Abstract 1203

Chronic obstructive pulmonary disease and previous infections had impact on infectious complications in patients with Chronic Lymphocytic Leukemia treated with venetoclax: a multicentre SEIFEM study.

F. Autore[1], A. Visentin[2], M. Deodato[3], C. Vitale[4], E. Galli[1], A. Fresa[1], R. Fazzi[5], A. Sanna[6], J. Olivieri[7], I. Scortechini[8], M.I. Del Principe[9], P. Sportoletti[10], L. Schiattone[11], N. Maschio[12], D. Facchinelli[13], M. Coscia[4], A. Tedeschi[3], L. Trentin[2], I. Innocenti[1], A. Candoni[14], A. Busca[4], L. Pagano[1]*, L. Laurenti[1]*.

(1) Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma; (2) Università degli Studi di Padova, Padova; (3) ASST Grande Ospedale Metropolitano Niguarda, Milano; (4) A.O.U. Città della Salute e della Scienza di Torino, Torino; (5) Azienda Ospedaliera Universitaria Pisana, Pisa; (6) Azienda Ospedaliera Universitaria di Careggi, Firenze; (7) Clinica Ematologia di Udine, Udine; (8) Azienda ospedaliero Universitaria delle Marche, Ancona; (9) Università degli studi di Roma Tor Vergata, Roma; (10) A.O. Santa Maria della Misericordia di Perugia, Perugia; (11) Presidio Ospedaliero S.Spirito di Pescara, Pescara; (12) Istituto Oncologico Veneto IOV-IRCCS, Padova; (13) Ospedale San Bortolo, Vicenza; (14) Università degli Studi di Modena e Reggio Emilia, Modena.

*equally contributed

INTRODUCTION

Infections became the major source of morbidity and mortality in patients with Chronic Lymphocytic Leukemia (CLL) due to its typical immune dysfunction and cytotoxic treatment-related factors. Patient-specific risk factors include age, comorbidities, number and type of prior lines of therapy, disease stage, refractoriness to treatment, and type of therapy.

The increasing use of targeted therapies aimed to increase antitumor efficacy beyond that of standard chemoimmunotherapy regimens, in addition to reduce general toxicity and in particular infectious complication. Rates, risk and spectrum of infections with the use of chemo-immunotherapic agents are well described and supported by clinical guidelines.

Treatment with the new molecules is increasingly common in routine clinical practice, but data on infection incidence are extrapolated generally from clinical trials and real-world data are lacking. Clinical trials evaluating the efficacy of these therapies are typically not powered to detect differences in infections.

OBJECTIVES

Over the last 2 decades, introduction of new therapies has led to the emergence of a different spectrum of infections. Full spectrum and outcomes of infections with the use of venetoclax remains undefined beyond clinical treatment trials with limited duration of follow-up. Dedicated studies evaluating patterns of infection, risk factors and clinical outcomes in patients managed in non-trial settings are lacking.

Patients with CLL are often elderly, with other comorbidities, heavily treated, and experienced serious infections.

The aim of the present study is to describe the infectious complications in patients with LLC treated with venetoclax in routine clinical practice, to evaluate the incidence of clinically or microbiologically documented bacterial, fungal and viral infectious complications and to identify additional factors of infectious risk in these patients.

METHODS

The retrospective multicenter study included CLL patients treated since 2017 with venetoclax single agent until progression or toxicity or venetoclax plus antiCD20 antibody (mainly rituximab as part of VR protocol for 24 months or obinutuzumab as part of VO protocol for 12 months).

Infections were identified by reviewing patients' medical records and laboratory data.

Table 1: Patients characteristics with subdivision in the two subgroups (venetoclax single agent and venetoclax plus antiCD20 antibody) with significant differences between them.

		GENERAL 287 pts	VEN 151 pts	VEN plus antiCD20 136 pts	p value
Age	med	70	72	68	**0,002**
Gender	F/M	84/203	43/108	41/95	0,756
CIRS	≤6 / >6	209/78	110/41	99/37	0,991
Smoking	no/yes	233/54	125/26	108/28	0,447
Diabetes	no/yes	254/34	137/14	116/20	0,156
COPD	no/yes	247/40	131/20	116/20	0,721
CrCl <70	no/yes	170/117	80/71	90/46	**0,023**
IgG	med (mg/dL)	585	552	618	**0,038**
Binet	A/B/C	33/121/133	18/68/65	15/53/68	0,504
Del13	yes	97	56	41	0,273
+12	yes	37	20	17	0,899
Del11	yes	66	34	32	0,744
Del17	yes	82	54	28	**0,005**
TP53 mut	yes	85	56	29	**0,001**
Previous PCT	med	2	2	1	**<0,001**
Lymphocytes	med (x 10^9/L)	27	17	35	0.104
Neutrophils	med (x 10^9/L)	3.1	3	3.2	0,267
Platelets	med (x 10^9/L)	129	130	128	0,730
Hemoglobin	med (g/dL)	11.7	11.8	11.6	0,692
Previous infection	no/yes	193/94	88/63	105/31	**<0,001**
Previous pneumonia	no/yes	257/30	130/21	127/9	0,108

RESULTS

A total of 287 patients with CLL received venetoclax during the study period from 16 different institutions.

Median age was 70 years (range 40–93) and 203 (70.7%) patients were male. According to Binet 33 (11.5%) patients were in stage A, 121 (42.2%) in stage B and 133 (46.3%) in stage C. Del17/p53 mut were isolated in 85 (29.6%) of the patients. 78 (27.2%) had a baseline CIRS >6 and when analyzing the comorbidities 117 (40.8%) showed a renal impairment (CrCl <70), 40 (13.9%) COPD, 34 (11.8%) diabetes; 54 (18.8%) patients have been defined as smokers. Data on previous infections analyzing the frame period of one year before venetoclax start showed infections in 94 (32.7%) patients, of whom 30 (10.4%) were pneumonia.

The whole population was divided in two groups, if venetoclax was given as monotherapy (151 patients, 52.6%) or associated to antiCD20 antibody (136 patients, 47.4%). The median number of prior treatment regimens was 2 in the first group and 1 in the second. Comparing the two groups, patients of the first group were older, more frequently had del17/TP53mut, renal impairment and lower basal levels of IgG. They also showed more previous infections in the 12 months before the beginning of the treatment with venetoclax. Basal characteristics of the two groups are summarized in Table 1.

We registered 284 infections of any grade. When comparing time of first infection of any grade between the patients treated with venetoclax and those treated with venetoclax plus antiCD20 antibody, we registered a trend toward a higher rate of infection in the latter group after the first year (p=0.066; figure 1). This difference was not confirmed when we focused on infections of grade 3-4 (p=0.521; figure 2).

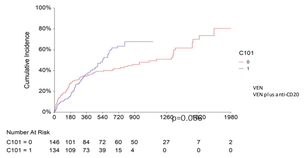

Figure 1: Time of first infection of any grade between the patients treated with venetoclax and those treated with venetoclax plus antiCD20 antibody.

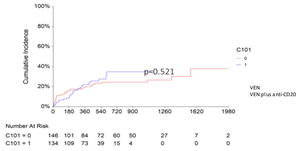

Figure 2: Time of first infection of grade 3-4 between the patients treated with venetoclax and those treated with venetoclax plus antiCD20 antibody.

One-hundred eighty-one infections of grade 1-2 developed in 114 patients (39.7%) during the study.

The majority of infections involved the respiratory tract (106 events, 58.6%), followed by genitourinary tract (23, 12.7%) and gastrointestinal one (16, 8.8%). Pathogens implicated in the infections were isolated only in 57 (31.5%) cases: 36 viral, 18 bacterial and 3 fungal.

We recorded 103 episodes of infections of grade 3-4, occurred in 73 patients (25.4%). The most common site of infection involved the respiratory tract (71 events, 68.9%), then we registered sepsis (13, 12.6%) and gastrointestinal tract infections (7 events, 6.8%). Of 103 severe infections, 64 (62.1%) were microbiologically proven, of whom 40 were viral, 21 bacterial and 3 fungal.

When comparing patients with and without infection, COPD (p<0.001, OR 3.75), previous infections in the last 12 months (p<0.001, OR 3.15), renal impairment CrCl<70 (p = 0.049, OR 1.62), previous treatments (p=0.023; OR 1.196) and stage A (p=0.001; OR 0.2) were more frequently associated with infection in univariate analysis. In multivariate analysis COPD (p <0.001, OR 5.39) and previous infections (p=0.001, OR 2.57) resulted significant.

Univariate and multivariate analysis for infections of any grade are summarized below:

	Univariate analysis		Multivariate analysis	
	p value	Odds Ratio	p value	Odds Ratio
Age	0.810			
Gender	0.511			
CIRS > 6	0.312			
Smoke	0.063			
Diabetes	0.758			
COPD	**<0.001**	**3.75**	**<0.001**	**5.39**
Neutrophils < 1000	0.933			
CrCl < 70	**0.049**	**1.62**	0.241	
IgG	0.441			
LDH	0.817			
Stage B-C vs A	**0.001**	**0.200**		
Previous PCT	**0.023**	**1.196**	0.361	
Previous pneumoniae < 12 mo	0.243			
Previous infections < 12 mo	**<0.001**	**3.15**	**0.001**	**2.57**

Stratifying patients according to COPD and previous infections in the last 12 months we obtained 3 groups significantly different in terms of risk for infections (p <0.001; figure 3).

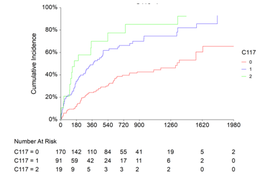

Figure 3: Stratification of patients according to the two risk factors for infections COPD and previous infections in the last 12 months: none risk factor (group 0), one of the two risk factors (group 1), both the risk factors (group 2).

	0 risk factor	1 risk factor	2 risk factors
Infections within 1 year	24%	49%	69%
Infections within 2 years	39%	66%	77%
Infections within 3 years	48%	74%	84%

When considering only grade 3-4 infections, risk factors significant in the univariate analysis were COPD (p <0.001, OR 3.23), smoke (p=0.033, OR 1.98) and previous infections (p=0.020, OR 1.91). COPD was the unique significant variable in multivariate analysis (p=0.008, OR 2.62).
Univariate and multivariate analysis for grade 3-4 infections are summarized in the following table:

	Univariate analysis		Multivariate analysis	
	p value	Odds Ratio	p value	Odds Ratio
Age	0.169			
Gender	0.913			
CIRS > 6	0.206			
Smoke	**0.033**	**1.98**	0.184	
Diabetes	0.326			
COPD	**<0.001**	**3.23**	**0.008**	**2.62**
Neutrophils < 1000	0.419			
CrCl < 70	0.219			
IgG	0.779			
Stage B-C vs A	0.942			
Previous PCT	0.532			
Previous pneumoniae < 12 mo	0.955			
Previous infections < 12 mo	**0.020**	**1.91**	0.090	

Treatment was withdrawn for infections in 80 patients (27.9%): in 58 (20.2%) treatment was temporarily discontinued, while in 22 (7.7%) discontinuation was permanent.
The temporary withdrawals had median length of 20 days (range 3-200), in 35 cases hospitalization was necessary.
These 58 patients were mainly male (46 out of 58, 79.3%), with a median age of 70 years (range 44-86) and 2 lines of previous treatment (range 1-8); in 23 cases (39.6%) they had infections in the previous 12 months and in 28 (48.3%) they were treated with venetoclax plus antiCD20. We registered 17 deaths, of whom 4 were due to infections.

Considering the 22 definitive withdrawals, they showed similar characteristics: mainly male (15 out of 22, 68.2%), with a median age of 71 years (range 55-86) and 2 lines of previous treatment (range 0-7); in 11 cases (50%) they had infections in the previous 12 months and in 9 (40.9%) they were treated with venetoclax plus antiCD20.
The infections that caused definitive withdrawals were mainly pneumonia (12 cases, 6 of whom from SarS-CoV2 infection) and sepsis (8 cases, 5 of whom after a SarS-CoV2 infection). Eighteen patients in this subgroup died of these infections during treatment with venetoclax monotherapy.

A total of 83 patients (28.9%) died and the median OS was 55 months. The main cause of death were CLL progression in 36 cases and infection in 22 cases.

CONCLUSIONS

This is a real-life study on 287 patients affected by LLC treated with venetoclax with the aim to describe the infectious complications in such population in routine clinical practice.

The analysis found a significant rate of infections, most of grade 1-2: 39.7% of the patients experienced a grade 1-2 infection; 25.4% a grade 3-4 infection.

The identification of additional infectious risk factors found a role of comorbidities such as COPD and previous infections; COPD resulted a risk factor also for infections of grade 3-4.

CONTACT INFORMATION

For information mail to francesco.autore@policlinicogemelli.it