up and the results of subsequent treatments in refractory or relapsed patients with disease progression.

Eligible patients were assigned to either cladribine 0.12 mg/kg/day in a 2-hour infusion and prednisone 30 mg/m$^2$/day for 5 consecutive days or chlorambucil 12 mg/m$^2$/day and prednisone 30mg/m$^2$/day for 7 consecutive days. Both regimens were repeated monthly. The patients received at least 3 courses of chemotherapy. Treatment was discontinued if a complete response was achieved after 3 courses. If there was a partial response, up to 3 additional courses were given. Patients with disease progression earlier than 12 months were crossed-over to the alternative arm, otherwise they were retreated with the same regimen. Patients failing to benefit from retreatment were treated with the alternative regimen. Indications for retreatment, second and third-line treatments were the same as for the first-line therapy. NCI–sponsored Working Group response evaluation and toxicity monitoring guidelines were applied.[2]

**Table 1.** Results of the first line treatment, re-treatment and second line treatment with cladribine + prednisone and chlorambucil + prednisone and third-line treatment with CHOP.

| *Characteristic* | | *2-CdA+P* | | | | *Chl+P* | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | *OR* | *CR* | *PFS* | *n* | *OR* | *CR* | *PFS* |
| 1st line | 126 | 109 (87%) CI: 81-93% | 59 (47%) CI: 38-56% | 18 | 103 | 58 (57%) CI: 47-66 | 12 (12%) CI: 6-18% | 17 |
| Re-treatment | 33 | 13 (55%) CI: 38-72% | 2 (6%) CI: 0-14% | 15 | 19 | 9 (47%) CI: 24-69% | 3 (16%) CI: 0-32% | 12 |
| 2nd line | 50 | 32 (64%) CI: 51-77% | 12 (24%) CI: 12-36% | 15 | 28 | 6 (21%) CI: 6-36% | 1 (4%) CI: 0-11% | 8 |
| 3rd line CHOP | 23* | 4 (17%) CI: 2-32% | 1 (4%) CI: 0-12% | NC | 40° | 10 (25%) CI: 12-38% | 3 (8%) CI: 0-16% | NC |

*n: number of patients; 2-CdA: cladribine; P: prednisone; Chl: chlorambucil; OR: overall survival rate; CR: complete response rate; PFS: progression free survival calculated from the end of therapy to progression or death (median duration in months); CI: 95% confidence intervals; CHOP: 3rd line treatment with CHOP in patients refractory to or relapsed after 1st line with 2-CdA+P or Chl+P; NC: not calculated; patients treated with 2-CdA+P, first-line therapy; *patients treated with Chl-P as first-line therapy.*

Of 229 patients enrolled 126 received cladribine + prednisone and 103 chlorambucil + prednisone. Overall response and complete response rates after the first and second line treatments were higher in patients treated with the cladribine combination than in patients treated with chlorambucil + prednisone (Table 1). Progression-free survival was longer after first treatment than after re-treatment in both groups. After third-line treatment (CHOP) a complete response was observed in only 4 (6%) of 63 patients and some kind of response in 14 (overall response rate of 22%). Grade 3/4 neutropenia was more frequent during retreatment with cladribine + prednisone (21%) ($p$=0.05) or chlorambucil + prednisone (26%) ($p$=0.005), than after the first treatment with the same protocols. Grade 3/4 thrombocytopenia was also more frequent during retreatment with the cladribine-containing regimen (55%). Infections and fever of unknown origin were more frequent during retreatment with cladribine + prednisone (73%) than with chlorambucil + prednisone but they were similar during retreatment with chlorambucil + prednisone (47%) ($p$=0.4). The frequencies of grade 3/4 neutropenia, thrombocytopenia and anemia were similar after the second line treatment with cladribine + prednisone or chlorambucil + prednisone. The median overall survival for patients treated with cladribine + prednisone as the first line treatment was 3.32 years and for patients treated originally with chlorambucil + prednisone 3.75 years ($p$=0.63) (Figure 1A). By the last data collection, a total of 151 patients had died, 82 (65%) in the cladribine group and 69 (67%) in the chlorambucil group. Infections and progression of chronic lymphocytic leukemia were the most frequent

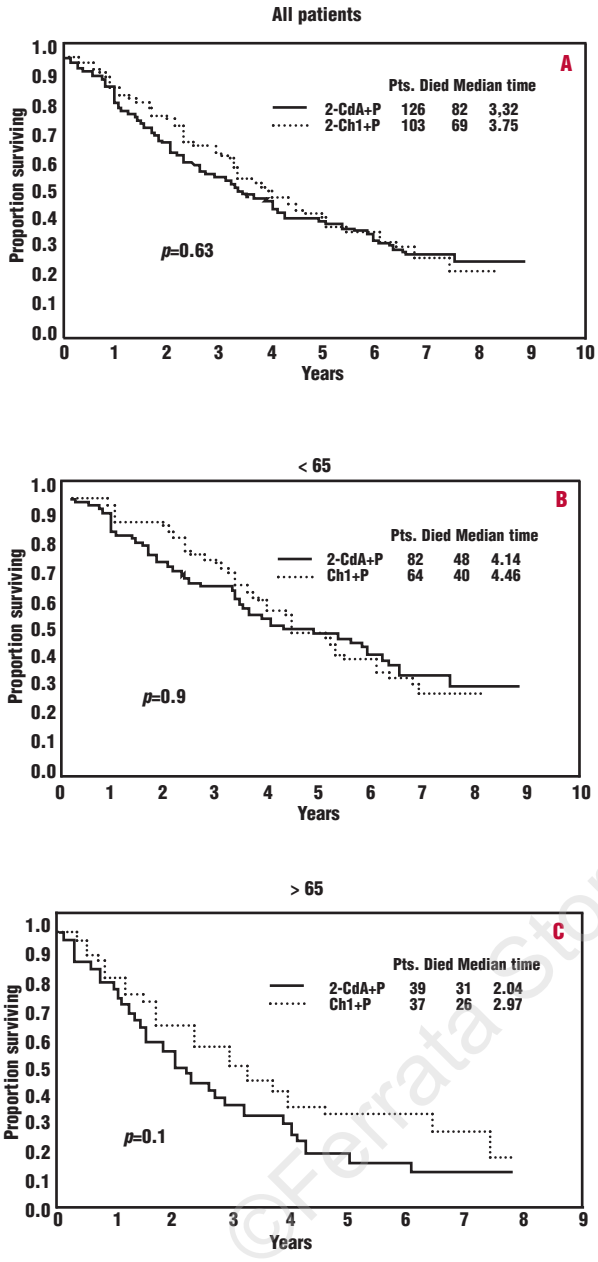


**Figure 1.** Overall survival time calculated from the first day of first line treatment to the last day of follow-up or death of patients treated with cladribine+prednisone (2-CdA+P) (continuous line) or chlorambucil+prednisone (Chl+P) (dotted line) for all patients (A) and for patients up to 65 years old (B) or older than 65 years (C) (long-term follow-up).

causes of death in both groups. Autoimmune hemolytic anemia or idiopathic thrombocytopenia was the cause of death in 7 (6%) patients treated initially with cladribine + prednisone and in 3 patients treated initially with chlorambucil + prednisone ($p$=0.3). Second cancers and Richter's syndrome were the cause of death in 5 and 4 patients, respectively.

In our study, survival for patients treated with cladribine + prednisone as first-line therapy and as second-line therapy was not significantly different and our updated results confirm our earlier observation.[1] However, we found a trend for longer survival for elderly patients treated initially with chlorambucil + prednisone, possibly due to a higher toxicity of cladribine in this population of patients (Figure 1C). This suggests that chlorambucil still has an important role as initial treatment, especially in older patients.

It should be underlined that in a randomized study published by Rai *et al.*,[3] also designed as a cross-over study, overall survival in patients treated with first-line fludarabine and chlorambucil was similar. Our observations are also consistent with conclusions of a meta–analysis including data from 5 randomized clinical trials comparing efficacy of fludarabine as a first-line therapy with alkylating agents-based regimens.[4] Overall survival in this analysis was similar for fludarabine-treated patients and those receiving alkylating agent-based therapy by 5-6 years of follow-up. Ten years ago, when we designed our study, the monoclonal antibodies rituximab and alemtuzumab were not readily available and there were not enough data concerning their use in chronic lymphocytic leukemia.[5] We, therefore, decided to use CHOP as third-line treatment, with inadequate response. The high efficacy of alemtuzumab in patients resistant to fludarabine[6,7] and encouraging results of combined treatment with rituximab and purine analogs[8,9] indicate that monoclonal antibodies applied alone or in combination with chemotherapy should be an option in patients with chronic lymphocytic leukemia refractory to purine analogs.

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## References

1. Robak T, Blonski JZ, Kasznicki M, Blasinska-Morawiec M, Krykowski E, Dmoszynska A, et al. Cladribine with prednisone versus chlorambucil with prednisone as first-line therapy in chronic lymphocytic leukemia: report of a prospective, randomized, multicenter trial Blood 2000;96:2723-9
2. Cheson BD, Bennett JM, Rai KR, Grever MR, Kay NE, Schiffer CA, et al. Guidelines for clinical protocol for chronic lymphocytic leukemia; recommendations of the National Cancer Institute-Sponsored Working Group. Am J Hematol 1989;79:152-63.
3. Rai KR, Peterson BL, Appelbaum FR, Kolitz J, Elias L, Shepherd L, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Eng J Med 2000; 343:1750-7.
4. Zhu Q, Tan DC, Samuel M, Chan ES, Linn YC. Fludarabine

in comparison to alkylator –based regimen as induction therapy for chronic lymphocytic leukemia: a systemic review and meta-analysis. Leuk Lymphoma 2004;45:2239-45.
5. Robak T. Monoclonal antibodies in the treatment of chronic lymphoid leukemias. Leuk Lymphoma 2004;45:205-19.
6. Rai KR, Freter CE, Mercier RJ, Cooper MR, Mitchell BS, Stadtmaner FA. Alemtuzumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. J Clin Oncol 2002;20:891-7.
7. Keating MJ, Flinn I, Jain V, Binet JL, Hillmen P, Byrd J, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: result of a large international study. Blood 2002;99:3554-61.
8. Byrd JC, Rai K, Peterson BL, Appelbaum FR, Morrison VA, Kolitz JE. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB9011. Blood 2005;105:49-53.
9. Robak T, Smolewski P, Urbanska-Rys H, Góra-Tybor J, Blonski JZ, Kasznicki M. Rituximab followed by cladribine in the treatment of heavily pretreated patients with indolent lymphoid malignancies. Leuk Lymphoma 2004;45:937-44.

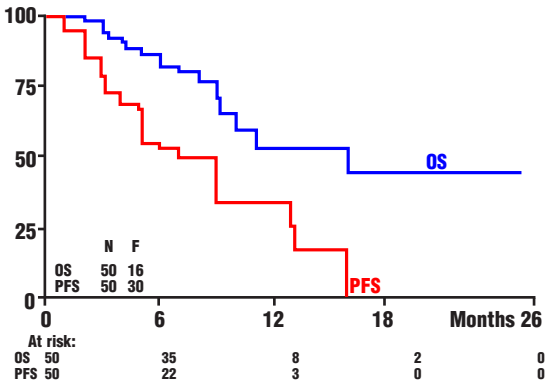


Figure 1. Overall survival and progression-free survival.

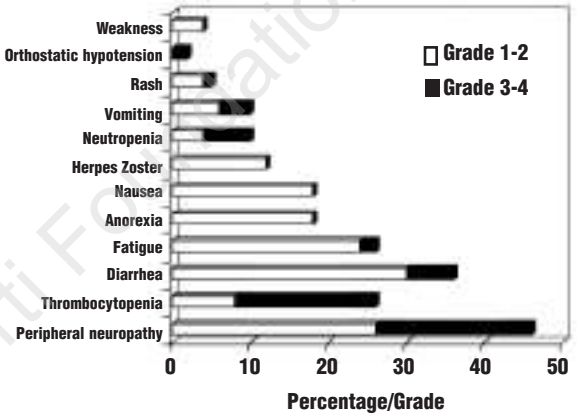


Figure 2. Observed toxicity of bortezomib.

*Multiple Myeloma*

## Analysis of the efficacy and toxicity of bortezomib for treatment of relapsed or refractory multiple myeloma in community practice

**The clinical data on the efficacy and toxicity of bortezomib as treatment for multiple myeloma patients are restricted to prospective phase II studies in expert myeloma centers. Here we report a multi-institutional analysis of the efficacy and toxicity of bortezomib in patients with relapsed or refractory multiple myeloma who were treated in community centers in a compassionate need program.**

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Between November 2002 and December 2004, 50 patients with relapsed or refractory multiple myeloma were treated with bortezomib in centers in the Netherlands. The clinical data of these patients were obtained by means of case research. The mean age of the patients was 59 years (range 37–87); 33 patients had IgG, 10 patients IgA, 6 patients light-chain and 1 patient non-secretory myeloma. The median number of prior treatments was 3 (range 1-5). Twenty-nine patients were treated with high-dose melphalan with autologous stem cell support and 8 patients had received an allogeneic stem cell transplant.

Patients treated in the compassionate need program received up to eight 3-weekly cycles of bortezomib. Within each cycle, bortezomib 1.3 mg/m$^2$ was administered as an intravenous bolus twice weekly on days 1, 4, 8 and 11. Treatment was withheld in case of any grade ≥3 non-hematologic toxicity or grade 4 hematologic toxicity considered to be drug-related. Treatment was resumed at a dose of 1.0 mg/m$^2$ after resolution of the non-hematologic toxicity to grade 2 or better and for hematological toxicity to an absolute neutrophil count ≥0.5×10$^9$/L and platelet count ≥20×10$^9$/L. Responses were evaluated based on the EBMT criteria.[1] NCI Toxicity Criteria (version 2.0) were used to grade the non-hematologic toxicity. At the time of analysis, 33 patients (66%) were still alive. The median follow-up from the start of bortezomib treatment was 7 months (range 2-26 months). A clinical response was observed in 23 patients (46%), including complete response in 2 patients, partial response in 15 and minimal response in 6 patients. The median time to response was 6 weeks and the median duration of response was 9 months. The median progression-free survival was 7 months and the median overall survival was 15 months. (Figure 1). Response to bortezomib occurred in 5 of the 15 patients with a complete or partial deletion of chromosome 13.

Univariate and multivariate analyses of variables such as number of prior treatment regimens, treatment with thalidomide or dexamethasone, abnormalities of chromosome 13, serum β2 microglobulin and serum albumin levels did not show any statistically significant differences in progression-free survival and overall survival. This could be partly due to the small sample size involved. Seven patients who had no response after two treatment cycles of bortezomib alone continued treatment and received oral dexamethasone (20 mg) on the day of and the day following each bortezomib dose. One of these patients, who was previously refractory to corticosteroids, had an additional response on the combination therapy. Further investigations into the possibility of synergy between