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(Article begins on next page)

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Response to the conjugate pneumococcal vaccine (PCV13) in patients with chronic lymphocytic leukemia (CLL)

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Abstract

Pneumococcal (PC) vaccination is recommended for patients with chronic lymphocytic leukemia (CLL). However, response to vaccines has been investigated in a small series of CLL patients. We analyzed the antibody response and outcomes of 112 CLL patients who received the 13-valent pneumococcal conjugate vaccine (PCV13). An immune response was defined by a twofold increase in the PC-IgG levels assessed by ELISA. The median age of patients was 68 years, 23.2% showed IgG levels ≤ 400 mg/L, 6.3% progressive disease, 52% unmutated IGHV. Twenty-two (19.6%) patients were treatment-naïve and 90 (80.4%) previously treated (40.2% front-line chemoimmunotherapy; ibrutinib first/advanced-line, 9.8%/21.4%; idelalisib advanced-line, 8.9%). Nine (8%) patients developed an immune response, eight treatment-naive, and one on front-line ibrutinib. No responses were observed in patients previously treated with chemoimmunotherapy. Age ≥ 60 years ($p = 0.007$), IgG levels < 400 mg/L ($p < 0.0001$), prior treatment ($p < 0.0001$), and signs of disease progression ($p = 0.04$) were associated with a lower response rate. Pneumonia-free survival was significantly shorter in patients with clinical signs of progressive disease (HR, 8.39), prior pneumonia (HR, 7.03), and TP53 disruption (HR, 2.91). In conclusion, our results suggest that vaccination should be offered at diagnosis to CLL patients with early stage and stable disease who have better resources for an effective immune response.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in western countries, accounting for ~30% of all leukemias[1, 2]. Different degrees of humoral and cell-mediated immunodeficiency have been described in patients with CLL due to defects in functions of B and T-lymphocytes, NK cells, neutrophils, and macrophages [3, 4] . Hypogammaglobulinemia is also frequently observed in patients with advanced disease and in some patients with early stage CLL [5,6,7,8,9]. CLL-related immune perturbations are worsened by FCR (fludarabine, cyclophofsphamide, and rituximab) chemoimmunotherapy and translate in an increased risk of infections, one of the leading causes of morbidity and mortality [10, 11]. Defects in immunity and

severe infections have also been described in patients treated with B-cell receptor (BCR) pathway inhibitors [12,13,14,15]. Immune deficiency increases the likelihood of contracting pneumonia due to *Streptococcus pneumoniae* [16, 17]. For adults aged 18–64 years with hematologic cancer, the rate of pneumococcal disease in 2010 was 186 per 100,000 [18]. As vaccination might result in a relevant benefit in reducing morbidity and mortality associated with pneumococcal infection, the 13-valent pneumococcal conjugate vaccine (PCV13) has been recommended for adults with immunocompromising conditions [18,19,20]. From this perspective, pneumococcal vaccination has also been recommended by several guidelines for CLL patients who show a relevant increase in the risk of invasive pneumococcal disease compared with the general population [21,22,23,24,25,26]. However, the immune response to vaccines has been investigated in a relatively small series of patients with CLL, and little is known about the response to vaccines in patients receiving BCR pathway inhibitors[27,28,29,30,31,32,33]. In this study, we investigated prospectively the immune response and outcomes of 112 unselected patients with CLL who received the PCV13.

Patients and methods

Patients

Between November 2015 and February 2018, 112 patients diagnosed with CLL according to the iwCLL guidelines [23], from four hematology institutions, underwent pneumococcal vaccination and were included in this study. Eight patients who refused vaccination and seven lost to the follow-up were excluded from the study. The referring physicians collected demographic and clinical data of these patients from medical records. Data included the clinical characteristics of patients (gender, age, and pneumonia within 24 months before vaccination), previous treatments (number and type), disease status at the time of vaccination; the biologic characteristics of CLL (beta2-microglobulin, serum IgG levels, CD38 expression, IGHV mutation status, FISH cytogenetic profile, and *TP*53 mutation. Outcomes after vaccinations (vaccine-related adverse events, pneumonia events, disease progression, death, and causes of death) were also analyzed.

Twenty-two (19.6%) patients were treatment-naïve and 90 (80.4%) previously treated. Prior treatment included front-line FCR or BR (bendamustine, rituximab) chemoimmunotherapy in 45 patients (40.2%: BR, 13 patients; FCR, 32 patients) and BCR pathway inhibitors in 45 (40.2%; ibrutinib first/advanced-line, 11/24 patients; idelalisib advanced-line, 10 patients) (Table 1).

Pneumococcal vaccination

All patients received a single-dose 0.5-mL intramuscular injections of the Pneumococcal 13-valent Conjugate Vaccine (PCV13; Prevenar13®; Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]).

Clinical diagnosis of pneumonia and infection

Pneumonia was diagnosed in the presence of the typical clinical signs of lung infection (>38 °C, cough, tachypnea, hypoxemia) and radiographic findings consistent with pneumonia from either chest x-ray or chest computed tomography. The microbiological assessment of patients with pneumonia was not mandatory, and it was made according to the local clinical protocol.

Immune response to the PCV13 and anti-pneumococcal IgG levels

A centralized assessment of the serological response to the PCV13 was made on serum samples stored at −80 °C. Measurement of anti-pneumococcal IgG (PC-IgG) levels was assessed at baseline, before vaccination, and after 3 and 6 weeks from PCV13. PC-IgG levels were evaluated by using a commercial ELISA kit (VaccZyme anti-PCP IgG Enzyme immune Assay, Binding Site, Birmingham, UK) according to the manufacturer's instructions. As described in prior published studies [34, 35], the immune response to the PCV13 was considered as adequate in the presence of a twofold increase in the baseline PC-IgG levels. As the protective levels of PC-IgG have not been universally defined, we arbitrarily considered as protective levels ≥ 40 mg/L, which is the median value of levels of PC-IgG that has been identified in 231 blood donors by Parker et al. [36].

Statistical analysis

The primary end point of this study was to define the overall proportion of CLL patients who developed an immune response to the PCV13. Overall survival (OS) was calculated from PCV13 to the last follow-up or death, Pneumonia-free survival (PnFS) was evaluated from the date of PCV13 to the occurrence of pneumonia, last follow-up, or death. PnFS was analyzed according to the baseline clinical and biologic characteristics of patients, the immune response to PCV13, and PC-IgG levels. Survival curves were calculated according to the Kaplan and Meier method. Differences in survival were analyzed using the Log-Rank test in univariate analysis and using the Cox logistic regression model in multivariate analysis, after the assessment of the proportionality of hazards. Factors included in the multivariate analysis derived from univariate analysis. Confidence intervals (CIs) have been calculated at the 95% level. All statistical tests were two sided. A p value of <0.05 was considered significant. All analyses have been performed using the IBM SPSS v.21.0 statistical software.

Results

Clinical and biologic characteristics of patients

The baseline demographic, clinical, and biologic characteristics of the 112 CLL patients who received the PCV13 and were included in this study are described in Table 1. The median follow-up from PCV13 was 16 months (range, 6–38 months), the median age of patients at the time of vaccination, 68 years (range, 43–86 years), and the median time from CLL diagnosis, 73 months (range, 6–304 months). A prior pneumonia event, within 24 months before PCV13, has been recorded in 26 (23.2%) patients. Fifty-two percent of patients was IGHV unmutated (TN patients, 21.4%, FCR patients, 51.6%; BR patients, 44%; IBR patients, 62.8%; IDL patients, 66.7%). At the time of vaccination, 26 (23.2%) patients showed IgG levels ≤ 400 mg/dl. Fourteen patients with hypogammaglobulinemia received immunoglobulin support after a median time of 13 months (range, 4–28 months) from PCV13 due to recurrent infections (pneumonia, 8; other infections, 6). The median time between FCR or BR discontinuation and PCV13 was 40 months (range, 15–65 months) and 8.5 months (range, 7–15 months), respectively. The median time between the start of ibrutinib or idelalisib and PCV13 was 34 and 22 months, respectively. At the time of vaccination, seven (6.3%) patients (FCR, 2; BR, 2; IDL, 3) showed clinical signs of active disease (enlarged lymph-nodes ± increased lymphocytosis) which required treatment within six months from PCV13.

Safety of the PCV13

PCV13 vaccine has been well-tolerated in the majority of patients. Mild side effects have been reported in four cases (febrile reaction, 1; pain and erythema in the injection site, 1; ecchymosis in the injection site, 1; headache, 1).

PC-IgG levels and immune response to PCV13

PC-IgG levels were assessed before and after PCV13 in all patients. PC-IgG levels were evaluated in 104 patients at week three (8 patients were evaluated at week 6 only) from vaccination, and in 104 at week 6 (8 patients were evaluated at week 3 only).

The median value of PC-IgG levels before and after PCV13 was 26.4 mg/L (range, 3–270) and 27.6 mg/l (3–288), respectively. TN patients showed the highest median levels of PC-IgG after vaccination, 85 mg/dl (range, 12–288 mg/dl) followed by patients treated front-line with ibrutinib, 54 mg/dl (range, 13–136 mg/dl). The median levels of PC-IgG appeared not increased after vaccination in the other groups of patients (Fig. 1).

Thirty-four (30%) patients showed PC-IgG levels ≥ 40 mg/L at baseline (six of the 26, 23.1%, with prior history of pneumonia). Only 4 of the 78 (5.1%) patients with PC-IgG levels at baseline <40 mg/L increased their levels to ≥40 mg/L after vaccination.

Overall, nine patients (8%) developed an adequate immune response, defined as a twofold increase in the baseline PC-IgG levels (Table 2 and Fig. 1). Immune response was recorded in 8/22 (36%) TN patients, and in 1/11 patients vaccinated while on front-line therapy with ibrutinib.

All patients with an immune response showed baseline IgG levels > 400 mg/dl with PC-IgG levels ≥ 40 mg/L. Patients previously treated with chemoimmunotherapy, and those who received a BCR inhibitor after prior chemoimmunotherapy did not show an immune response (Table 2).

Factors associated with a significant lower rate of immune response were: age ≥ 60 years ($p = 0.007$), baseline IgG levels < 400 mg/dl ($p < 0.0001$), prior treatment ($p < 0.0001$) and clinical signs of disease progression ($p = 0.04$) (Table 2).

Clinical outcome after PCV13

Twenty-nine (26%) patients experienced pneumonia after PCV13. Pneumonia was observed in 2/9 patients with an effective immune response and in 6/40 (15%) with PC-IgG levels ≥ 40 mg/mL. In all cases, the radiologic pictures were consistent with pneumonia of bacterial etiology. Accordingly, a response to empiric antibiotics was successful in 26/29 (89.7%) cases. No response to treatment was seen in three (10.3%) patients with hypogammaglobulinemia who died without an identified microbial agent. Other causes of death were CLL progression in three patients, Richter syndrome in two, cerebral hemorrhage in one, cardiovascular event in one.

Survival

The estimated 36 months OS probability from PCV13 was 86.7% (Fig. 2a). Patients who experienced pneumonia showed significantly lower survival than those who did not develop pneumonia (36 months OS, 68.5% vs. 97.6%; $p < 0.0001$) (Fig. 2b). No differences in the survival probability have been observed according to the PC-IgG levels (≥40 mg/L vs. ≤40 mg/L) and immune response to PCV13.

The 36 months PnFS from PCV13 was 54.7%. Immune response to PCV13, PC-IgG levels, and baseline IgG levels revealed no significant impact on the PnFS probability (Table 3). Factors associated with a significantly lower PnFS were the presence of a pneumonia event within 24 months before PCV13 ($p < 0.0001$; Fig. 3a), clinical signs of progressive disease (<0.0001; Fig. 3b), and a low neutrophils count (<1.0 × 109/L; $p = 0.04$). Patients with TP53 disruption also showed a significantly lower PnFS ($p = 0.01$; Fig. 3c), while the IGHV mutational status did not show a significant effect. When the impact of prior treatment was analyzed, a significantly lower PnFS was observed in patients previously treated with BR as compared to those treated with FCR ($p = 0.009$; Table 3). No patients on front-line therapy with ibrutinib developed pneumonia after PCV13. The 12-month PnFS of R/R patients was 87.1% for patients on ibrutinib and 63.5% for those on idelalisib ($p = 0.02$). In multivariate analysis, the presence of clinical signs of progressive disease at the time of PCV13 (HR, 8.39 [95% CI, 2.71–25.97]) and a prior pneumonia event (HR, 7.03 [95% CI 3.33–14.86] showed a significant and independent impact on PnFS. When the analysis was restricted to the patients who had deletion 17p and/or TP53 mutation assessed, TP53 disruption also revealed an independent impact on PnFS (HR, 2.91 [1.22–6.99]).

Discussion

This study was carried out to better define, in a large series of CLL patients, the extent of an immune response to the pneumococcal vaccination. The heterogeneity of clinical, biologic, and treatment characteristics of patients included in this study limits the interpretation of our results. In addition, the immune response to the PCV13 was measured by titration of the PC-IgG levels only while no functional tests were performed. Nevertheless, the proportion of patients with an adequate response to PCV13 was lower than expected, 8%, and low in all the subsets of investigated patients.

Patients who developed an immune response were younger, with previously untreated and stable disease, and normal IgG levels. These characteristics suggest a higher likelihood of preserved immune functions. Conversely, an ineffective response was more frequent in patients with clinical factors that are associated with impaired immune functions, older age, prior treatment, active disease, and hypogammaglobulinemia. Despite the increase in the PC-IgG levels, a low proportion of TN patients developed an adequate immune response, 36%. A similar rate of responses to the PCV13, 33.3%, was observed by Svensson et al. in 63 previously untreated patients with CLL [30]. These findings suggest that, even in the absence of prior treatment, a higher proportion of TN patients than expected, show defects in immune functions [4, 37]. None of the patients who were vaccinated after at least 6 months from FCR or BR chemoimmunotherapy displayed an immune response. Moreover, no responses were observed either in the 44 R/R patients vaccinated while on BCR pathway inhibitors given after prior chemoimmunotherapy. These findings are in line with the results of a study that showed the lack of an adequate immune response in 4 R/R patients who received the PCV13 while on ibrutinib [31]. Low immune response to the influenza vaccine was also recorded in CLL patients vaccinated while on ibrutinib. Sun et al. [32] observed a seroconversion for at least 1 influenza strain in 5/19 (26%) patients and Douglas et al. [33] in 1/14 (7%).

Clinical signs of progressive disease and prior chemoimmunotherapy were associated not only with an inadequate immune response, but also with an inferior PnFS. In turn, the development of pneumonia, observed in 25% of patients, had an adverse impact on survival. These findings further indicate a close relationship between active disease and infections in CLL [38, 39].

Patients who developed an immune response to PCV13 did not show a significantly higher PnFS. On the contrary, while only 1/11 patients on front-line therapy with ibrutinib showed an immune response, all were pneumonia free at 2 years from vaccination. It should be considered the small number of patients with an immune response, and that different infectious agents, other than pneumococcus, could be involved in the occurrence of pneumonia. Moreover, the antibody response should be considered as a surrogate marker for the clinical efficacy of vaccines [40]. Preserved cellular immunity may have played an important synergistic role in protecting against infectious agents.

Pronounced defects on innate and adaptive immunity, due to prior chemoimmunotherapy and BCR inhibitors, could have resulted in the lack of immune response, and in the marked frailty to infections observed in R/R patients [13, 1441,42,43,44]. Close monitoring for infections, immunoglobulin replacement in the presence of hypogammaglobulinemia, could be more effective measures than vaccination for these patients. The increased number of reports on bacterial and opportunistic infections in patients receiving BCR pathway inhibitors has led to recommendations for the clinical management of patients treated with these agents [45,46,47].

In conclusion, the results of this study showed that a limited proportion of young patients, chemo free, with stable disease, and normal IgG levels, developed an effective immune response to the PCV13. These findings suggest that vaccination should be offered at diagnosis to patients with early stage and stable disease who have better resources for an effective immune response. A sequential approach combining the PCV13 followed by the 23-valent pneumococcal polysaccharide vaccine (PPV-23) could be more effective and should be evaluated in CLL patients. Prospective studies investigating the immune response and the clinical benefit of pneumococcal vaccination should be explored in larger series of CLL patients who receive front-line treatment with BCR and BCL2 inhibitors.

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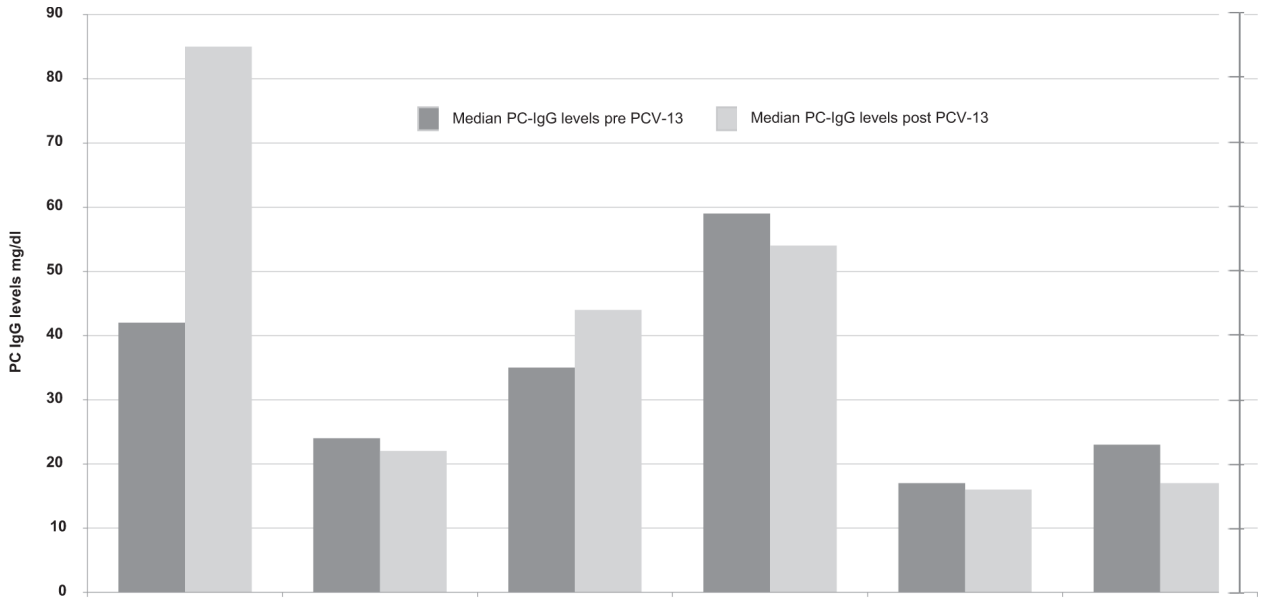
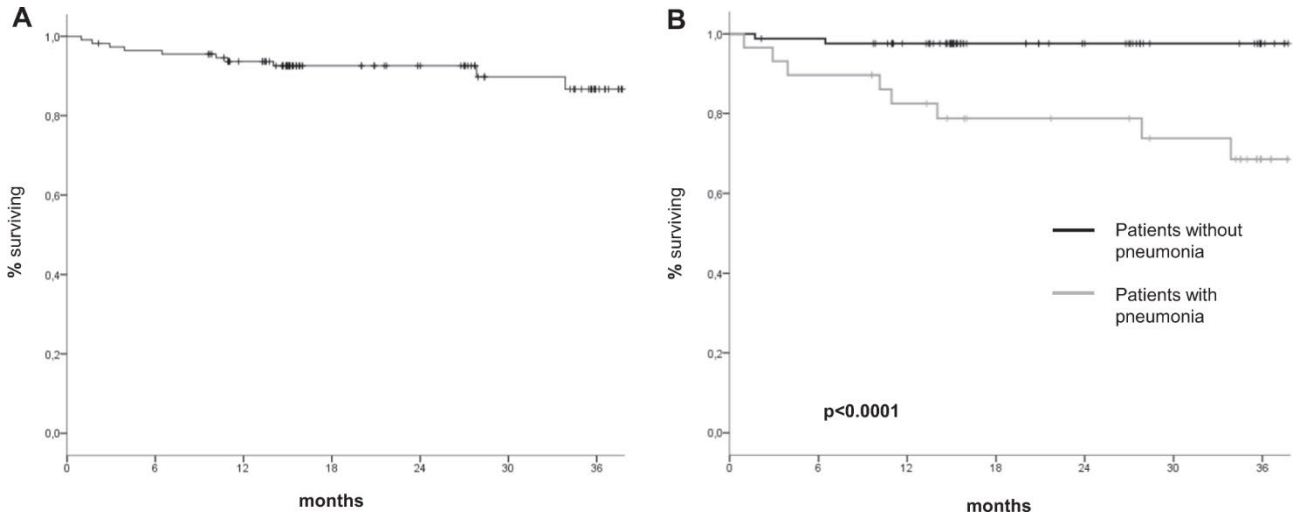
Fig.1



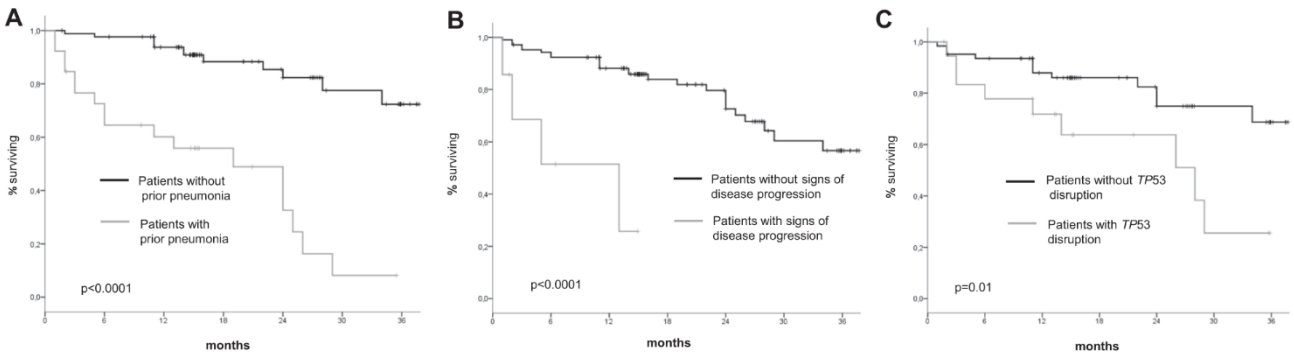
	TN N=22	FCR N=32	BR N=13	IBR 1st line N=24	IBR >1st line N= 24	IDL>1st line N= 10
Pre PCV-13, median mg/dl (range)	42 (11-122)	24 (3-135)	35 (11-270)	59 (14-134)	17 (3-97)	23 (5-69)
Post PCV-13, median mg/dl (range)	85 (12-288)	22 (3-145)	44 (10-270)	54 (13-136)	16 (3-103)	17 (3-63)
% patients with immune response	36	-	-	9	-	-

Fig. 2: Survival probability.



a Overall survival probability from PCV13. b Survival probability from PCV13 by pneumonia. Patients without pneumonia, black line; patients with pneumonia, gray line.

Fig. 3: Pneumonia-Free Survival (PnFS)



a PnFS by a pneumonia event within 24 months before PCV13. Patients without prior pneumonia, black line, patients with prior pneumonia, gray line. b PnFS by clinical signs of disease progression. Patients without clinical signs of disease progression, black line; patients with clinical signs of disease progression, gray line. c PnFS by *TP*53 disruption. Patients without *TP*53 disruption, black line; patients with *TP*53 disruption, gray line.

Table 1 Baseline characteristics of patients.

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	All patients *N* (%)	TN patients *N* (%)	FCR-treated patients *N* (%)	BR- treated patients *N* (%)	IBR- treated patients[a] *N* (%)	IDL-treated patients *N* (%)
No of patients	112	22 (19.6)	32 (28.6)	13 (11.6)	35 (31.3)	10 (8.9)
Median time from CLL, months (range)	73 (6–304)	80 (6–261)	56 (12–269)	80 (41–173)	81 (19–234)	120 (8–304)
Median time from PCV, months (range)	16 (5–38)	15 (13–37)	27 (6–38)	16 (6–36)	22 (10–38)	10 (5–36)
Gender M/F	80/32	18/4	24/8	9/4	21/14	8/2
Median age, years (range)	68 (43–87)	64 (43–86)	60 (44–66)	68 (53–86)	72 (58–87)	74 (58–83)
Median Hb g/dl (range)	13.6 (9.5–17.2)	14.8 (12.1–16.6)	13.4 (10.7–16.9)	13.9 (9.9–16.8)	13.5 (9.5–17.2)	12.4 (10.9–14.1)
Median lymphocytes $\times 10^9$/L (range)	5.9 (0.7–110.2)	16.6 (3.9–90.4)	2.3 (0.9–78.9)	2.3 (0.7–46.6)	5.4 (1.1–110.2)	7.9 (1.3–23.8)
Median neutrophils count $\times 10^9$/L (range)	3.5 (0.5–9.7)	4.1 (0.6–8.0)	2.9 (0.9–5.5)	3.6 (1.4–4.9)	3.5 (0.5–9.5)	3.0 (2.2–9.7)
Median number prior treatments (range)	–	–	–	–	1 (0–5)[a]	3 (1–7)
Median time from CIT discontinuation, months (range)	–	–	40 (15–65)	8.5 (7–15)	–	–
Median time on KIs, months (range)	–	–	–	–	34 (12–45)	22 (9–35)
Clinical signs of progressive disease[b]	7 (6.3)	0	2 (6.3)	2 (15.4)	0	3 (30.0)
Median IgG levels, mg/dl (range)	563 (25–1890)	813 (238–1890)	497 (57–1162)	474 (25–797)	545 (217–1730)	641 (195–1220)
Prior pneumonia within 2 years before PCV13	26 (23.2)	3 (13.6)	5 (15.6)	6 (46.2)	7 (20.0)	5 (50.0)
Del17p and/or*TP*53 mutation	19/81 (23.5)	2/9 (22.2)	2/27 (7.4)	0/9	9/26 (34.6)	6/10 (60.0)
IGHV unmutated	51/98 (52.0)	3/14 (21.4)	16/31 (51.6)	4/9 (44.4)	22/35 (62.8)	6/9 (66.7)
CD38 positive	36/105 (34.3)	5/20 (25.0)	8/30 (26.7)	4/12 (33.3)	15/33 (45.5)	4/10 (40.0)

TN treatment-naïve patients, FCR fludarabine, cyclophosphamide, BR bendamustine, rituximab, IBR ibrutinib, IDL idelalisib, PCV pneumococcal conjugate vaccine, CIT chemoimmunotherapy, KIs kinase inhibitors, Ig immunoglobulins, IGHV immunoglobulin heavy chain variable region mutations. a11 patients received IBR front-line therapy. bPatients with clinical signs of progressive disease (enlarged lymph-nodes ± increased lymphocytosis) which required treatment within six months from PCV13.

Table 2 Immune response to the PCV13 according to the baseline characteristics of patients.

	All patients *N* (%)	Immune response present *N* (%)	Immune response absent *N* (%)	*p* value
All patients	112	9 (8.0)	103 (92.0)	–
Gender M	80 (71.4)	6(66.7)	74 (71.8)	0.74
Gender F	32 (28.6)	3(33.3)	29 (28.2)	
Patients < 60 years	31 (27.7)	6 (66.7)	54 (52.4)	0.007
Patients ≥ 60 years	81 (72.3)	3 (33.3)	49 (47.6)	
Neutrophils count < 1.0×10^9/L	4 (3.6)	0 (0)	4 (3.6)	0.55
Neutrophils count ≥ 1.0×10^9/L	108 (96.4)	9 (100)	99 (96.4)	
IgG levels < 400 mg/L	26 (24.5)	0	26 (25.2)	0.07
IgG levels ≥ 400 mg/L	80 (75.5)	9 (100)	77 (74.8)	
IgG PCV levels ≥ 40 mg/dl	40 (35.7)	9 (100)	31 (30.1)	<0.0001
IgG PCV levels < 40 mg/dl	72 (64.3)	0 (000)	72 (69.9)	
Pneumonia prior PCV	26 (23.2)	2 (22.2)	26 (25.2)	0.95
No pneumonia prior PCV	86 (76.8)	7 (77.8)	77 (74.7)	
Number of prior treatment = 0	22 (19.6)	8 (88.9)	14 (13.6)	<0.0001
Number of prior treatments = 1	67 (59.8)	1 (11.1)	66 (64.0)	
Number of prior treatments >= 2	23 (20.6)	0	23 (22.4)	
Prior treatment with FCR	32 (28.6)	0	32 (31.1)	NE
Prior treatment with BR	13 (11.6)	0	13 (12.6)	
Ongoing treatment with 1° line IBR	11 (9.8)	1 (11.1)	20 (19.4)	NE
Ongoing treatment with >1° line IBR	24 (21.4)	0	14 (13.6)	
Ongoing treatment on >1° line IDL	10 (8.9)	0	9 (8.7)	
Del17p and/or *TP*53 mutation present	19 (23.5)	1 (11.1)	13 (24.1)	0.36
Del17p and/or *TP*53 mutation absent	62 (76.5)	8 (88.9)	41 (75.9)	
IGHV unmutated	51 (52.0)	2 (33.3)	24 (49.0)	0.34
IGHV mutated	47 (48.0)	4 (66.7)	25 (51.1)	
CD38 positive	36 (34.3)	3 (33.3)	25 (40.3)	0.94
CD38 negative	69 (65.7)	6 (66.6)	37 (59.7)	
Clinical signs of disease progression present[a]	7 (6.3)	2 (22.2)	7 (6.8)	0.04
Clinical signs of disease progression absent[a]	105 (93.7)	7 (77.8)	96 (93.2)	

FCR fludarabine, cyclophosphamide, BR bendamustine, rituximab, IBR ibrutinib, IDL idelalisib, PC pneumococcal, PCV pneumococcal conjugate vaccine, Ig immunoglobulins, IGHV immunoglobulin heavy chain variable region mutations, NE not evaluated.

aPatients with clinical signs of active disease (enlarged lymph-nodes ± increased lymphocytosis) which required treatment within six months from PCV13.

Table 3 Pneumonia-free survival (PnFS) from PCV13 according to patient characteristics.

	All patients	%1 year PnFS	%2 years PnFS	%3 years PnFS	*p* value
Gender M	80 (71.4)	86.6	72.1	48.7	0.72
Gender F	32 (28.6)	84.4	65.3	65.3	
Patients < 60 years	31 (27.7)	90.1	79.7	73.1	0.13
Patients ≥ 60 years	81 (72.3)	84.6	65.5	43.7	
Neutrophils count < 1.0×10^9/L	4 (3.6)	50.0	-	-	0.04
Neutrophils count ≥ 1.0×10^9/L	108 (96.4)	87.4	78.0	55.5	
IgG levels < 400 mg/L	26 (24.5)	88.3	68.2	47.7	0.72
IgG levels ≥ 400 mg/L	80 (75.5)	85.5	72.3	58.1	
Post PCV IgG PC levels ≥ 40 mg/dl	40 (35.7)	89.6	76.2	76.2	0.09
Post-PCV IgG PC levels < 40 mg/dl	72 (64.3)	84.0	66.3	46.9	
Pneumonia prior PCV	26 (23.2)	60.2	32.6	-	<0.0001
No pneumonia prior PCV	86 (76.8)	93.7	82.3	72.3	
Number of prior treatment 0	22 (19.6)	86.4	40.9	-	0.26
Number of prior treatments = 1	67 (59.8)	89.4	74.3	60.2	
Number of prior treatments > 2	23 (20.6)	75.9	66.4	-	
Prior treatment with FCR	32	90.6	79.3	73.6	0.009
Prior treatment with BR	13	76.9	26.0	-	
Ongoing treatment with 1° line IBR	11	100	100	-	0.02
Ongoing treatment with >1° line IBR	24	87.1	75.9	42.2	
Ongoing treatment on >1° line IDL	10	63.5	-	-	
Del17p and/or*TP*53 mutation present	19 (23.5)	71.8	63.8	25.5	0.01
Del17p and/or*Tp*53 mutation absent	62 (76.5)	87.9	74.9	68.7	
IGHV unmutated	51 (52.0)	87.5	69.9	55.9	0.58
IGHV mutated	47 (48.0)	82.5	70.7	53.0	
CD38 positive	36 (34.3)	91.5	67.1	40.3	0.98
CD38 negative	69 (65.7)	83.3	71.9	58.2	
Clinical signs of disease progression present[a]	7 (6.3)	51.4	-	-	<0.0001
Clinical signs of disease progression absent[a]	105 (93.7)	88.1	72.6	56.6	
Immune response to PCV present	9 (8.0)	88.9	44.4	-	0.98
Immune response to PCV absent	103 (92.0)	85.9	71.3	55.5	

FCR fludarabine, cyclophosphamide, BR bendamustine, rituximab, IBR ibrutinib, IDL idelalisib, PCV pneumococcal conjugate vaccine, Ig immunoglobulins, IGHV immunoglobulin heavy chain variable region mutations.

aPatients with clinical signs of progressive disease (enlarged lymph-nodes ± increased lymphocytosis) which required treatment within six months from PCV13.