special report

memo (2019) 12:200–202
https://doi.org/10.1007/s12254-019-00521-y

memo
magazine of european medical oncology

# Highlights on chronic lymphocytic leukemia presented at the 2018 American Society of Hematology Meeting

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Received: 5 August 2019 / Accepted: 20 August 2019 / Published online: 17 September 2019


**Summary** Chronic lymphocytic leukemia (CLL) treatment strategies have improved and changed dramatically in the last few years. Insights presented at the last American Society of Hematology meeting changed standards of care in the first-line treatment. In patients <70 years with unmutated CLL, ibrutinib is the new standard resulting in a survival benefit compared to FCR (fludarabine, cyclophosphamide and rituximab). There was no progression-free survival or overall survival benefit in the subgroup of mutated patients for ibrutinib-based regimens. A randomized trial again showed no benefit of rituximab when added to ibrutinib compared to ibrutinib alone. Moreover, several promising treatment strategies in the relapsed/refractory setting were presented. The combination of ibrutinib with venetoclax reduces tumor lysis syndrome risk and generates MRD (minimal residual disease) negativity.

**Keywords** Immunochemotherapy · First-line therapy · Ibrutiunib · Venetoclax · Novel drugs

## Introduction

At the last American Society of Hematology (ASH) meeting, important and partly practice-changing data in the treatment of chronic lymphocytic leukemia (CLL) were presented. This article summarizes the author's personal highlights concentrating on relevant clinical data in the treatment of CLL.

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## Results

### *First-line therapy*

#### Challenging immunochemotherapy

Fludarabine, cyclophosphamide and rituximab (FCR) has been the standard first-line treatment for young and fit patients with CLL with a complete remission (CR) rate after 6 cycles of 40–72%, and undetectable bone marrow minimal residual disease (MRD) rate after 6 cycles of 43–58%. Patients with mutated *IGHV* status have favorable long-term outcomes after receiving first-line FCR with a plateau on the PFS curve. Ibrutinib, an inhibitor targeting BTK, is approved for patients with relapsed CLL. At the last ASH meeting, randomized data comparing standard immunochemotherapy with targeted therapy were presented.

A large randomized phase III study (ECOG-ACRIN Cancer Research Group, E1912) compared standard FCR with ibrutinib-based therapy in untreated younger patients with CLL [1]. Patients ($N=519$) with or without 17p deletion and younger than 70 years were included and randomly assigned in a 2:1 ratio to receive ibrutinib 420 mg per day and rituximab (IR) or 6 cycles of FCR. The primary endpoint was progression-free survival (PFS) with a secondary endpoint of overall survival (OS). IR was superior to FCR independent of age, sex, performance status or the presence of with or without 11q deletion (HR = 0.352; 95% CI 0.223–0.558; $p<0.0001$). The HR for OS also favored the IR arm. IR was superior to FCR in patients without the immunoglobulin variable heavy chain (IGVH) mutation, but not in patients with the mutation. Grade 3–4 adverse events were observed in 58% of IR-treated and 72% of FCR-treated patients. In particular, the rate of neutropenia or infections was significantly higher in the FCR treatment arm.

In conclusion, these findings establish ibrutinib as a novel standard of care in younger patients with CLL, at least in patients with mutated IGVH mutational status.

In another study ibrutinib alone or in combination with rituximab resulted in superior PFS compared with bendamustine plus rituximab (BR) in untreated patients with CLL (ALLIANCE trial) [2]. Patients ($N=547$) were older than 65 years, had a creatinine clearance ≥40 ml/min and no significant life-limiting intercurrent illness or need for warfarin treatment. With a median follow-up of 32 months, the median PFS was 41 months in the BR treatment arm, and not reached in the ibrutinib arm, with or without rituximab ($p<0.0001$). There was no difference comparing ibrutinib alone versus in combination with rituximab. Therefore, ibrutinib represents a treatment option for elderly patients with treatment naïve CLL showing better PFS compared to BR. However, data show clearly that there is no benefit in adding rituximab to ibrutinib.

The next phase III study comparing chemotherapy-based with targeted-therapy-based treatment options included 229 patients aged ≥65 years, or patients younger than 65 years with coexisting conditions (CIRS score >6, creatinine clearance <70, or TP53 mutation) (iLLUMINATE study) [3]. Patients were randomized 1:1 to receive ibrutinib with obinutuzumab or chlorambucil with obinutuzumab. The primary endpoint was PFS. The ibrutinib-based regimen prolonged PFS significantly (HR 0.231; $p<0.0001$). PFS rates at 30 months were 79 and 31% for ibrutinib and chlorambucil, respectively. Ibrutinib with obinutuzumab treatment was tolerable with new safety signals.

In summary, these three studies are practice changing in the management of CLL patients. There was no PFS or OS benefit in the subgroup of patients with mutations. But at least in patients <70 years with unmutated CLL, ibrutinib is the new standard of care resulting to a survival benefit compared to FCR.

### Novel drugs and novel drug combinations

A study using another BTK inhibitor, acalabrutinib included 99 patients [4]. The overall response rate (ORR) was 97% and the median PFS was not reached. Another study included relapsed/refractory (R/R) and untreated high-risk patients [5]. The ORR of acalabrutinib treatment was 90%.

The combination of ibrutinib, fludarabine cyclophosphamide, and obinutuzumab (iFCG) was evaluated in patients with mutated IGVH and without TP53 aberrations [6]. All 42 patients achieved a response after 3 month with 90% MRD negativity in the bone marrow. Grade 3–4 neutropenia occurred in 46% of patients.

Another study combined ibrutinib and the bcl-2 inhibitor venetoclax in patients with treatment-naïve high-risk CLL [6]. A total of 80 patients were enrolled. The median age was 65 years (range 26–83 years). At 6 months of the combination, 71% patients achieved CR and 41% achieved MRD negativity in BM. At 12 months of combination 92% CRs were found and 68% had negative MRD in the BM.

## *Relapsed/refractory*

### Ibrutinib and venetoclax

Ibrutinib plus venetoclax combined treatment was also tested in the relapsed/refractory (R/R) setting (Bloodwise TAP Clarity Study) [7]. In this phase II trial ibrutinib and venetoclax were combined in 50 patients with relapsed or refractory CLL. After 8 weeks of ibrutinib monotherapy (420 mg/day), venetoclax was added. There were no cases of clinical tumor lysis syndrome (TLS) and only a single case of biochemical TLS (grade 3) which resolved with treatment. The primary end-point was the eradication of MRD in blood and bone marrow. After 12 months of combined therapy undetectable MRD was achieved in 23/40 (58%) patients in blood and 17/41 (41%) in BM. In summary, the combination of ibrutinib and venetoclax was well tolerated. Every patient responded and there was a high rate of MRD eradication, in some cases leading to the cessation of therapy.

A case series of patients ($N=8$) who participated in the MURANO trial with progression after time fixed venetoclax/rituximab treatment was presented [8]. Seven patients (87.5%) responded to subsequent ibrutinib. Therefore, ibrutinib might represent a reasonable treatment choice with activity for early relapsing patients after venetoclax-based treatment. However, it will be important and necessary to prove these novel data in larger patient series. In summary, the mechanism of action of ibrutinib and venetoclax are complimentary with a postulated synergistic activity in combined strategies as well as evident activity in sequential usage.

Another update of the MURANO trial shows a high rate of sustained MRD negativity even after drug cessation which leads to a prolonged PFS in this prospective analysis [9].

### Other drugs and strategies

Umbralisib (TGR-1202) is a next generation inhibitor. A phase I/II study investigating its combination with ublituximab, a chimeric CD20 monoclonal antibody, and with pembrolizumab, was presented [10]. R/R patients and patients with a Richter's transformation were included (in total 14 patients evaluable). The ORR rate in R/R patients was 90%, CR rate was 10%, and the 12 month PFS was 89%. In patients with Richter's transformation ORR was 50% (2/4 patients). The 2 responding patients had CR. Grade 3–4 neutropenia occurred in 43%.

Preliminary data of the phase II study (COSMOS) on safety and efficacy of anti-CD19 MOR208 treatment in combination with venetoclax in patients who dis-

continued prior BTK inhibitor therapy were presented [11]. In 10 evaluable patients the ORR was 100% (3CR, 7PR). Five of 6 evaluable patients were MRD negative.

Finally, CAR-T cells represent a novel treatment concept, also in CLL. Lisocabtagene maraleucel (liso-cel; JCAR017) is a CD19 targeted defined cell product. In a phase I study, the ORR was 81.3% with a CR rate of 43.8% in R/R CLL [12].

**Conflict of interest** D. Heintel received honoraria and travel support from AbbVie, Celgene, Janssen, Gilead, MSD, Roche, Takeda.

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