Clinical and Pharmacokinetic Phase I Study of BBR 3576 in Patients with Advanced Solid Tumors  - A Study of the Phase-I Study Group of CESAR-EWIV -

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Introduction

BBR 3576 is a derivative of Mitoxantrone and belongs to the anthracenedione-based anticancer agents. This derivative has shown in preclinical models an enhanced antitumor efficacy and a reduced cardiotoxicity. Because of its favourable preclinical profile this compound was introduced into a clinical development program, starting a phase-I study with a conventional intravenous administration mode (once every three weeks).

Demography

- Time of enrolment: May 2000 to March 2001
- Total no. of patients enrolled: 27
- No of patients evaluable for plasma pharmacokinetics: 26
- Dose Levels: 64, 90 and 150 mg/m²
- Mean age (SD): 59 (10)
- Male/female: 15/12
- Performance status: 0-1
- No. of prior chemotherapy regimens: 2-3
- No. with prior radiation therapy: 10
- Primary site of cancer: Ovar 3, Lung 3, Other 10
- No of patients with evaluable toxicity: 27
- No of patients evaluable for plasma pharmacokinetics: 26

Objective

- Determine the optimum dose of BBR 3576 administered as 1-hour infusion every three weeks in patients with advanced cancer
- Characterize the acute and chronic toxicities as well as the dose limiting toxicity (DLT)
- Characterize the pharmacokinetic and pharmacodynamic (PK & PD) profile
- Assess antitumor efficacy

Pharmacokinetics and Pharmacodynamics

- BBR 3576 has a slow distribution phase, followed by a prolonged elimination phase, a very large volume of distribution, a high systemic clearance and a long elimination half-life. The drug features a linear pharmacokinetics. The urinary excretion is less than 5%.
- Dose reductions should be considered in those patients with a combination of neutropenia and stomatitis
- Dose limiting toxicity (DLT) was observed at 125 mg/m²
- THERE WAS NO DLED AT 150 mg/m²

Safety

- No dose limiting toxicity up to 125 mg/m²
- 3 out of 6 patients treated at 150 mg/m² showed DLT: 1x Granulocytopenia (CTC grade IV) = DLT

Pharmacokinetics (PK) at 64, 90 and 150 mg/m² Dose Levels

- Cmax: 1298 (685), 1407 (677), 1879 (544)
- AUC x h: 2615 (1066), 3832 (1559), 4933 (1972)

PD, response, conclusion

Discussion

The phase I study was running very fast due to the accelerated escalation procedure which allowed dose doublings up to the first observed toxicity. The study was finished within 9 months despite the multicenter study design (3 centers). The drug was well tolerated and the MTD was 150 mg/m² with dose limiting hematological toxicity. The recommended dose (RD) for phase II studies is 150 mg/m² due to this toxicity profile.

Conclusions

- BBR 3576 is well tolerated as 1-hour infusion
- DLT was observed at 150 mg/m² (granulocytopenia)
- BBR 3576 has a slow distribution phase, followed by a prolonged elimination phase, a very large volume of distribution, a high systemic clearance and a long elimination half-life. The drug features a linear pharmacokinetics. The urinary excretion is less than 5%.
- The recommended dose (RD) for phase II studies is 150 mg/m²
- Dose reductions should be considered in those patients with a combination of neutropenia and stomatitis

Antitumor efficacy

The evaluation of the antitumor efficacy was not a primary endpoint of this phase I study.

Most of the patients have not received two or more treatment cycles necessary for the evaluation of antitumor efficacy.

No objective tumor response was observed

Literature

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