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PHASE II STUDIES

The fate of camptothecin glycoconjugate: report of a clinical hold during a phase II study of BAY 56-3722 (formerly BAY 38-3441), in patients with recurrent or metastatic colorectal cancer resistant/refractory to irinotecan

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Summary *Introduction* BAY 56-3722 (formerly BAY 38-3441) is a glycoconjugated campthotecin, which was considered an attractive drug to assess in colorectal cancer (CRC). *Patient and methods* Phase II study design evaluating the antitumor activity of BAY 56-3722 IV 320 mg/m^2 daily for 3 days every 3 weeks in patients with recurrent or metastatic inoperable CRC resistant to irinotecan. *Results* Twenty-four patients received the study treatment. Triggered by adverse events in two other studies with this compound the study was put on a clinical hold while the safety data were reviewed for the entire program. After the review Bayer decided to withdraw BAY 56-3722 from all clinical investigations. *Discussion* We felt it was our obligation to share this interrupted phase II study for two reasons: to report the fate of camptothecin glycoconjugate and to report the unique situation of a clinical hold during a phase II study.

Keywords Campthotecin · Colorectal cancer · Phase II · BAY 56-3722

Introduction

Since more than a decade the topoisomerase I inhibitor irinotecan has been one of the most important drugs in the treatment of metastatic CRC although its single agent activity in second line is only 20% and its toxicity is considerable [1]. Especially in the pre-cetuximab/panitumab and bevacizumab era new camptotecin analogues with improved activity and less toxicity were therefore warranted. BAY 56-3722 (formerly BAY 38-3441) is a camptothecin glycoconjugate that generates camptothecin upon cleavage. BAY 56-3722 consists of a carbohydrate (fucose) moiety attached to the camptothecin toxophore by a peptide spacer. The camptothecin delivered from BAY 56-3722 acts by binding to and stabilizing the topoisomerase-I-DNA complex, leading to an accumulation of double-stranded DNA breaks upon replication, ultimately causing cell death. The lactone form is associated with its antitumor activity, whereas the carboxylate form is inactive [2, 3].

BAY 56-3722 was considered an attractive drug to assess in CRC. First, there were in vitro data suggesting the utility of BAY 56-3722 in a variety of CRC lines. Secondly, the two main body tissues with highest levels of radioactivity after administration of BAY 56-3722 were liver (3.0%) and the large intestine (3.6%). This could provide a potential advantage for BAY 56-3722 over other chemotherapy agents in patients with metastatic tumors in the liver. BAY 56-3722 was evaluated in vivo in a panel of human tumor xenografts in nude mice [4]. In most of these experiments, BAY 56-3722 was tested in comparison with doses of topotecan and not with irinotecan, which would have been more appropriate. BAY 56-3722 was more efficacious at maximum tolerated dose than topotecan and exhibited less gastrointestinal toxicity and myelosuppression. In patients BAY 56-3722 has been studied on three schedules, once every 21 days, daily for 3 days every 21 days and daily for 5 days every 21 days [3, 5, 6]. In the phase I study where a daily ×5 schedule is explored, there appears to be a 4-fold increase in the camptothecin AUC comparing day 1 to day 5 suggesting that this schedule might be the most likely schedule to have antitumor activity [5].

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The present phase II study was designed in the beginning of this century to study the antitumor activity, safety and tolerability of BAY 56-3722 using a daily schedule for 3 days every 3 weeks.

Patients and methods

The study was conducted at 13 centers in Canada, the USA and the Netherlands. Patients received BAY 56-3722 IV over 30 min daily for 3 days every 3 weeks until objective evidence of tumor progression, unacceptable toxicity, consent withdrawn or until the investigator deemed that continuation of treatment adds no more benefit for the patient.

Tumor response measurements were made according to WHO criteria at baseline and every 6 weeks for the entire duration of treatment [7].

The study was planned to enroll a maximum of 140 evaluable patients. A three stage enrolment procedure would be used (null hypothesis: underlying response rate is less than or equal to 10%; alternative hypothesis: true response rate is more than or equal to 20%; one-sided alpha of 0.025; power of 90%). A futility analysis was planned when 20 evaluable patients were treated and followed for tumor response for a maximum of six cycles. If none of these patients responded (no PR or CR) to therapy termination of the study was warranted. If at least one patient responded (5%), an additional 60 patients were planned to be enrolled. The second futility analysis would count the number of responders out of the 80 patients at the end of maximum six cycles: if the number of responders would be less than 10% the likelihood of success would be sufficiently low to warrant discontinuation of the study. If the number of responders would be more than 20% the regimen would be considered active and the study might be closed in preparation for Phase III. Nevertheless, if 9–15 responders were obtained, additional 60 patients would be enrolled and response rate would be evaluated at the end of cycle 6 to determine if the drug was active enough to start Phase III.

Adverse events were graded by the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0 [8].

Informed consent and protocol were reviewed and approved by the appropriate local ethics or review boards before study initiation.

Patients were considered eligible if they had histologically confirmed recurrent or metastatic colorectal cancer with documented progression during or within 6 months after treatment with irinotecan. Required were adequate bone marrow, renal and liver functions and signed informed consent.

Results

Twenty-five patients were enrolled in this study. Twenty-four patients received at least one dose of study treatment and were therefore included in the safety evaluation. One patient did not qualify to receive study medication due to a protocol inclusion criteria violation.

Of the 24 patients in the safety population, 18 (75%) discontinued study treatment because of disease progression, 4 (17%) because of consent withdrawn, and 2 (8%) because of study termination by the sponsor. Of the four patients that withdrew consent, one withdrew it after only one dose of study drug, another one after cycle 1, a third patient due to opting for treatment with capecitabine, and the last patient due to clinical deterioration.

The futility analysis that was planned for this study after the first 20 eligible patients were enrolled could not be completed due to an initial clinical hold as well as later discontinuation of the BAY 56-3722 development program.

This study was put on a clinical hold while the safety data were reviewed for the entire BAY 56-3722 development program. This review was triggered by events in two other studies in the program. Once this review was completed, the clinical hold was removed (after 5 weeks). At the time of the clinical hold, only two patients were taken off study because of lack of the essential IRB approval to go through. At the time when the clinical hold was removed, patients had to undergo a new tumor assessment and show no disease progression in order to continue study drug treatment. Only one patient qualified; that patient received two additional cycles of treatment.

At least one treatment-emergent event was reported by 23 of the 24 patients (96%). One patient with non-insulin dependent diabetes and coagulant use experienced one episode each of grade 4 rectal bleeding and hypoglycemia. Grade 3 non-hematological adverse events were experienced by eight patients. Three patients experienced a total of four adverse events that were considered serious. Two of these events, grade 2 creatinine elevation and grade 3 renal/genitourinary-other (bilateral hydronephrosis), were considered possibly drug related. All four serious adverse events resolved. No patients developed grade 4 hematological or biochemical toxicities. Three patients had grade 3 toxicities.

Discussion

Development in systemic therapy options for CRC is moving fast. This study was conducted in the pre-cetuximab/panitumab and bevacizumab era. BAY 56-3722, selected for this phase II study, was a promising drug in diseases that were resistant to other topisomerase I

inhibitors because of the enhanced stability of the active lactone moiety of the drug with enhanced pre-clinical antitumor activity and a favorable toxicity profile. Based on three phase I studies further phase II studies in several tumor types were undertaken with the preferred BAY-56-3722 regimen. None of these studies have been published and we felt that this was an omission. Therefore we decided to share our results and the fate of this drug in the current publication. This study was put on a clinical hold while the safety data were reviewed for the entire program, because of excessive toxicity in three patients with hepatocellular carcinoma in two studies in the program, this study not being one of them. Since, after review, this toxicity appeared to be disease related, patients were allowed to continue treatment after 4 weeks provided that there was no disease progression in our study. During the clinical hold for toxicity reasons Bayer undertook a voluntary action to withdraw camptothecin glycoconjugate (BAY 56-3722, formerly BAY 38-3441) from further clinical development due to observed safety issues, lack of therapeutic benefit, and poor enrolment in other studies. Due to this decision we were not able to draw conclusions whether this drug is active or not in colorectal cancer. Prematurely stopped studies as a result of a decision of the sponsor not to further develop a study drug (based on results in other studies) are extremely rare and the (temporary) withdrawal of the drug during the study puts the patient and the treating physician/local study team in a difficult position. The clinical hold was undertaken for safety reasons in the first place which is easier to accept than for economic reasons. We felt it was our obligation to share this interrupted phase II study for two reasons: to report the fate of camptothecin glycoconjugate and to report the unique situation of a clinical hold during a phase II study.

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