A phase I / II trial of the HDAC inhibitor belinostat in combination with erlotinib in patients with non-small cell lung cancer

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Background

Belinostat (PXD101) is a histone deacetylase (HDAC) inhibitor. HDAC inhibitors, including belinostat, have shown marked in vitro and in vivo activity against a number of solid tumors and hematological cancers[1]. Belinostat is efficient as a single agent as well as in combination with other anticancer agents such as doxorubicin, paclitaxel, carboplatin, fluorouracil, bortezumib. Synergistic effect between HDAC inhibitors, incl. belinostat and EGFR inhibitors has been observed[2].
Belinostat has been well tolerated at doses up to 2000 mg daily in patients[3].
The main side effects are fatigue, nausea and vomiting.
The trial was designed as an open, non-randomized phase I / II trial to assess the efficacy and safety of belinostat in combination with erlotinib in patients with advanced non-small cell lung cancer, who were eligible for treatment with erlotinib.

Methods

The primary endpoint of the phase I part was to establish the maximum tolerated dose (MTD) and the dose limiting toxicity (DLT) of erlotinib (150mg/d) in combination with increasing doses of belinostat.
The study was designed as a 3+3 phase I trial.
All patients began with 4 weeks of erlotinib 150 mg/d. If this was tolerated, patients continued with the combination erlotinib and belinostat.
The belinostat dose steps were 500 mg, 1000 and 1500 mg, administered daily in 2 weeks on treatment, 1 week off treatment.
When one patient was enrolled at one dose level, there would be no further dose escalation for that individual patient. Three patients were planned at each dose level.
When the MTD was identified the trial was planned to expand to a phase II trial, and include 20 patients with non-small cell lung cancer.

Patient no 1	
Gender:	Female
Age:	61
Stage:	IV
Histology:	Adenocarcinoma
Performance status:	1
Prior lines of chemotherapy:	1
History of prior GI problems:	None

Patient no 2	
Gender:	Female
Age:	59
Stage:	IV
Histology:	Adenocarcinoma
Performance status:	1
Prior lines of chemotherapy:	2
History of prior GI problems:	None

Patient no 3	
Gender:	Female
Age:	58
Stage:	IV
Histology:	Adenocarcinoma
Performance status:	0
Prior lines of chemotherapy:	1
History of prior GI problems:	None

Patient no 4	
Gender:	Male
Age:	76
Stage:	IV
Histology:	Adenocarcinoma
Performance status:	1
Prior lines of chemotherapy:	1
History of prior GI problems:	None

Patient no 5	
Gender:	Male
Age:	70
Stage:	IV
Histology:	Adenocarcinoma
Performance status:	1
Prior lines of chemotherapy:	1
History of prior GI problems:	Minor problems

Results

From October 2010 until June 2011 five patients were enrolled in the phase I part of the trial.
Patient one and two started belinostat 500 mg after four weeks of erlotinib 150 mg/d.
Both patients experienced grade 3 diarrhea (NCI-CTCAE v4.0) and grade 2 nausea/vomiting in spite of supportive care with loperamid and antiemitics. Furthermore prolonged fatigue grade 3, anorexia and a decline in Performance Status (PS) from 1 to 2. The treatment was discontinued in both patients and the toxicity quickly resolved.
In accordance with the trial protocol, patient three was started on belinostat 250 mg.
Patient three experienced only grade 1 diarrhea and grade 1 nausea, but prolonged fatigue grade 3 and PS dropped from 0 to 1. The patient received 2 series of belinostat.
Patient four experienced grade 2 diarrhea, grade 2 rash and again grade 3 fatigue in the first series belinostat 250 mg.
Patient five experienced, in the first series of belinostat, grade 3 diarrhea and was hospitalized in PS 3 despite being treated with intensive supportive care prior to admission. All patients discontinued treatment and toxicity resolved.

Conclusion

The combination of the HDAC inhibitor belinostat and the EGFR inhibitor erlotinib resulted in severe and unacceptable toxicity. The trial has been closed.

References:

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