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Venetoclax in combination with chemotherapy in Richter transformation: a *real-life* experience

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OBJECTIVE

- To evaluate the *real-life* feasibility and efficacy of the *off-label* combination of Venetoclax with chemotherapy in CLL patients with histologically confirmed diagnosis of Richter transformation (RT) in Italy

CONCLUSIONS

- Data from this real-life experience are in line with previous studies confirming the feasibility and the activity of Venetoclax based combination in younger fit RT patients, where the high rate of initial response may bridge a significant proportion to allo-HSCT
- Selection of patients (particularly in elderly) because of significant hematological toxicity
- Due to the high rate of neutropenia and infection, it's strictly recommended: G-CSF prophylaxis, Ig status evaluation and anti-infective prophylaxis
- New ongoing studies with Venetoclax combinations are ongoing and the comparison with this real-life data may be worthwhile to better understand their therapeutic impact

INTRODUCTION

Richter Transformation (RT) is defined as the occurrence of an aggressive lymphoma in patients with a previous or concomitant diagnosis of chronic lymphocytic leukemia (CLL). Despite advances in the treatment of CLL patients, RT is still associated with a dismal prognosis with standard therapies[1]. New therapeutic options for RT are urgently required. Venetoclax, an anti-BCL2 inhibitor, in combination with chemoimmunotherapy (CIT) or other agents is showing promising results in RT both in clinical trials and outside clinical trials[2].

METHODS

- Observational restrospective multicenter study
- Data about chemotherapy regimens and Venetoclax schedule were collected
- The RT stage was defined according to Ann Arbor staging system
- The response assessment was defined by Lugano 2014 criteria
- Adverse events (AEs) were encoded according to NCI common terminology criteria for adverse events (ctcae) v5.0
- Data about biological CLL characteristics at the time of RT or at the last available evaluation, the clonal relationship between CLL and RT, and the previous CLL therapies were collected

RESULTS

- We analyzed data from 9 Italian centers between October 2018 and July 2024
- 20 RT patients were included; baseline characteristics are summarized in **Table 1-2**
- The median time from CLL diagnosis to RT was 6.5 years (0-17)
- The clonal relationship between CLL and RT was evaluated and demonstrated in 16 patients
- Venetoclax schedule:
  - 18/20 reached 400mg of Venetoclax dose
  - 17/20 patients received Venetoclax according to Davids et al[2], 2 patients for 2-weeks from day 2-15 and 1 patient continuously
- The responses are summarized in **Table 3**. Patients in CR at the end of treatment: 10
  - allo-HSCT: 5
  - venetoclax maintenance: 2
  - no other therapy: 3

Table 1. Baseline characteristics - CLL

Baseline characteristics	Patients (n=20, %)
Age (years) at RT	63.5 (33-73)
Sex (M/F)	15/5 (75/25)
ECOG at RT	
• 0-2	16 (80)
• 3-4	4 (20)
CLL	
Biological characteristics	
• Unmutated IGHV (n=17)	11 (64.7)
• Tp53 mutation (n=18)	7 (38.8)
• Del17p (n=19)	4 (21)
Median n° of previous therapies	2 (0-4)
Prior therapies received	
• Untreated	5 (25)
• 1° and 2° generation BTki	10 (9 ibrutinib, 1 acalabrutinib) (50)
• Venetoclax-based	4 (1 V monotherapy, 2 Ven-R, 1 Ven-O) (20)
• CIT	10 (50)
• CIT, more than one course	2 (10)

Table 2. Baseline characteristics - RT

RT	
COO (Hans algoritm)	
• Non-GCB (with 2 plasmoblastic differentation)	17 (85)
• CGB	2 (10)
• NA	1 (5)
Ann Arbor stage III-IV	18 (90)
Largest lymph node	
• ≥5cm	13 (65)
• ≥ 10cm	3 (15)
Extranodal disease	8 (40)
SUVmax PET median	19 (7-37)
• SUV>10	15 (75)
LDH elevated	19 (95)
Type of venetoclax association	
• R-(DA)-EPOCH based*	10 (50)
• R-CHOP based	9 (45)
• BFM	1 (5)
Median n° of combination therapy	4 (1-6)

*3/10 R-DA-EPOCH after initial R-CHOP (treatment escalation after the result of the clonal relationship analysis)

Table 3. Response during and after treatment

Patients evaluable for response	20/20
Response during treatment*	
• ORR	70% (14/20)
• CR	40% (8/20)
• PR	30% (6/20)
• SD/NR/PD	20% (4/20)
• NA	5% (1/20)
• Death during treatment	5% (1/20)
Final response	
• ORR	55% (11/20)
• CR	50% (10/20)
• PR	5% (1/20)
• SD/NR/PD	40% (8/20)
• Death during treatment	5% (1/20)
Allogeneic HSCT consolidation	7/19
• after venetoclax based-therapy	6
• after subsequent therapies (ICE e Ibrutinib)	1
Venetoclax mantainence:	2/19

* Evaluated after 2-4 cycles of therapy.

Table 4. Toxicity

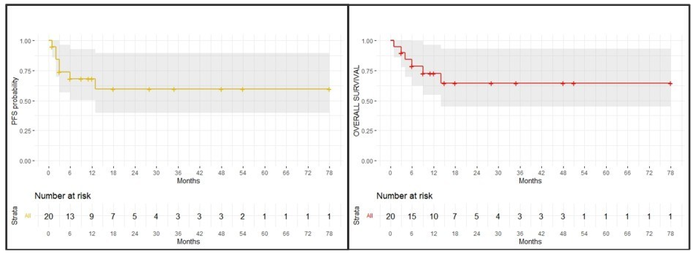
Toxicity (n=19)	Grade 1-2 (%)	Grade 3-4 (%)
Hematological		
Neutropenia	-	19 (100)
Febrile neutropenia	-	5 (26)
Anemia	10 (52)	9 (48)
Thrombocytopenia	9 (48)	5 (26)
Non-hematological		
Covid-19	2 (10)	3 (15)
Pneumonia	-	2 (10)
Sepsis/septic schock	-	2(10)
Fungal infection	-	1 (5)
Nausea	2 (10)	-
Mucositis	-	1 (5)
Costipation	1 (5)	-
Deep vein thrombosis	1 (5)	-
Subdural hematoma	1 (5)	-

Definitive Venetoclax dose reduction at 100-200 mg: 5 patients (25%)
- grade 3-4 neutropenia: 4
- fungal infection: 1

No cases of tumor lysis syndrome (TLS) were recorded during venetoclax ramp-up.

5 deaths: 3 disease progression, 1 lung cancer and 1 sepsis and MOF during treatment

Figure 1. PFS and OS



- Median follow up of 11.5 months (1-78)
- Patients alive in CR: 10 (including 5 who received allo-HSCT without any other treatment)
- Median PFS and OS: not reached

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DISCLOSURES

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