Background: Inactivation of proteasome function allows for increased apoptosis and the potential for additive antitumor effects. Carfilzomib (C) has anti-tumor effects via inactivation of proteasome function and increased apoptosis in at least an additive fashion with other antitumor agents. The proteasome is a multicatalytic proteinase complex that degrades a wide variety of protein substrates through the action of threonine proteases. Carfilzomib (PX-171) is a tetrapeptide ketoepoxide-fenilbutanamido) pentanamida C39H55N5O7 that inhibits the 20S proteasome by various threonine protease activities. Carfilzomib plus Irinotecan is a well-tolerated combination with anti-tumor activity in heavily pretreated patients. NF-κB is a transcription factor that regulates gene expression and is known to play a role in inflammation and tumor progression. NF-κB regulates the transcription of genes that control cell survival, angiogenesis, and cell adhesion and it is known to be hyperactive in many tumors (3). NF-κB inhibits apoptosis by inhibiting the expression of genes such as Fas, Bak and Bax, which are important for cell death.

Materials & Methods:

Primary Objective:

To determine the MTD of 28-day cycle 1 of I (D1, 8, 15) and C (D1, 2, 8, 9, 15, 16) using a standard 3+3 Phase I design. Toxicity and response were evaluated using NCI CTCAE version 4.0.

Secondary Objectives:

- Response rate
- Tumoral proteasome expression in PBMC
- Tumor protocol expression in PBMC
- Pharmacokinetics

Combination C+I is a well-tolerated combination with anti-tumor activity in heavily pretreated patients. The primary Phase 1 dose of carfilzomib (280 mg/m2) is in combination with irinotecan 125 mg/m2. A Phase 2 study is ongoing through the Lung Cancer Research Team. This study was supported by grants from the University of Kentucky, Lexington, KY.

Results:

- Carfilzomib plus Irinotecan is a well-tolerated combination with minimal toxicity in heavily pretreated patients.
- No prior chemotherapy (within 14 days), surgery (within 28 days) or radiotherapy (within 28 days) of enrollment.

Response Assessment:

Complete Response (CR)/Partial Response (PR) calculated using the 2010 version of the RECIST guidelines.

Conclusions:

- Carfilzomib plus Irinotecan is a well-tolerated combination with minimal toxicity in heavily pretreated patients.
- No prior chemotherapy (within 14 days), surgery (within 28 days) or radiotherapy (within 28 days) of enrollment.

References:

1. Carfilzomib plus Irinotecan is a well-tolerated combination with minimal toxicity in heavily pretreated patients.
2. Dose level 2 (20/36 mg/m2) has met the criteria for the Phase II dose, with a total of 5 out of 6 patients experiencing Grade 3 hematoma and somnolence after a fall (unrelated).
3. The primary Phase 1 dose of carfilzomib (280 mg/m2) is in combination with irinotecan 125 mg/m2.
4. Carfilzomib 280 mg/m2 is administered weekly for 4 weeks and then twice a week for 2 weeks.
5. Carfilzomib is also included in the circulating and secreted cell-free plasma compartment.

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