PB2011 CHIDAMIDE COMBINED WITH THALIDOMIDE, CYCLOPHOSPHAMIDE AND DEXAMETHASONE (TC2D) AS AN ORAL QUADRUPELT REGIMEN FOR RELAPSED/REFRACTORY MYELOMA PATIENTS: INITIAL RESULTS OF A PHASE IIa, MULTICENTER TRIAL

**Topic:** 14. Myeloma and other monoclonal gammopathies - Clinical

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**Background:** Research has showed histone deacetylase (HDAC) is overexpressed in plasma cells. Panobinostat was the first HDAC inhibitor (HDACi) approved by FDA for patients with relapse and refractory multiple myeloma (RRMM) in 2015. Chidamide is an oral subtype-selective HDACi, independently developed in China and approved for peripheral T-cell lymphoma. Preclinical findings have demonstrated the anti-myeloma activities of chidamide in vitro and in vivo.

**Aims:** Here we report the initial efficacy and safety of this prospective, phase IIa, multicenter clinical trial with the chidamide based oral quadruplet regimen in patients with RRMM (ChiCTR2000035100).

**Methods:** The TC2D regimen (thalidomide 100mg on days 1-28, chidamide 5mg on days 1-24, cyclophosphamide 50mg on days 1-24, dexamethasone 20mg on days 1,8,15,22) was administered to patients with RRMM of a 28-day cycle. Overall response rate (ORR) was based on patients whose response ≥MR and clinical beneficial rate (CBR) was calculated in patients completed at least 3 cycles and reached ≥SD.

**Results:** A total of 32 patients were enrolled as of June 30, 2021, with a median age of 63.5 years (range 49–74). 82% (19/23) of which had unfavorable cytogenetics (defined by the presence of del (17p) or p53 mutation, t (4:14), t (14:16), t (14:20), amp (1q)). 75% were double refractory to bortezomib and lenalidomide. 43% (14/32) were heavily pre-treated (>3 lines). 59% (19/32) of patients completed ≥ 3 cycles at the cut-off date (Table 1).

With the median follow-up of 6 months (range 0.7–19.5), the median progression free survival (PFS) was 3.3 months and the 6-mon PFS rate was 27.5% (Fig1a). Median overall survival (OS) has not reached yet, 6-mon survival rate was 82%, and the estimated 12-month survival rate was 65% (Fig 1b). Study end points were death (8 cases, 25%), and disease progression (24 cases, 75%). Patients who received ≥3 cycles of treatment had a superior median PFS (3.8 vs 1.4 months, P=0.01) than < 3 cycles. Of the 28 patients whose follow-up time more than 3 months, ORR was 25% and CBR was 46.4%, respectively. Better CBR (56.3% vs. 33.3%) and ORR (31.3% vs. 16.7%) were observed in patients received less than 3 prior lines, although with no significant statistical difference. Stratified analysis of PFS and OS showed no significant differences in sex, age, clinical classification, cytogenetic risk, prognosis score (DS and ISS staging system), and the status of ASCT.

Grade 3/4 adverse events were mainly hematological toxicity (neutropenia 28%, anemia 34%, thrombocytopenia 15.6%), which could be tolerated. Fatigue was reported in 68.8% (22/32) of the patients. The incidence of all-cause infection was 37.5% (12/32). There were no treatment related deaths observed.

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Summary/Conclusion: To our knowledge, this is the first report of chidamide-based oral quadruplet regimen for patients with RRMM. Preliminary results suggested efficacy and relatively high safety, and different groups of patients could benefit from this regimen. A longer treatment period may strengthen this effect. The most common adverse events were hematological toxicity which could be controlled. Choices of treatment are also influenced by physical and emotional impact of hospitalization or frequent hospital visits, which reflects the patient’s ability to continue their treatment and quality of life. Hospitalization and intravenous fluids are not involved in this regimen, which bring far more convenience and could be a cost-effective alternative for patients. Updated results will be presented at the following trial.

| Table 1: Baseline characteristics of patients (n=32) |
|-------------------------------------------------|
| **Characteristics** | **N=32** | **%** |
| Gender | Male | 14 | 43.8 |
| Median Age (range) | 63.5 (46,74) | |
| Stage | 15 | 46.9 |
| Subtypes Type-1 | 3/10 | 9.4/10.9 |
| Subtypes Type-2 | 17/15 | 53.1/46.9 |
| Cyto genetic risk | High-risk/non-high-risk/missing | 19/4/9 | 59.4/12.5/28.1 |
| Prognostic score | stage 2/ stage 3 | 4/7/1 | 12.5/34.4/3.1 |
| Prognostic score 195 | stage 1/ stage 2/ stage 3 | 7/17/1 | 21.9/21.9/12.5 |
| Previous treatment | 17/1 | 53.1/3.1 |
| Median Age | 3(1.8) | |
| Treated with 1 or 2 lines | 10 | 56.3 |
| Treated with 3 lines | 14 | 43.8 |
| Previous ASCI/ no ASCI/ missing | 4/5 | 12.5/71.9/15.6 |
| Drop resistance situation | 3 | 9 |
| Bortezomib resistance | 4 | 12.5 |
| Lenalidomide resistance | 24 | 75 |
| Double resistance | 24 | 75 |