A Phase I/II Study of Tosedostat with Cytarabine or Azacitidine in Older Patients with AML or High-Risk MDS

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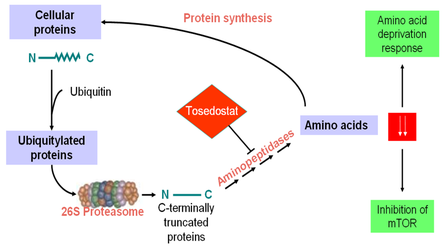
Abstract

BACKGROUND: The aminopeptidase inhibitor tosedostat is an orally bioavailable novel chemotherapeutic, functioning through enzymatic blockade of intracellular protein degradation and resynthesis. Encouraging results have been observed with tosedostat monotherapy in Phase I and II trials of relapsed and refractory elderly AML patients.
AIMS: This Phase I/II trial explores the safety, tolerability and activity of tosedostat in combination with cytarabine or azacitidine in older patients with AML or high-risk MDS.
METHODS: Eligibility includes age ≥ 60 years, with relapsed/refractory AML or high-risk MDS having failed prior HMA and/or lenalidomide therapy. All subjects received tosedostat 120mg orally once daily for 28 day cycles, with either subcutaneous (SQ) cytarabine at starting dose of 7.5mg BID for 10 days, or azacitidine (AZA) IV/SQ at starting dose of 50mg/m² daily for 7 days, per investigator's choice. A modified 3+3 design was used in the Phase I to identify the MTD independently for both arms. Escalation to the predefined target dose levels of 10mg SQ cytarabine BID for 10 days, or azacitidine 75 mg/m² IV/SQ daily for 7 days per 28 day cycle was achieved. Dose escalation to 180mg daily tosedostat was allowable for patients not achieving a CR after 4 weeks on therapy.
RESULTS: From November 2012 to April 2013, the Phase I portion completed enrollment with a total of 18 patients (10 AZA; 8 cytarabine). Six patients discontinued prior to completion of cycle 1 for reasons other than drug related toxicity or progressive disease and were replaced; they are considered as non-responders in the primary efficacy analysis. Median age was 73 (range 60-81), and 56% were male. 13 patients (72%) had t-AML, of which 11 (61%) had prior MDS. The median number of prior treatments was 2 (range 1-6) and 11 (61%) had received prior HMA therapy. Median WBC count was 5 x 10⁹/L (range 0.3-44.2), with median PB blasts of 27% (range 0-95%), and BM blasts 57% (range 6-90%). The majority (61%) of patients had complex cytogenetics or cytogenetics including chr 5 and/or 7; six patients (33%) had diploid cytogenetics. Median duration on study was 49 days (range 13-369), with median OS of 3.1 mo (range 0.4-12.2) and an overall response rate (ORR) of 33% (CR/CRp/MLFS 17%, PR 17%). ORR was 50% (CR/CRp/MLFS 25%, PR 25%) in fully evaluable patients remaining on study for > 28 days. Median OS for patients with CR/CRp/MLFS and PR was 7.3 and 3.5 months, respectively, while OS for unevaluable patients or those with progressive disease was 29 days. The presence of a diploid karyotype (p=0.001) or WBC count <4x10⁹/L (p=0.036) associated with an improved ORR.
The most common non-hematologic toxicities (%; grade ≥3) included pleural and pericardial effusions (72% ;0%), dyspnea (67%; 0%), peripheral edema (61%; 6%), pneumonia (56%; 50%) fatigue (50%; 0%), diarrhea (50%; 0%), and cough (39%; 0%). Additional cardiac toxicities included systolic dysfunction (17%; 6%), QTc prolongation (50%; 6%) and myocardial infarction (11%; 11%). One fatal acute coronary artery event on cycle 2, day 2 of tosedostat was considered probably related to study drug.
CONCLUSION: The combination of tosedostat with low-dose cytarabine or azacitidine appears effective in a population with an overall very poor prognosis. Additional safety and efficacy evaluations are ongoing.

Background

- Aminopeptidases catalyze the hydrolytic cleavage of amino acids from proteins or polypeptides at the NH2 terminal amino acid peptide bond, leading to protein degradation and the release of free AA's.
- Aminopeptidase inhibition disrupts normal protein turnover, resulting in decreased intracellular free amino acid content
- Tosedostat is an orally available aminopeptidase inhibitor with promising *in vitro* and early clinical trial AML activity
- Leads to upregulation of the amino acid deprivation response (AADR), a stress response including upregulation of amino acid transporters, activation of stress-related pathways (NFkB), pro-apoptotic regulators (NOXA) and mTOR inhibition via phosphorylation leading to decreased protein synthesis.[1]



Methods/Study Design

- Single Institution Phase I/II Study Design
- Tosedostat 120mg orally once daily for 28-day cycles WITH either:
  - A.) Cytarabine SQ twice daily days 1 to 10
    - Starting dose of 7.5mg
  - B.) Azacitidine IV/SQ once daily days 1 to 7
    - Starting dose of 50mg/m2
- Modified 3 + 3 dose escalation design to identify the maximum tolerated dose independently for both arms.
- Escalation to the pre-defined target dose levels of cytarabine 10mg SQ and azacitidine 75mg/m2 was achieved
- Dose escalation to 180mg tosedostat was allowable for patients not achieving a CR after 4 weeks on therapy
- Hydroxyurea allowable for the first 28 days on study

Eligibility

- Patients with relapsed/refractory AML or high-risk MDS having failed prior HMA and/or lenalidomide therapy
- Untreated patients not otherwise eligible for or refusing standard therapy also eligible for Phase I portion
- Age ≥ 60 years
- ECOG Performance Status 0-2
- Normal organ functions (creatinine ≤ 2.0, bilirubin ≤ 1.5x ULN, ALT/AST ≤ 3x ULN)
- Left ventricular ejection fraction ≥ 50% within 28 days start

Response Criteria

AML

- **Complete Remission (CR):**
  - ≤ 5% blasts in bone marrow aspirate
  - ANC ≥ 1000/mm³ and Platelet count ≥ 100,000/mm³
- **Complete Remission with Incomplete Platelet Recovery (CRp):**
  - ≤ 5% blasts in bone marrow aspirate
  - ANC ≥ 1000/mm³ and Platelet count < 100,000/mm³
- **Morphologic Leukemia Free State (MLFS):**
  - ≤ 5% blasts in bone marrow aspirate
- **Partial Remission (PR):**
  - 6 to 25% blasts in bone marrow aspirate, with at least 50% reduction from baseline

MDS

- Response by IWG criteria[2]

Overall Survival

- From start of treatment to last follow-up or death at any time; analysis performed using Kaplan-Meier method according to intention-to-treat principle

Table 1: Trial Design/Dosing Schema

Tosedostat 120mg oral once daily WITH:

Dose Level	Arm A: Cytarabine BID days 1 - 10	Arm B: Azacitidine Daily days 1 – 7
0	10mg	75mg/m²
-1	7.5mg	50mg/m²

Table 2: Patient Characteristics (n=18)

Characteristics	%, or Median [range]
Age	73 [60-81]
Male	56%
Therapy-related AML	72%
# Prior Therapies	2 [1-6]
WBC (x10⁹/L)	5 [0.3-44.2]
Peripheral Blasts	27% [0-95]
Bone Marrow Blasts	57% [6-90]
Cytogenetics	
Diploid	33%
-5/5q or -7/7q	55%
Complex	61%
Other	6%
Molecular Analysis	
DNMT3A	17%
JAK2-V617F	11%
NRAS	11%
KRAS	11%
FLT3-ITD	6%
IDH1	6%
Concomitant Hydoxyurea	39%
Schedule:	
Arm A (Cytarabine)	44%
Arm B (Azacitadine)	66%
180mg Tosedostat Escalation	22%

Table 4: Overall Responses

Response	No. (%)
Median Duration on Study	49 days (13-369)
CR/CRp	1 (6%)
MLFS	2 (11%)
PR	3 (17%)
Overall Response Rate***	6 (33%)
Median Overall Survival	3.1 mo (0.4-12.2)
Univariate Analysis	*P*-value
Diploid Karyotype	0.001
WBC < 4x10⁹/L	0.036

***** ORR was 50% (CR/CRp/MLFS 25%; PR 25%) in fully evaluable (n=12) patients remaining on study for > 28 days.**

Table 5: Toxicities (n=18)

Treatment Toxicities*	(all %; grade ≥3)
Dyspnea/Shortness of Breath	(67%; 17%)
Peripheral Edema	(67%; 6%)
Pleural/Pericardial Effusions	(33%; 0%)
Pneumonia	(56%; 50%)
Fatigue	(50%; 0%)
Diarrhea	(50%; 0%)
Cough	(39%; 0%)
QTc Prolongation	(72%; 0%)
Myocardial Infarction**	(11%; 11%)
Decreased Ejection Fraction	(28%; 28%)
Atrial Fibrillation/Flutter	(17%; 0%)
Hypertension	(22%; 11%)

***Toxicities regardless of attribution**

**** One fatal acute coronary event on cycle 2, day 2 (tosedostat 180mg daily and AZA 75mg/m² was considered probably related to study drug**

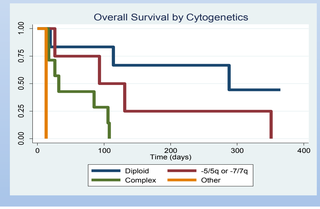
Safety

- In June 2013, the FDA placed a partial clinical hold on tosedostat due to a potential increased risk of cardiotoxicity
  - An independent expert panel of clinician researchers and cardiologists has been convened for comprehensive safety review
  - Results anticipated early 2014

Results

- Median duration on study was 49 days (range 13-369).
- 10 patients (56%) received >1 cycle of tosedostat, and one patient remains active on study in MRD negative CR, now Cycle 10 of tosedostat 120mg + cytarabine
- 4 patients (22%) were escalated to tosedostat 180mg oral once daily
- Median OS was 3.1 months (range 0.4-12.2).
- ORR of 33% (CR/CRp/MLFS 17%; PR 17%).
- ORR was 50% (CR/CRp/MLFS 25%; PR 25%) in fully evaluable patients (n=12) remaining on study for > 28 days.

Figure 1: Overall Survival



Conclusions

- Therapeutic options for relapsed/refractory AML are limited, and development of effective agents for this indication is an unmet clinical need.
- The completed Phase I portion identifies the combination of tosedostat and cytarabine or azacitidine to be effective in a population with an overall very poor prognosis.
- The presence of diploid karyotype and a WBC count < 4x10⁹/L predict for improved response on univariate analysis.
- The phase II expansion, including up to 30 patients per arm, will evaluate tosedostat 120mg orally daily in combination with cytarabine 10mg SQ BID days 1- 10, or azacitidine IV/SQ 75mg/m² days 1-7 per 28 day cycle

References

1. Van Herpen CM et al, Br J Cancer 2010;103:1362-8
2. Cheson BD et al, Blood 2006; 108: 419-425

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Disclosures

No disclosures