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Review Article

The Role of Venetoclax in the Treatment of Acute Myeloid Leukemia

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ABSTRACT:

The treatment of elderly patients with acute myeloid leukemia (AML) is very difficult, with limited available options until recently. For these groups of patients, who consist an unmet medical need, Venetoclax has shown impressive efficacy in recent phase II and III clinical trials. Venetoclax is a potent inhibitor of the BCL-2 antiapoptotic protein which is overexpressed in various hematologic malignancies, like chronic lymphocytic leukemia (CLL), B- Non Hodgkin lymphomas and AML. Although the clinical pipeline of Venetoclax in CLL is extended and started many years ago, in AML and for random reasons has not been until lately studied. However, recent phase II trials of Venetoclax in combination with hypomethylating agents and low dose cytarabine (LDAC) has shown unprecedented responses and overall survival rates and led to marketed authorization of these combinations in USA and in Europe. More recent phase III studies confirmed these findings. Moreover, Venetoclax is currently tested in various combinations and in various disease settings (with inductions chemotherapy for younger or older AML patients, as maintenance etc.). Finally, several ongoing phase III trials with newer targeted therapies use Venetoclax combinations (mainly with hypomethylating agents) as the comparator arm, suggesting that this combination is currently considered the new standard of care for newly diagnosed AML patients not eligible for intensive chemotherapy.

KEY WORDS: *Venetoclax, AML, Treatment, Mechanism of action, Clinical trials*

INTODUCTION

Acute Myeloid Leukemia (AML) is the most common acute leukemia in the adult population. According to SEER[1] (Surveillance, Epidemiology and End Results) and National Cancer Institute, the incidence of AML is estimated to be 4 cases per 100.000 persons per year. However, for the subgroup of elderly (older than 65 years of age) this incidence increases and it is estimated to be 10 cases per 100.000 persons per year. According to these estimations, it is obvious that AML is mainly a disease of the elderly.

Age affects remarkably the therapeutic decisions of AML, because elderly patients are often less tolerable to aggressive chemotherapeutic regimens and therefore are frequently considered "unfit" for induction chemotherapy. Moreover, it is very common that elderly patients present poor prognostic features at diagnosis (unfavorable cytogenetic characteristics, secondary AML etc).[2] Juliusson and colleagues[3] studied the outcome of 2767 patients with AML that had been registered in the Swedish Acute Leukemia Registry between 1997 and 2005 and found that age is an independent adverse prognostic factor even for patients considered "fit" for induction chemotherapy. However, among long term survivors in the Swedish Acute Leukemia Registry, there were also elderly patients who had received aggressive chemotherapy. This means that age should not be the sole parameter for a physician when deciding the treatment for a newly diagnosed AML patient.[3]

For the majority of elderly patients (>65 years of age) with newly diagnosed AML, who are considered "unfit"

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for intensive chemotherapy the therapeutic options were limited until very recently. Low Dose Cytarabine (LDAC) and hypomethylating agents (Azacitidine and Decitabine) were the only commercially available treatments for this population in Europe, however with very modest response and survival rates (Table 1).[4-6]

Currently, there is an intensified research effort for the identification of new potentially active targeted therapies, especially for elderly AML patients. Research is based mainly on the better understanding of the complicated molecular landscape in AML,[7] which results in the development of several new drugs that specifically target the recurrently identified mutations. Table 2 summarizes the most important clinical data of novel agents for the treatment of elderly AML patients.[8-17] All drugs in table 2 have already received commercial approval from FDA (Food and Drug Administration) in USA. Some of them have also received EMEA (European Medicines Agent) approval. However, there are many other novel agents (for example guadecitabine,[18] a novel hypomethylating agent and quizartinib,[19,20] a FLT3 inhibitor), which failed to produce therapeutic advantage for elderly newly diagnosed AML populations, when tested in phase III trials.

Data from table 2 shows that Venetoclax,[12-15] a BCL-2 inhibitor, presents remarkable efficacy in combination with currently available treatments for elderly AML patients and therefore is considered a very promising therapeutic option for these patients. The present review aims to summarize data on the role of Venetoclax in the treatment of AML including: the pathophysiologic mechanism of action and published clinical data.

Venetoclax mechanism of action (MOA)

Apoptosis is facilitated through two different pathways,[21,22] both of which end up to the activation of the caspase complex, the mediator of apoptosis. The first pathway is the "death receptor" pathway, which is activated by binding of members of TNF superfamily to their cell surface receptors. Upon binding an enzymatic cascade leads to caspase 8 activation. The second pathway is the mitochondrial pathway, which is regulated by the members of the BCL2 (B Cell Lymphoma 2) superfamily.

The BCL2 superfamily consists of three protein groups:[23] the multidomain (many –BH subunits) pro-apoptotic BCL-2 group (BAK and BAX proteins belong to this group), the multidomain antiapoptotic BCL-2 group (BCL2, BCLXL, MCL1 and others belong to this group) and finally the BH3-only domain pro-apoptotic group (BIM, PUMA, BID, BAD, NOXA, BIK, BMF belong to this group).

Two members of the 1st group, BAK and BAX are responsible for the formation of pores on the mitochondrial membrane. BAK and BAX molecules are activated by the BH3-only members and create a complex on the mitochondrial membrane (mitochondrial outer membrane permeabilization-MOMP).[24] The BH3-only pro-apoptotic proteins are released from the antiapoptotic members (e.g. BCL2). Upon MOMP formation, cytochrome C is released from the mitochondrion, along with Smac and other intramitochondrial proteins and this leads to the activation of other caspases beyond 8, the final step of the pathophysiology of apoptosis.[25]

Under normal conditions apoptosis is strictly controlled through a fine balance between pro-apoptotic and antiapoptotic members of the BCL-2 family. The antiapoptotic BCL2 members sequester the BH3-only proteins and prevent excess apoptosis.[24] On the other hand, under stress conditions (e.g. radiation, growth factor deprivation) apoptosis is facilitated. In the case of malignant cells this balance is disrupted. The antiapoptotic molecules, like BCL2, are increased resulting in reduced release of BH3-only proteins and impaired MOMP formation, which leads to inhibition of apoptosis.[25,26]

In hematologic malignancies increased expression of antiapoptotic proteins is observed. In a review by Tzifi F and coworkers,[27] the authors describe that different panel of antiapoptotic proteins are overexpressed in every hematologic malignancy. BCL2 overexpression in all leukemias and especially in chronic lymphocytic leukemia (CLL) and AML has been reported. However, this finding was originally observed in CLL and because of this, research on BCL2 targeting has been focused initially on CLL and not

TABLE 1. Commercially available treatment options in Europe for elderly AML patients until recently[4-6]

	Dose	Response	Median Survival	Reference
Low Dose Cytarabine (LDAC)	20 mg/m^2 sc x10 days	11-19% (CR=9%)	<6 months	Burnett et al. Cancer 2007;109:1114–24
Decitabine	20 mg/m^2 iv x 5 days	CR+CRp+CRi=28%	7.7 months	Kantarjian H, et al. J Clin Oncol. 30:2670–2677, 2012
Azacitidine	75 mg/m^2 sc x 7 days	CR+CRi=27.8%	10.4 months	Dombret H, et al. Blood 2015

TABLE 2. FDA (+/- EMEA) approved novel agents for elderly AML patients[8-17]

Drug	Class	The most important published data	Approval status
CPX-351 (Vyxeos®)	liposomic encapsulated structure with fixed molecular ratio of Cytarabine: Daunorubicin (5:1)	Phase III study with 309 pts with newly diagnosed AML (60-75 years): CPX-351 vs 7+3 OS: 9.56 m vs 5.95 m RR: 47.7% v 33.3%	FDA and EMEA approval *for elderly patients fit for intensive chemotherapy*
Enasidenib (IDHFA®)	IDH2 inhibitor	Phase I/II study in 239 R/R AML pts with IDH2 mutations: RR= 40.3%, CR=19.3%, OS=9.3 m (19.7 m for CR pts)	FDA approval
Ivosidenib (TIBSOVO®)	IDH1 inhibitor	Phase Ib/II study in 28 R/R AML pts and IDH1 mutations: RR=78%, CR+CRi=42.9%, transfusion independence=41.2%	FDA approval
Venetoclax (VENCLEXTA®)	BCL-2 inhibitor	1. Phase II study with Ven and HMA in 145 newly diagnosed AML pts >65 years of age: CR+CRi=73%, OS=NR 2. Phase II study with Ven and LDAC in 82 newly diagnosed AML pts >65 years of age: CR+CRi=54%, OS=10.1 m, 18.4 m for CR+CRi pts **Confirmatory Trials:** 3. Phase III (VIALE-A) study with AZA +/-Ven in 431 newly diagnosed AML pts ineligible for IC: OS=14.7 m for Ven+AZA vs 9.6 m for AZA arm 4. Phase III (VIALE-C) study with LDAC +/- Ven in 211 newly diagnosed AML pts ineligible for IC: for 18 m FU, OS=8.4 m for Ven+LDAC vs 4.1 m for LDAC arm	FDA and EMA approval
Gilteritinib (XOSPATA®)	FLT3 inhibitor	Phase III (ADMIRAL) study: 341 R/R AML pts randomized either to receive Gilderitinib or selected chemo: OS=9.3 vs 5.6 m CR+CRi=34% vs 15.3%	FDA and EMEA approval
Glasdegib (DAURISMO®)	Hedgehog pathway inhibitor	Phase II (BRIGHT 1003) study: 115 newly diagnosed AML pts unfit for IC randomized (2:1) to Glasdegib+LDAC or LDAC alone OS: 8.3 vs 4.3 months (HR=0.46, p=0.0002)	FDAand EMA approval

Pts: patients, AML: acute myeloid leukemia, OS: overall survival, m: months, RR: response rate, CR: complete response, FDA: Food and Drug Administration, EMEA: European Medicines Agency, CRi: CR with incomplete marrow recovery, Ven: Venetoclax, HMA: hypomethylating agents, LDAC: low dose Cytarabine, AZA: azacitidine, IC: intensive chemotherapy, FU: follow up, NR: not reached, R/R: relapsed/refractory

on AML.[27] Interestingly for many years it was known that MCL1 (myeloid cell leukemia 1) the main antiapoptotic protein is overexpressed in AML.[26] Inhibitors of MCL1 are in early clinical phase.[28]

The pharmacologic antagonism for the antiapoptotic properties of the BCL2 protein became feasible by the use of small molecules that mimic BH3-only proteins (BH3 mimetics).[29] These small molecules replace the BH3-only members from their hydrophophic "pocket" that exist on the BCL2 protein. BH3-only members are released with subsequent MOMP formation which finally results in apoptosis.

The first pioneering work was done with anti-sense oligonucleotides (e.g. oblimersen) in several hematologic malignancies.[28] Despite the initial enthusiasm, the outcomes of the BCL2 inhibition by the anti-sense oligonucleotide were short-lived and not reproducible, due to short half –life of the molecule, in comparison to the longer BCL2 half-life.[31,32]

Subsequently the research focused on small oligopeptide BH-3 mimetic molecules (e.g. obatoclax).[33] Initial efforts were disappointing because the oligopeptides had decreased affinity to BCL2 protein (Ki>100 nM) and many off-target actions which resulted to excessive toxicity. Several adverse events were reported, like severe thrombocytopenia, due to this nonspecific BCL2 inhibition, which affected many other antiapoptotic members, like BCLXL. Platelets significantly express BCLXL and this was the reason of severe thrombocytopenia with the first BH3 mimetics.[33,34]

All the above led Abb Vie company to create a new small BH3-mimetic molecule, the ABT-199 (Venetoclax) which has considerably increased affinity to the BCL2 protein (Ki<1nM) and reduced affinity to BCLXL (Ki>100 nM).[35] Venetoclax replaces the BH3-only molecules BIM and BAX, by binding to the same site on the BCL2 molecule. BIM and BAX are released and initiate the mitochondrial apoptotic cascade as described earlier.

Because BCL2 is expressed in neoplastic as well as in normal cells, it is reasonable that one should seek for a "therapeutic index" in BCL2 inhibition.[28] According to this, the inhibition should affect mainly the malignant cells and to a far lesser extent the normal cells. This "therapeutic index" is achieved through the BCL2 overexpression in malignant cells in contrast to normal cells. However, more important than the mere quantity of BCL2 is the BCL2 that is bound to BH3-only proteins,[36] which means the protein that is ready or "primed" to release the pro-apoptotic molecules. In malignant cells, like those of CLL and AML, BCL2 is fully "primed", resulting in a very low inhibition cut-off.[36] On the other hand, BCL2 is much less "primed" in normal cells, which results in high inhibition cut-off.[28,37]

Clinical trials with Venetoclax in AML

The initial clinical trials with Venetoclax have focused on CLL and non-Hodgkin lymphomas.[29] Venetoclax presented impressive activity in CLL, either as monotherapy or in combination with other agents and has already received approval for CLL treatment in USA and Europe.[38] Many clinical trials with Venetoclax in other lymphoid malignancies are ongoing.

The clinical investigation of Venetoclax in AML started with delay.[28,29] However, the recent clinical data and especially data from the randomized phase III studies, VIALA-A and VIALE-C[14,15] shows that Venetoclax has the potential to change the treatment landscape of this difficult to cure hematologic malignancy.

A short description of the most important clinical trials with venetoclax in AML is provided below.

The multicenter open-label phase II trial (M14-212)[30] studied the monotherapy with Venetoclax in patients with relapsed/refractory (R/R) or newly diagnosed AML, ineligible to receive intensive chemotherapy. The study recruited 32 patients (30 R/R and 2 newly diagnosed) who were treated with Venetoclax monotherapy with daily increasing doses starting from 20 mg and increasing up to 800 mg/d (or 1200 mg/d for those not achieving complete remission-CR- after the 4th week of treatment). Six patients (19%) achieved CR and CR with incomplete hematologic recovery-CRi. It should be noted that 4 out of 12 patients that carried IDH1/2 mutations (33%) achieved CR and CRi. All responses were short-lived (median duration 2.5 months) and the dose increase to 1200 mg/d in non-responders was not efficacious. There was no single case of clinical or laboratory tumor lysis syndrome (TLS). In this trial patients received intensive hydration along with prophylactic measures for hyperuricemia before and during the ramp-up phase, for TLS prevention. The majority of patients (84%) presented a serious adverse event (SAE) with the most common being febrile neutropenia (28%) and pneumonia (16%).

Although Venetoclax monotherapy in AML provided some promising results, responses seem to be modest and short-lived. It has been shown that resistance to venetoclax monotherapy may be mediated by other prosurvival proteins, such as MCL1, that sequester endogenous BH3-only proteins (eg, Bim) released by Venetoclax on BCL-2 binding.[39] Several drugs—including anthracyclines, hypomethylating agents (HMAs), and cytarabine—have demonstrated the ability to down-regulate MCL1 expression and act synergistically with venetoclax against AML cells in preclinical studies.[40,41] The findings of these preclinical studies and the fact that until recently HMAs and LDAC were the only available treatment options for elderly AML populations in first-line treatment setting led to two phase 1b/II studies with Venetoclax combinations with these agents.

In the phase Ib/II trial (NCT02203773),[12] 145 newly diagnosed AML patients older than 65 years of age, ineligible for intensive chemotherapy received the combination of Venetoclax and Azacitidine (75 mg/m^2 sc or iv for 7 days) or Decitabine (20 mg/m^{2}iv for 5 days) in 28-day cycles, until disease progression or unacceptable toxicity. Venetoclax was finally decided to be given (in the extension or phase II part of the study) at the final dose of 400 mg/d in 60 patients or at the final dose of 800 mg/d in 74 patients. In both combinations, Venetoclax was given with a daily increase beginning with the dose of 100 mg. The median age of the patient population was 74 years

and 49% of them had unfavorable cytogenetic findings. Moreover, 25% of the patients had secondary AML. For a median duration of 8.9 months, 67% of the patients presented CR and CRi and especially for those receiving Venetoclax at the final dose of 400 mg/d the CR and CRi rate was 73%. Among patients with poor prognostic characteristics, 60% achieved CR and CRi. More elderly patients (>75 years of age) had similar high responses with 65% achieving CR and CRi. The median duration of complete remission (CR and CRi) was 11.3 months, while median overall survival (OS) was 17.5 months for the whole cohort and was not reached for those receiving Venetoclax at the final dose of 400 mg/d. The most common adverse events (in more than 30% of the patients) were nausea, diarrhea, constipation, neutropenia, febrile neutropenia and thrombocytopenia. No case of TLS was noted. Prophylactic measures for TLS were also applied during the inpatient ramp-up phase of Venetoclax.

Venetocax has also been tested in combination with LDAC in a group of 82 newly diagnosed AML patients, ineligible for intensive chemotherapy, in the setting of a phase 1b/II trial (NCT02287233).[13] Patients received Venetoclax at the final dose of 600 mg/d in combination with subcutaneous LDAC (20 mg/m^2/d for 10 days) in 28-days cycles, until disease progression or unacceptable toxicity. The median age of patients was 74 years (63-90), 49% of them had secondary AML, 32% had poor prognostic cytogenetic characteristics and 29% had received a hypomethylating agent for preexisting myelodysplastic syndrome. The complete response rate (CR/CRi rate) for the whole cohort and for those not previously treated with a hypomethylating agent was 54% and 62% respectively, with median duration of response 8.1 (5.3-14.9) months and 14.1(5.5-not reached) months respectively and median OS of 10.1 (5.7-14.2) months and 13.5 (7-18.4) months respectively. The most common adverse events grade 3 or higher were febrile neutropenia (42%), thrombocytopenia (38%) and neutropenia (34%). No single case of TLS was observed in this trial as well. Prophylactic measures for TLS were also applied in this study.

With the impressive results of the last two phase Ib/II trials, Venetoclax received accelerated marketed authorization from FDA in 1-Nov-2018.[38] The authorization concerned patients not eligible to receive intensive chemotherapy and Venetoclax is administered at the final dose of 400 mg/d with hypomethylating agents (either Azacitidine or Decitabine) or at the final dose of 600 mg/d with LDAC. FDA and EMEA required further confirmatory phase III clinical trials in order the authorization to continue to exist or to be granted respectively. The results of these studies were reported very recently.

In the first study, the M15-656[14] (NCT02993523) or VIALE-A, which was a multicenter randomized double – blinded placebo-controlled phase III study, 431 newly diagnosed AML patients ineligible for intensive chemotherapy were randomized in a 2:1 ratio to receive Venetoclax or placebo at the final dose 400 mg/d (after of 3day ramp up in cycle 1) with subcutaneous or intravenous Azacitidine (75 mg/m^{2}for 7 days, in 28-day cycles). The treatment in both arms was administered until disease progression or unacceptable toxicity. The primary endpoint of VIALE-A study was OS and CR/CRi rate. After a median follow up of 20.5 months the Venetoclax/Azacitidine arm presented OS of 14.9 months vs 9.6 months in the Azacitidine arm ($p<0.001$). This difference accounts of 34% reduction of the risk of death when the patients receive the Venetoclax/Azacitidine combination. Statistically significant difference was also noticed in the CR/CRi rate: 66% vs 28% respectively ($p<0.001$). Responses in patients with de novo AML were 66% vs 30% and in patients with secondary AML were 67% vs 23% respectively. The most common grade 3 or higher adverse events were mainly hematologic: thrombocytopenia (45%/38%), neutropenia (42%/29%) and febrile neutropenia (42%/19%). Laboratory TLS was observed in 1% of patients in the Venetoclax/Azacitidine arm.

Molecular subgroup analysis of the VIALE-A has once again showed that mutations in IDH1 or IDH2 result in favorable response to Venetoclax combinations. A pooled analysis of the phase 1b (NCT02203773) and VIALE-A studies showed that CR and complete remission with partial hematologic recovery (CRh) for patients with an IDH1 mutation was 59% with Venetoclax/Azacitidine vs 9% with Azacitidine/placebo. CR/CRh for patients with an IDH2 mutation was 80% and 6% respectively.[42] This improvement was also seen in OS (17.4 months versus 2.2 months for IDH1 mutated patients and Not Reached-NR-versus 12.7 months for IDH2 mutated patients).

For FLT3 mutated patients, the ORR for Venetoclax/Azacitidine in VIALE-A was 70%, compared with 36% for Azacitidine. Despite a higher ORR for Venetoclax/Azacitidine among patients with either FLT3–tyrosine kinase domain (TKD) or internal tandem dublication (ITD), OS was better among patients with FLT3–TKD (median OS 19.2 v 10.0 months) than those with FLT3-ITD (median OS 11.5 v 8.5 months).[43]

In a more recent pooled analysis of VIALE-A and the phase Ib study (NCT02203773) Venetoclax and Azacitidine combination showed to be able to overcome the bad prognostic value of poor cytogenetic versus Azacitidine monotherapy (OS: 23.4 versus 11.3 months respectively) and only TP53 mutations retain adverse prognosis in the era of Venetoclax combinations (OS: 5.2 versus 4.7 months respectively).[44]

In a second study with similar design, the M16-043[15] (NCT03069352) or VIALE-C, 211 newly diagnosed AML patients not eligible for intensive chemotherapy were

treated with Venetoclax or placebo (randomization with 2:1 ratio) at the final dose of 600 mg/d (after a 4day ramp up period) in combination with subcutaneous LDAC (20 mg/m^2 for 10 days, in 28-day cycles) until disease progression or unacceptable toxicity. The primary endpoint of this trial was OS. The planned primary analysis showed a 25% reduction in the risk of death with Venetoclax and LDAC (OS=7.2 months vs 4.1 months with LDAC alone), but this difference was not statistically significant. Unplanned analysis with additional 6-month follow up showed a statistical difference in OS: 8.4 months for the Venetoclax combination arm vs 4.1 months for the LDAC monotherapy ($p = 0.04$). CR+CRi rate was 48% and 13% respectively. Most common grade 3 and higher adverse events were again hematologic: neutropenia (47% vs 16%), thrombocytopenia (45% vs 37%) and febrile neutropenia (32% vs 29%). Eight patients, all in the Venetoclax arm (6%), presented TLS (4 clinical and 4 laboratory).

The results of the phase III combination trials of Venetoclax led to the commercial authorization of the drug by EMA in April 2021 and full authorization by FDA in October 2020. In Europe, Venetoclax received approval in combination with HMAs as 1st line treatment of newly diagnosed AML patients not eligible for intensive chemotherapy.[45]

Management of toxicity during Venetoclax combinations treatment

Venetoclax is a CYP3A4 substrate; therefore dose modifications are needed when using other drugs metabolized by CYP3A4 such as azole antifungals. Based on pharmacokinetic studies, the dose of Venetoclax should be reduced by 50% for moderate inhibitors CYP3A4 (e.g. fluconazole, isavuconazole, ciprofloxacin, erythromycin, calcium-channel blockers) and by at least 75% for strong inhibitors (e.g. posaconazole, voriconazole, clarithromycin).[46,47]

Tumor lysis syndrome (TLS) is a significant risk associated with Venetoclax because of the effective induction of apoptosis by bcl2 inhibition. In contrast to CLL, the TLS incidence in AML trials was very reduced, either due to less tumor burden or to better TLS mitigating strategies that were used upfront in AML studies.[12-15] Factors associated with increased risk for TLS have been reported to be bulky disease (e.g. high bone marrow infiltration by blast cells), increased white blood cell count, high lactate dehydrogenase level, hyperuricemia, and underlying kidney disease. Given the higher sensitivity to Venetoclax, NPM1 and IDH1/2 mutations might also be additional risk factors for TLS.[48] For all AML patients that start treatment with Venetoclax combinations appropriate hydration and uric acid-lowering drugs (allopurinol and/or rasburicase) are indicated prior to treatment initiation. Cytoreduction with hydroxyurea to lower white blood cell count (WBC) to at least 25,000 or below should also be instituted. Venetoclax should be started at the lower dose of 100 mg and escalated in a daily ramp-up schedule according to tolerance and TLS labs. A 3–5- day ramp-up, depending on the final dose of Venetoclax, is appropriate in AML: if the patient is not on azole or other CYP3 active medications, then Venetoclax ramp up should be as follows: 100 mg on day 1, 200 mg on day 2, and 400 mg on day 3 and thereafter and if combined with LDAC, then up to 600 mg on day 4 and thereafter. TLS labs are recommended prior to, 6-8 hours after each new dose of Venetoclax, and 24 h after final dose.[45,48] With these TLS mitigation strategies and depending on the predefined risk of individual patients, it is not unreasonable to initiate Venetoclax-based therapy as outpatient, at least for lower risk patients. In an ongoing Phase 3b, single-arm, open-label study at 15 centers in the United States (NCT03941964), 59 newly diagnosed AML patients not eligible for intensive chemotherapy who were deemed by the investigators as low risk for TLS (mainly not TLS at baseline, WBC<25000/μL, clearance creatinine>30 ml/min) received Venetoclax with HMA (azacitidine and decitabine) with Venetoclax ramp-up in an out-patient setting. Only 2 patients (3%) presented laboratory TLS, which was subsequently successfully treated and the patients received the final dose of Venetoclax.[49]

Myelosuppression is very common either early or with prolonged use of Venetoclax-based combinations and nearly all patients will need dose or duration modification of venetoclax and/or HMA or LDAC therapy at some point of their treatment. For the decision of treatment modifications very important is the achievement of complete morphological remission (CR), which has to be checked somewhen between the 3rd and the 4th week of the 1st cycle.[48,50] In case of residual disease, no treatment modification should be instituted, and the patient should proceed with the next treatment cycle, maintaining the original combination doses and durations. If CR is achieved and in the incidence of grade 4 neutropenia/thrombocytopenia or febrile neutropenia, treatment has to be stopped and resumed upon grade 1 or complete resolution of the toxicity, initially at the same dose and duration of Venetoclax and in subsequent events at reduced duration; 21 or later 14 days-cycles. GCSF support can be instituted as clinically indicated in any time point for possible reduction of length of neutropenia.[48,50] The dose/duration of HMA can also be reduced according to the prescribing information of the drugs.[51,52] The minimum duration of Venetoclax should not be less than 7 days and the minimum dose of Azacitidine should not be less than 25 mg/m2 for 5 days, while for Decitabine not less than 10 mg/m2 for 3-4 days. Dose reductions of Venetoclax (e.g. to 300 or 200 mg) have not been tested.[48] After the

achievement of CR, bone marrow examination can be performed after 2 or 3 months and in every case that is clinically indicated, e.g. prolonged myelosuppression, sudden myelosuppression after an uncomplicated period etc.

Despite optimal dose modifications and treatment delays, the median duration of neutropenia with Venetoclax can range from 7 days to 25 days or even more[53] and this increases the possibility of an invasive fungal infection. The incidence of invasive fungal infections with Venetoclax-based therapies in prospective and retrospective studies using non-azole antifungal prophylaxis (e.g. echinocandin) or no prophylaxis has ranged between 8 and 24%.[12,53] Most cases occurred in patients who did not respond or in relapsed/refractory (r/r) patients.[53] For the European Society of Hematology in the previous Meeting in June 2021, antifungal prophylaxis is not recommended or moderately recommended in most settings of AML treatment with novel agents (including Venetoclax). It is strongly recommended if the novel AML agent is administered with intensive chemotherapy during induction treatment. Dose adaptations of some of the AML novel agents (including Venetoclax) are moderately recommended with limited evidence if antifungal prophylaxis is administered with a strong CYP3A4 inhibitor due to expected increased exposure.[55]

Clinical trials with other Venetoclax combinations

Combination of Venetoclax with intensive chemotherapy

Given the previous impressive results of Venetoclax in AML in the elderly populations and the non-overlapping toxicity with conventional chemotherapy, excluding myelosuppression, Venetoclax has been tested in combination with intensive salvage regimens in fit patients with AML. In an ongoing phase Ib/II study from MDACC (NCT03214562), Venetoclax in combination with fludarabine, high-dose cytarabine and idarubicin (FLAG-IDA) in 62 newly diagnosed and r/r AML leaded to the composite CR rate of 76 % with 89 % (24 out of 27) in untreated AML subgroup. For this trial venetoclax 400 mg on day 1-14 was considered safe for the phase II dose expansion cohort. The 1-year OS was 92% in newly diagnosed, and 52% in r/r AML patients in first salvage regimen. Fifty-two percent of patients (n=32) were successfully bridged to allogeneic SCT, including 5 patients receiving a second transplant. Thirty and 60-day mortality rates were 0 and 4.8%, respectively.[56]

In a phase Ib study (CAVEAT) that enrolled fit, older patients (median 73years) with newly diagnosed AML, 51 were treated with venetoclax in combination with a 2-day idarubicin and 5-day cytarabine (5+2) regimen. During induction, a 7-day ramp-up from 50 mg to 600 mg (days -6 to 0) was followed by an additional 7 days of venetoclax combined with cytarabine 100 mg/m2 on days 1-5 and idarubicin 12 mg/m2 intravenously on days 2-3. Consolidation (4 cycles) included 14 days of venetoclax (days -6 to 7) combined with cytarabine (days 1-2) and idarubicin (day 1). The CR/CRi rate was 72%: 97% and 43% in de novo and secondary AML patients, respectively. The median OS for the whole population was 11months, and early death occurred in four patients.[57]

Venetoclax has also been combined with the liposomal daunorubicin and cytarabine (CPX 351). In an ongoing phase II study with r/r and newly diagnosed AML patients, initial results from 18 patients showed that CPX-351 and 7-day Venetoclax was tolerable, with acceptable toxicities. The recommended phase II dose was venetoclax 300mg on day 2-8. There was encouraging activity in high-risk patients (9 patients with adverse cytogenetics responded), particularly in those with no prior Venetoclax exposure. Almost all responders were able to move on to allogeneic stem cell transplantation (SCT).[58]

Several studies of Venetoclax combinations with intensive chemotherapy (NCT03709758, NCT03586609) or phase II and III studies that compare Venetoclax+HMA with standard chemotherapy in young AML patients (NCT04801797, NCT05177731) are currently recruiting patients.

Combination of Venetoclax with novel targeted AML therapies

As recurrent driver mutations are common in AML, and recently approved targeted agents have shown promise in these subtypes of leukemia, Venetoclax is being actively investigated in combination with novel targeted agents in AML.

In a dose escalation and dose expansion cohort phase Ib study with r/r FLT3 mutated AML patients, Venetoclax has been studied in combination with the 2nd generation FLT3 inhibitor, Gilderitinib. Fourty-two from 55 patients (76.4%) achieved complete morphological response. The median OS was 10.5 (6.8, NE) months and not reached for those who proceeded to allogeneic SCT (14 patients).[59] Given these promising results several ongoing clinical trials with Venetoclax with or without HMA along with FLT3 inhibitors are ongoing (e.g. NCT03735875, NCT04140487, NCT05010122).

Venetoclax is currently tested in combination with the IDH1 inhibitor, Ivosidenib, in two doses, 400 mg/d and 800 mg/d, with or without Azacitidine in a phase Ib/II study for newly diagnosed and r/r AML patients.[60] Preliminary results from the first 25 patients have shown expected and tolerable safety profile, high CR and MRD rates with the doublet and the triplet, especially at higher doses of Venetoclax, and durable responses across the disease subgroups. The recruitment of this study remains open.

Other Active clinical trials with Venetoclax combinations

Venetoclax in AML is being currently tested in combination with anti-CD33 monoclonal antibodies, the antibody drug conjugate, Gemtuzumab Ozogamycin, and Lintuximab-Ac225 (NCT04070768, NCT03867682), with the oral formulation of Decitabine, ASTX727, (NCT04657081, NCT04817241), with the CDK inhibitors, Dinaciclib and Alvocidib (NCT03484520, NCT03441555), with the NEDD8 activating enzyme inhibitor, Pevonedistat, (NCT 041722844, NCT04266795), with the JAK1 and 2 inhibitor, Ruxolitinib, (NCT04278768), with the anti-CD123 antibody drug conjugate, IMNG632, (NCT04086264), with the IRAK4 kinase inhibitor, CA4948, (NCT04278768), with the TIM3 immune checkpoint inhibitor, MBG453, (NCT04150029), with the anti-sense oligonucleotide, BP1001, (NCT02781883), with the MCL1 inhibitor, S64315, (NCT03672695), with the potent and selective RARA agonist (in non APL AML patients), SY-1425, (NCT04905407), with Uproleselan, which is an E-Selectin antagonist (NCT04964505) and with several other novel therapies in phase I and II studies.

Furthermore, the combination of Venetoclax and Azacitidine, either parenteral or oral, is currently tested as maintenance therapy for AML patients, in CR1 after intensive chemotherapy, who are not eligible for SCT (VIALE-M, NCT04102020).

Especially for the AML patients with TP53 mutations, who consist an unmet medical need, because of disappointing survival rates even with approved Venetoclax combinations (OS 5.7 months with Venetoclax and Azacitidine versus 4.9 months with Azacitidine)[61] the current investigational landscape is very active. New agents that specifically target TP53 mutant cells like APR-246 (Eprenetapopt) or the CD47 epitope of leukemia cells, a "do not eat me" signal for macrophages, have shown activity in TP53 mutated AML patients. In a phase I/II trial (NCT04214860), interim results from 30 out of 51 TP53 mutant AML patients who were treated with the Eprenetapopt-Venetoclax-Azacitidine combination showed 53% CR+CRi.[62] The anti-CD47 monoclonal antibody, Magrolimab, is being tested with Venetoclax and Azacitidine in newly diagnosed and r/r AML patients in an ongoing phase I/II study (NCT04435691). Initial results from the first 25 patients were presented in the 2021 ASH Meeting.[63] In specific, among the 8 newly diagnosed patients with TP53 mutation, 7 were evaluable (1 still in cycle 1) with a CR/CRi in 100% (7/7), CR in 86% pts (6/7), MRD negativity by multicolor flow cytometry in 57% (4/7), and 6/7 remain in remission for a median follow up time of 3.4 months.[63] Other anti-CD47 monoclonal antibodies, like Evorpacept and Lemzoparlimab are currently being tested in combination with Venetoclax for AML patients (NCT04755244, NCT04912063) in various disease settings.

CONCLUSIONS

Inhibition of BCL2 is considered a very promising treatment option for elderly AML patients. Venetoclax, a novel BCL2 inhibitor, has proved efficacy as monotherapy, however the results are even more impressive with combinations either with hypomethylating agents or with LDAC. Rates of complete remission and overall survival are unprecedented in this patient population, who are considered ineligible for intensive chemotherapy. The recently published data from the confirmatory phase III randomized trials of Venetoclax combinations with Azacitidine and LDAC established the leading role of Venetoclax in the treatment of this group of AML patients. Other combinations with induction chemotherapy in younger and older AML patients or combinations with new targeted therapies are promising new dynamics of Venetoclax. The therapeutic landscape of AML is changing and Venetoclax will certainly play a key role in it.

Conflict of Interest: None.

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