Outcomes of first-line treatment for chronic lymphocytic leukemia with 17p deletion

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ABSTRACT

Although uncommon in treatment-naive patients with chronic lymphocytic leukemia, deletion 17p is a high-risk disease characteristic. We analyzed and reported outcomes for 63 patients with deletion 17p chronic lymphocytic leukemia who received first-line therapy at our institution; at time of first treatment, 81% had unmutated immunoglobulin heavy chain variable gene and 58% had complex karyotype. Forty-nine patients (76%) received first-line fludarabine, cyclophosphamide, rituximab-based therapy, 6 (11%) received rituximab-based and 8 (13%) received lenalidomide-based treatment. Overall, the complete plus nodular partial remission rate was 33%; on multivariable model, higher complete plus nodular partial remission rate was observed in patients with less than 50% cells positive for deletion 17p, and a higher probability of achieving at least a partial remission was observed with fludarabine, cyclophosphamide, rituximab-based treatment. After a median follow up of 33 months (range 1-89 months), the estimated median progression-free survival was 14 months (95% confidence interval 10-18) and estimated median overall survival was 63 months (95% confidence interval 43-83). In multivariable analysis, factors independently associated with longer progression-free survival were response to treatment and absence of complex karyotype. Achievement of complete plus nodular partial remission rate and mutated immunoglobulin heavy chain variable gene were independently associated with longer overall survival in multivariable model. Complex karyotype was associated with increased risk for Richter's transformation. New first-line strategies and agents must aim at both improving response and maintaining remission in patients with deletion 17p, particularly in the presence of complex karyotype.

Introduction

Deletion 17p (del(17p)) is highly correlated with unfavorable outcomes with current standard treatments for chronic lymphocytic leukemia (CLL), making patients with this abnormality who need treatment very high-risk.[1,2] Genomic aberrations involving the short arm of chromosome 17 (17p13)[3] can affect *TP53*, a tumor suppressor gene that plays a critical role, both in CLL progression and sensitivity to chemotherapy.[4,5] At the time of diagnosis, abnormalities in the short arm of chromosome 17 are reported in approximately 5% of patients by conventional cytogenetic[6-8] and up to 9% by fluorescence *in situ* hybridization (FISH).[2] In patients with relapsed and refractory CLL, the prevalence can be in up to 50% of patients on trial.[9] Using high-resolution sequencing techniques, over 90% of patients with del(17p) have concurrent *TP53* mutations. However, up to 40% of patients with *TP53* mutations do not have concurrent del(17p).[10-13] This is important since mutations in *TP53* identified by gene sequencing only are also associated with high-risk for poor outcomes in CLL.[12,14-16]

Although del(17p) is associated with high-risk disease in patients who have indications and progress to need treatment, only 52-53% of CLL patients with del(17p) developed an indication for first-line therapy during a 3-year observation time.[17,18] In fact, patients with early stage CLL by modified Rai criteria and mutated *IGHV* gene can have very extended time-to-first treatment.[18,19]

However, once treatment is needed, response to standard first-line agents and regimens is very poor and response duration is short.[20] Although the overall response rate (ORR) reported with standard-of-care first-line fludarabine, cyclophosphamide and rituximab (FCR) was 70%, the median progression-free survival (PFS) was short at 11.3 months.[21,22] Disappointing results were also described for first-line alemtuzumab, both as monotherapy (ORR 64%; median PFS 10.7 months)[23] and in combination with methylprednisolone (ORR 85%; median PFS 11.8 months)[24] or dexamethasone (ORR 97%; median PFS 17 months).[25] P53-independent mechanisms of action have been described for rituximab and lenalidomide,[26,27] but no complete remissions were reported with these agents as first-line treatment of patients with del(17p) CLL.[28,29]

The results for first-line regimens described above are limited by the small number of patients with del(17p) enrolled in the studies (range 1-21 patients). Moreover, no analyses of concomitant clinical and biological factors have been provided. Here, we provide a retrospective analysis of outcomes for first-line treatment for 63 patients with del(17p) CLL.

Methods

Patients

This is a retrospective analysis of 63 patients with del(17p) CLL who received first-line treatment at M.D. Anderson Cancer Center

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(MDACC) between January 2004 and November 2012. Patients must have had an indication for treatment according to the 1996 NCI-WG guidelines and the 1996 NCI-WG criteria were used to assess response to treatment and PFS.[30] All patients provided written informed consent on MDACC institutional review board (IRB)-approved protocols, according to MDACC IRB guidelines and were treated on therapeutic clinical trial with indicated agents or regimens. CLL therapy was classified as follows.

1) FCR-based regimens, which included:
- FCR plus mitoxantrone (FCMR);
- FCR plus granulocyte-macrophage colony-stimulating factor (GM-CSF);
- FCR plus alemtuzumab (CFAR);
2) rituximab-based regimens, which included:
- rituximab plus high-dose methylprednisone (HDMP);
- rituximab plus GM-CSF;
3) lenalidomide-based treatment regimens, which included;
-lenalidomide monotherapy;
-lenalidomide combined with rituximab.

Routine laboratory and cytogenetic analyses

Pre-treatment laboratory testing included evaluation of the somatic mutation status of the immunoglobulin heavy chain variable gene (IGHV), and expression of CD38 by flow cytometry and ZAP70 by immunohistochemistry on bone marrow as previously described.[31,32]

Conventional metaphase cytogenetic karyotype analysis was performed on bone marrow aspirate specimens cultured for 24 h without mitogens or for 72 h with lipopolysaccharide, using standard techniques. Twenty Giemsa-banded metaphases were analyzed, and results were reported using the International System for Human Cytogenetic Nomenclature. Interphase FISH analysis was performed on 200 nuclei obtained from bone marrow samples after culturing cells 24 h without stimulation. The Vysis CLL probe panel (Vysis) was used according to the manufacturer's recommendations. The panel includes probes specific to TP53 (17p13.1), ATM (11q22.3), D13S319 (13q14.3), LAMP1 (13q34), and the centromeric region of chromosome 12 (12p11.1-q11).

Statistical analysis

Progression-free survival (PFS) and overall survival (OS) were calculated from the date of first treatment to the date of progression and death, respectively. For non-responders, PFS was calculated from date of first treatment to disease progression. Survival distributions were calculated using the method of Kaplan and Meier. Univariable comparisons were made using the log rank test. Cox regression was used for survival multivariable analysis. Categorical and continuous variables were evaluated using the χ^2 or Fisher exact test, or the Mann-Whitney test, as appropriate. Logistic regression was used for multivariable analysis of categorical variables. All *P*-values were two-sided. $P \leq 0.05$ was considered significant; only factors that were significant in univariable analyses were used to develop multivariable models.

Results

Patients' characteristics

Patients' characteristics at time of first therapy are shown in Table 1; all were positive for del(17p) by FISH at first treatment. At time of diagnosis, FISH data were available only for 54 patients; 50 (93%) had del(17p) positive FISH at time of diagnosis and 4 (7%) acquired positivity by time of first treatment. Median time from diagnosis to first treatment was 15 months (95% confidence interval (CI) 11-19). At first treatment, median percentage of cells with del(17p) by FISH at time of first treatment was 72% (range 7-97%): 7-25% cells in 19% of patients, 26-50% in 11%, 51-75% in 22%, 76-100% in 48%. Del(17p) was the sole FISH abnormality in 26% of cases, and was associated with deletion 13q in 38% of cases, trisomy 12 in 19%, and deletion 11q in 17% of cases. Del(17p) was associated with one other FISH abnormality in 58% of cases, with two other FISH abnormalities in 11%, and three others in 5% of cases. Conventional cytogenetic analyses identified chromosome 17 abnormalities in 28% of patients, and demonstrated complex karyotype (3 or more abnormalities) in 54% of patients. At time of diagnosis, conventional cytogenetics was available for 20 patients and complex cytogenetics was present in 4 (20%) of them; 4 (20%) patients who showed non-complex cytogenetics at diagnosis developed a complex karyotype at time of first treatment, and the remaining 14 (60%) patients remained non-complex.

Table 1. Patients' characteristics at time of first treatment (n=63).

Patient characteristics (N=63)	Median [range]; number (%)
Age (years)	62 [40-83]
Male	38/63 (59)
Rai stage III-IV	27/63 (42)
ALC (K/uL)	77 [2-370]
HGB (g/dL)	12 [7-15]
PLT (K/uL)	150 [51-580]
Bulky LN (≥5cm)	7/63 (11)
B2M (mg/L)	4.8 [1.9-18.3]
BM-lymphocytes (%)	83 [26-97]
Unmutated *IGHV* gene	47/58 (81)
ZAP70 positive (IHC)	41/57 (72)
CD38 ≥30% positive	26/60 (43)
Del(17p) cells: 7-25%	11/63 (19)
26-50%	7/63 (11)
51-75%	14/63 (22)
76-100%	31/63 (48)
Complex karyotype	29/54 (54)
FCR-based	49/63 (76)
Rituximab-based	6/63 (11)
Lenalidomide-based	8/63 (13)

ALC: absolute lymphocyte count; HGB: hemoglobin; PLT: platelets; LN: lymph nodes; B2M: beta-2 microglobulin; BM: bone marrow; IGHV: immunoglobulin heavy chain variable gene; IHC: immunohistochemistry; FCR: fludarabine, cyclophosphamide and rituximab.

Table 2. Multivariable model for response to treatment.

Variables	n	CR/nPR (%)	OR (95% CI)	P	ORR (%)	OR (95% CI)	P
Del(17p) cells ≤50%	18	61	8.24 (1.73-39.38)	0.008	–	–	–
FCR-based	49	–	–	–	71	2.89 (1.40-5.97)	0.004

N: number; CR: complete remission; nPR: nodular partial remission; OR: odds ratio; CI: confidence interval; ORR: overall response rate; FCR: fludarabine, cyclophosphamide, rituximab. The ORs were adjusted in the multivariable logistic regression model. Variables not significant (P>0.05) in multivariable analysis for CR/nPR were age ≥65 years, bulky lymphadenopathy, use of FCR-based treatment. Variables not significant (P>0.05) in multivariable analysis for ORR: age ≥65 years.

Response to treatment

Forty-nine (76%) patients received FCR-based, 6 (11%) received rituximab-based, and 8 (13%) lenalidomide-based first-line treatment. Nineteen (30%) patients achieved complete remission (CR), 2 (3%) nodular partial remission (nPR), and 18 (30%) partial remission. The overall response rate (ORR) was 63%; 27% of patients were primary refractory and did not achieve remission. Thirty-eight patients had a FISH analysis repeated at time of response evaluation and 23 of 38 (60%) were negative for del(17p). Of these 23 patients, 14 were in CR, 2 in nPR, 7 in PR. All patients in nPR/PR with negative FISH had at least 5% tumor burden in the bone marrow specimen. Median percent of cells with del(17p) by FISH among the remaining 15 patients was 23% (range 12-86): 7-25% cells in 53% of patients, 26-50% in 27%, 51-75% in 7%, 76-100% in 13%. None of them was in CR. Minimal residual disease (MRD) evaluation by 4-color flow cytometry was available for 17 patients who achieved a CR and 13 (76%) were MRD-negative. All the MRD-negative patients had been treated with an FCR-based regimen (6 with FCR and 7 with CFAR).

Factors associated with achievement of CR/nPR on univariable analyses were age under 65 years (OR 11.50, 95%CI: 2.37-55.76; *P*=0.01), absence of bulky lymphadenopathy (≥5 cm) (OR 6.25, 95%CI: 1.10-35.58; *P*=0.04), 50% or less cells with del(17p) (OR 1.76, 95%CI: 1.19-2.62; *P*=0.007) and treatment with an FCR-based regimen (OR 1.33, 95%CI: 1.06-2.35; *P*=0.003). Comparable response rates and survivals were observed for patients with 7-25% or 26-50% del(17p) positive cells and for patients with 51-75% or 76-100% del (17p) positive cells; therefore, a cut-off point of 50% was selected for our analyses. Factors not correlated with achievement of CR/nPR in univariable analyses (*P*>0.05) were: sex, Rai stage III-IV, absolute lymphocyte count (ALC) ≥30 K/μL, hemoglobin (HGB) ≤10 g/dL, platelet count (PLT) ≤100 K/μL, B2M ≥4 mg/L, bone marrow (BM)-lymphocytes ≥80%, unmutated IGHV, ZAP70 positive, CD38 ≥30%, complex karyotype. The only factor associated with achievement of CR/nPR on multivariable model was 50% or less cells with del(17p) (OR 8.24, 95%CI: 1.73-39.38; *P*=0.008) (Table 2).

Factors associated with achieving at least PR in univariable analyses were age under 65 years (OR 2.50, 95%CI: 1.35-4.65; *P*=0.03), and treatment with an FCR-based regimen (OR 2.80, 95%CI: 1.36-5.76; *P*=0.005). Factors not significantly correlated with achieving at least PR in univariable analyses (P>0.05) were: sex, Rai stage III-IV, ALC ≥30 K/μL HGB ≤10 g/dL, PLT ≤100 K/μL, B2M ≥4 mg/L, BM-lymphocytes ≥80%, bulky lymphadenopathy, unmutated IGHV, ZAP70 positive, CD38 ≥30%, >50% cells with del(17p), and complex karyotype. The only factor associated with achieving at least PR in multivariable model was the use of FCR (OR 2.89, 95%CI: 1.40-5.97; *P*=0.004) (Table 2). Of note, the 15 patients who received CFAR, an alemtuzumab-containing regimen, did not have a significantly higher CR/nPR rate (*P*=0.36) or a higher achievement of at least PR (*P*=1).

Progression-free and overall survival

The median follow-up time was 33 months (range 1-89); the overall estimated median PFS was 14 months (95%CI:

Table 3. Multivariable model for progression-free survival and overall survival.

Variables	2yrs-PFS	HR (95% CI)	*P* value	5yrs-OS	HR (95% CI)	*P* value
Mutated *IGHV*	–	–	–	77%	0.34 (0.13-0.62)	0.05
No complex karyotype	50%	0.44 (0.22-0.94)	0.03	–	–	–
CR/nPR	68%	0.35 (0.12-0.74)	0.005	76%	0.20 (0.07-0.57)	0.03
PR	17%	0.32 (0.13-0.79)	0.01	–	–	–

PFS: progression free survival; yrs: years; HR: hazard ratio; CI: confidence interval; OS: overall survival; IGHV: immunoglobulin heavy variable gene; CR: complete remission; nPR: nodular partial remission; PR: partial remission. The HRs were adjusted in the multivariable Cox regression model. Variables not significant (P>0.05) in multivariable analysis for PFS were age ≥65 years, del(17p) cells >50%, treatment with FCR-based regimen.

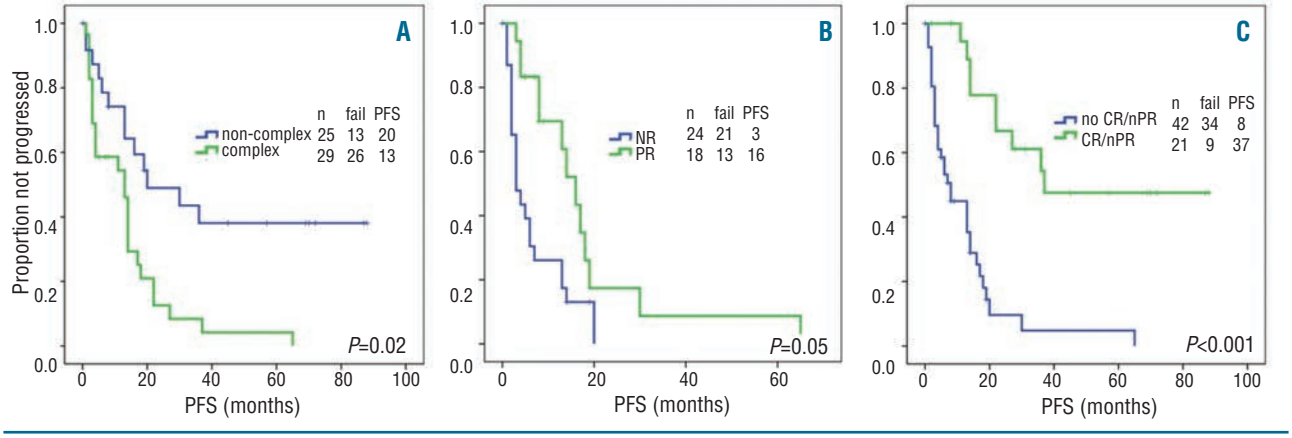

Figure 1. Factor associated with longer PFS. (A) Median PFS was longer for patients with non-complex cytogenetic (20 *vs.* 13 months; *P*=0.02); there were 26 events among 29 patients with complex cytogenetic; there were 13 events among 25 patients with non-complex karyotype. (B) Median PFS was longer for patients achieving a PR (16 *vs.* 3 months; *P*=0.05); there were 13 events among 18 patients achieving a PR; there were 21 events among 24 patients not responding to therapy. (C) Median PFS was longer for patients achieving CR/nPR (37 *vs.* 8 months; *P*<0.001); there were 9 events among 21 patients achieving CR/nPR; there were 34 events among 42 patients not achieving CR/nPR.

10-18); 43 (67%) patients progressed after first-line treatment. In univariable analyses, factors associated with longer PFS were age under 65 years (HR 0.53, 95%CI: 0.28-0.99; *P*=0.04), >50% cells with del(17p) (HR 0.73, 95%CI: 0.57-0.94; *P*=0.009), absence of complex karyotype (HR 0.36, 95%CI: 0.18-0.72; *P*=0.02) (Figure 1A), achievement of PR (HR 0.38, 95%CI: 0.18-0.79; *P*<0.05) (Figure 1B) or CR/nPR (HR 0.16, 95%CI: 0.07-0.36; *P*<0.001) (Figure 1C), and treatment with an FCR-based regimen (HR 0.49, 95%CI: 0.23-0.99; *P*=0.05). Factors not significantly correlated with PFS in univariable analyses (*P*>0.05) were: sex, Rai stage III-IV, ALC ≥30 K/μL, HGB ≤10 g/dL, PLT ≤100 K/μL, B2M ≥4 mg/L, BM-lymphocytes ≥80%, bulky lymphadenopathy, unmutated IGHV, ZAP70 positive, and CD38 ≥30%. The multivariable model included the following factors as independently associated with a longer PFS: absence of complex karyotype (HR 0.44, 95%CI: 0.22-0.94; *P*=0.03), achievement of CR/nPR (HR 0.35, 95%CI: 0.12-0.74; *P*=0.005) or of PR (HR 0.32, 95%CI: 0.13-0.79; *P*=0.01) (Table 3).

The estimated median OS was 63 months (95%CI: 43-83); 28 (44%) patients died during follow up. In univariable analyses, factors associated with longer OS were mutated IGHV (HR 0.26, 95%CI: 0.06-0.99; *P*=0.05) (Figure 2A), and achievement of CR/nPR (HR 0.19, 95%CI: 0.06-0.96; *P*=0.001) (Figure 2B). Factors not significantly correlated with OS in univariable analyses (*P*>0.05) were: age >65 years, sex, Rai stage III-IV, ALC ≥30 K/μL, HGB ≤10 g/dL, PLT ≤100 K/μL, B2M ≥4 mg/L, BM-lymphocytes ≥80%, bulky lymphadenopathy, >50% cells with del(17p), complex cytogenetic, ZAP70 positive, CD38 ≥30%, treatment with FCR-based therapy, and achievement of PR. The multivariable model included the following factors as independently associated with longer OS: mutated IGHV (HR 0.34, 95%CI: 0.13-0.62; *P*=0.05) and achievement of CR/nPR (HR 0.20, 95%CI: 0.07-0.57; *P*=0.03) (Table 3). Of note, the 15 patients who received CFAR, an alemtuzumab-containing regimen, did not have a significantly longer PFS (*P*=0.79) or OS (*P*=0.83). Nineteen patients received an allogeneic stem cell transplant, but only 5 after achieving a response with first-line therapy. All the 5 patients transplanted in first remission are still alive. Fifteen (23%) patients developed Richter's transformation (RT) after a median time of 12 months (range 1-27 months) from first treatment. Eight of 28 (29%) deaths were related to RT, whereas the remaining 20 were related to CLL complications (severe infection, fatal bleeding) or progressive disease. Patients with complex karyotype had a significantly higher probability of developing RT than patients with less than 3 clonal chromosome abnormalities by karyotype (34% *vs.* 8%; *P*=0.03). Factors not significantly correlated with development of RT in univariable analyses (*P* >0.05) were: age >65 years, sex, Rai stage III-IV, ALC ≥30 K/μL, HGB ≤10 g/dL, PLT ≤100 K/μL, B2M ≥4 mg/L, BM-lymphocytes ≥80%, bulky lymphadenopathy, >50% cells with del(17p), unmutated IGHV, ZAP70 positive, CD38 ≥30%, treatment with FCR-based therapy, achievement of CR/nPR or of PR. During follow up, 14 (22%) patients developed secondary cancers, but no death was related to these events.

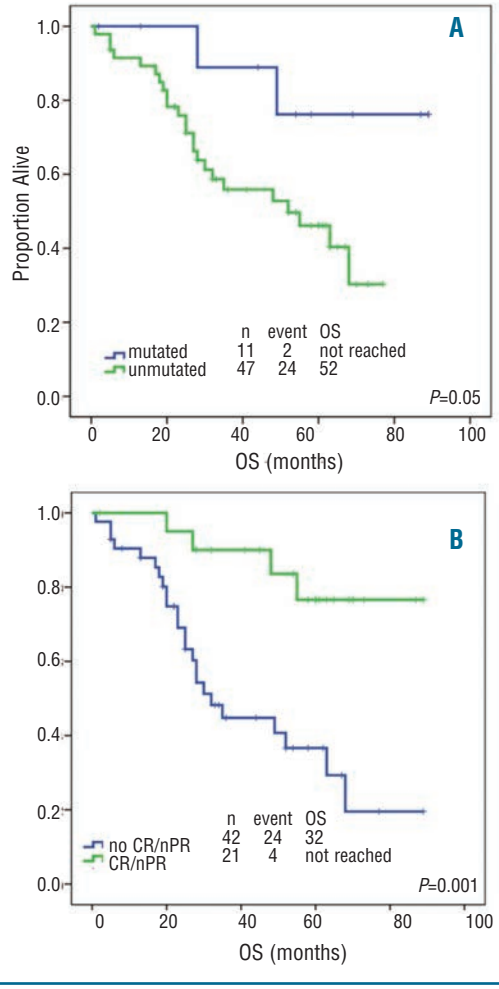

Figure 2. Factor associated with longer OS. (A) Median OS was longer for patients with mutated IGHV (not reached *vs.* 52 months; *P*=0.05); there were 2 deaths among 11 patients with mutated IGHV; there were 24 deaths among 47 patients with unmutated IGHV. (B) Median OS was longer for patients achieving CR/nPR (not reached vs. 32 months; *P*=0.001); there were 4 deaths among 21 patients achieving a CR/nPR with initial therapy; there were 24 deaths among 42 patients not achieving a CR/nPR with initial therapy.

Discussion

Del(17p) is a rare genomic aberration in untreated patients with CLL, reported in 5-9% of patients at diagnosis.[2] Del(17p) is more commonly seen in relapsed or refractory CLL, present in up to 50% of unselected patients enrolled on trials for relapsed disease.[9] The presence of del(17p), either by conventional cytogenetic or FISH analysis, is highly correlated with inferior response to standard treatment and shorter survival in CLL.[1,2] PFS after first-line treatment is short, both with chemoimmunotherapy and potentially p53-independent treatments, such as monoclonal antibodies and immunomodulatory drugs like lenalidomide.[20] However, such results come from studies including small numbers of patients with del(17p) CLL, ranging from 1 to 21 cases. We report features and outcomes for a larger cohort of patients who received first-line treatment for their del(17p) CLL. The majority of patients in our cohort received FCR-based treatment.

Among the 63 patients included in our study, 81% had unmutated IGHV at time of first treatment. This finding is consistent with previous reports associating unmutated IGHV with likelihood to progress to first-line treatment in this genomic subgroup.[18]

Overall, CR/nPR rate and ORR to first-line therapy were 33% and 63%, respectively. A higher likelihood of achieving at least a PR was observed for FCR-based regimens than for rituximab- or lenalidomide-based treatment. Of note, none of the 10 patients with del(17p) included in the 2 first-line studies of the immune-modulating agent, lenalidomide, achieved CR.[28,33,34] Given the retrospective nature of our analysis and the fact that it is not a randomized evaluation of treatment regimens, it is difficult to draw firm conclusions about the most appropriate first-line therapy for these patients, although it did not appear that we could identify a regimen that seemed to stand out above the others. In our analysis, higher CR/nPR rate was associated with "low burden" del(17p) by FISH. The percentage of cells positive for del(17p) by FISH may give an indirect measure of cells with preserved p53 function. Patients with a lower number of cells carrying del(17p) and then a higher p53 functionality may be more sensitive to therapy. Unfortunately, we did not systematically perform *TP53* sequencing in these patients. Interestingly, approximately 5-10% of CLL patients with del(17p) are not likely to have a concomitant *TP53* mutation, but they have poor outcomes similar to those with mutated *TP53*. This may partially reduce the relevance of sequencing *TP53* in patients already carrying del(17p).[12,13] However, *TP53* sequencing remains an important evaluation in patients who do not have del(17p), as in the presence of such mutations they are at similar high risk for poor outcomes and may need different treatment.

Not surprisingly, del(17p) persisted in bone marrow of patients with refractory disease, whereas it was not detected in some patients who cleared their disease and responded to treatment. In a few cases who achieved PR or nPR, del(17p) was not detected at time of response assessment. FISH analysis was not performed on persisting lymph nodes, so that its presence in sites other than bone marrow cannot be ruled out. Moreover, FISH has a limited sensitivity (5%) for the detection of del17p, even in samples where all cells are CLL cells. In addition, pre-treatment FISH interrogates 200 nucleated cells, most of which are CLL cells, while in patients who have undergone debulking with treatment, the 200 cells evaluated with routine FISH are likely a minority of CLL cells, thus limiting the interpretation of a negative result post treatment. Ultra deep next generation sequencing is capable of detecting small *TP53* mutated cells down to a sensitivity of 0.01%.[35] It would be interesting to perform such analysis in cases that had a negative FISH despite achieving nPR/PR. It would also be interesting to investigate whether the disappearance of the clone carrying del(17p) is associated with improved outcome, as this may influence the subsequent therapeutic plan.

In our study, the median PFS after first-line treatment was only 14 months. One of the factors associated with a longer PFS in multivariable analysis was achievement of CR/nPR. This is anticipated since it has already been shown that disease eradication is associated with longer survival in CLL.[36]

FISH analysis is a reliable technique to detect genomic aberrations in interphase cells, which may not be identified by techniques that require cell division such as conventional metaphase karyotype analysis. Given the relatively low fraction of proliferating CLL cells in blood and bone marrow, FISH is the preferred method to identify specific cytogenetic abnormalities in CLL. Metaphase cytogenetic analysis can identify multiple abnormalities at the same time, with no limits related to probe specificity. In our study, patients with more than 3 clonal chromosome abnormalities by conventional cytogenetic analysis (defined as complex karyotype) had a significantly shorter PFS in multivariable analysis and a higher chance of developing RT. This finding could have both diagnostic and therapeutic relevance. The presence of multiple concurrent cytogenetic abnormalities is associated with unfavorable outcomes, and may be an indicator of genetic instability. Patients with del(17p) and complex karyotype at time of first treatment may need more proactive management, including maintenance therapy and early stem cell transplant. This needs to be confirmed in prospective analysis. Metaphase karyotype was consistent from diagnosis to time of first treatment in the majority of patients. However, in up to 20% of cases, complex karyotype developed only at time of first treatment. Given the unfavorable prognosis associated with this feature, metaphase karyotype should be reassessed when treatment is indicated.

Mutation status of *IGHV* was correlated with OS, but not with PFS after first-line therapy. This apparent discrepancy might be explained with an unfavorable correlation between unmutated *IGHV* and progression after salvage therapy, including stem cell transplant. However, an analysis of factors associated with response to salvage therapy goes beyond the purpose of this report.

Patients with del(17p) CLL who receive first-line treatment are at high risk for poorer response to treatment (chemoimmunotherapy, monoclonal antibodies, and immunomodulatory agents), and short PFS and OS. Clearly, treatments with new and novel (p53-indepencent) mechanisms of action need to be explored. Trials investigating the efficacy of B-cell receptor inhibitors, such as Bruton Tyrosine Kinase (BTK) and PI3-kinase inhibitors, or pro-apoptotic agents, such as Bcl-2 inhibitors, are ongoing in our and other centers for relapsed patients with del(17p). Clearly there is a need for active and well-tolerated agents such as these for previously untreated del(17p) CLL.[37,38] Activity and tolerability of these agents appear promising for treatment-naïve patients with del(17p), particularly given the limited activity of short duration with standard chemoimmunotherapy, monoclonal antibody, and lenalidomide in this population. We feel that it is important to consider additional routine evaluation for these patients, including metaphase karyotype and *TP53* gene sequencing, to identify patients at ultra-high risk and for whom allogeneic stem cell transplant can be considered early. We look to whole exome sequencing in patients with del(17p) to provide additional insights into the biology of this subgroup of patients, and to potentially help identify new agents or treatment strategies in order to improve outcomes for these patients.

Disclosures

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Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org

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