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Phase I – II study to assess the feasibility and activity of the triple combination of 5-fluorouracil/folinic acid, carboplatin and irinotecan (CPT-11) administered by chronomodulated infusion for the treatment of advanced colorectal cancer. Final report of the BE-1603 study☆

Étude de phase I-II évaluant la faisabilité et l'activité d'une chronothérapie combinant l'administration de 5-fluorouracil/acide folinique, carboplatine et irinotecan (CPT11) pour le traitement du cancer colorectal avancé. Rapport final de l'étude BE-1603

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ABSTRACT

Thirty-six metastatic colorectal cancer patients received every 2 weeks, as first- (17) or second-line (19) treatment a combined chronotherapy with CPT-11 (infused at day 1 from 2 to 8 a.m.; peak at 5 a.m.), given with 5FU (700 mg/m^2 per day; days 2–5) and folinic acid (300 mg/m^2 per day; days 2–5) both infused from 10 p.m. to 10 a.m. with a peak at 4 a.m., and carboplatin (40 mg/m^2 per day; days 2–5; infused from 10 a.m. to 10 p.m.; peak at 4 p.m.). The doses of CPT11 could be easily pushed from 120 to 180 mg/m^2 in successive cohorts in the phase I part of the study (11 cases). Twenty-five patients were then treated in the phase II of the trial. The overall toxicity was mild leading to dose-reductions in only 11–13% courses. The tumoral activity was interesting with 81% responses and 94% tumour control. Also prolonged survivals were recorded with 8.8 months of progression free and 15.6 months overall survivals. More prolonged survivals were observed in chemotherapy naive patients. Seven patients (19%) could be reoperated from their residual disease.

Mots clés:
Cancer colorectal
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Polychimiothérapie

RÉSUMÉ

Trente-six patients porteurs d'un cancer colorectal métastatique ont reçu en première (17) ou seconde ligne (19) thérapeutique une chronothérapie associant l'irinotecan (CPT11) (au j1 perfusé de 2 à 8 heures avec un pic à 5 heures) à du 5FU et de l'acide folinique (respectivement 700 et 300 mg/m^2 par jour – j2 à j5 ; infusion de 22 heures à 10 heures avec pic à 4 heures) et du carboplatine (40 mg/m^2 par jour – j2-j5 ; infusion de 10 heures à 22 heures avec pic à 16 heures). Les cures étaient répétées toutes les deux semaines. Le CPT11 a pu être monté de 120 à 180 mg/m^2 (troisième cohorte) dans la phase I de l'étude qui a comporté 11 patients, les toxicités clinique et biologique n'étant pas limitantes. Vingt-cinq patients ont ensuite été traités dans la phase II. La toxicité fut globalement faible amenant seulement une réduction de dose dans 11–13 % des cures. L'efficacité clinique s'est avérée intéressante avec 81 % de taux de réponses et 94 % de contrôle tumoral et des survies sans progression et globale prolongées (respectivement 8,8 et 15,6 mois). Les survies furent plus longues chez les sujets recevant le traitement en première ligne. Dix-neuf pour cent des patients ont pu être réopérés de leur maladie résiduelle.

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1. Introduction

The golden standard for chemotherapy of advanced colorectal cancer implies to combine to a 5-fluorouracil (5FU) – folinic acid (FOL) base, a platinum derivative (LOHP-oxaliplatin) or irinotecan (CPT11). The addition of either drug has been proved active in terms of response rate or survivals both as first- or second-line treatments [1–7].

The chronobiological-based administration [8–10] of 5FU–FOL and LOHP (FOLFOX) has been able not only to significantly reduce prominent toxicities (i.e., mucitis, diarrhoea, neurological) of the combination, but also to improve tumoral outcome, at least when the same chemotherapy program in terms of duration was applied [10–14].

Recently we have reported an interesting therapeutic index for a chronotherapy association including 5FU, FOL and carboplatin (carbo) [8,15–17]. This chronotherapy schedule delivered 4 days every 2 weeks (FFC4-10) initially tested in a phase II with half of the patients previously treated [15], was further assessed in a large phase II as first-line treatment [16]. The exceptional tolerance of the protocol, as well as its clear tumoral activity (60% response rate; median time to progression, 11 months and median survival, 27 months with 55% still alive at 2 years) was evidenced [16].

Thus, due to this good tolerance, it was expected to still improve overall results by the addition of CPT 11 to this FFC4-10 association. In fact, Italian phase II trials has suggested that a quadrichemotherapy (FOLFOXIRI) could improve the tumour outcome of patients suffering from metastatic colorectal cancer [18,19]; however further randomized comparison between FOLFOXIRI and FOLFIRI failed to confirm the initial phase II results [20].

In animal studies, CPT11 has shown a reproducible chronotolerance but also a chronoefficacy in monotherapy or in association with, precisely, oxaliplatin [21].

In human, a randomized evaluation comparing standard CPT11 delivery to a 6 hours chronomodulated administration with an early morning peak (5 a.m.) has suggested a better toxicity profile for the chronoschedule with less asthenia, diarrhoea and anorexia [22]. We report here the final results of a phase I-II study assessing the feasibility of an association of FFC 4-10 (with carboplatin) chronotherapy with CPT11 of first- or second-line therapy of metastatic colorectal cancer. A preliminary report on 17 cases has already been published [23]. The hours of CPT11 infusion has been derived from animal and preliminary human data [21,22]. The trial was conducted in accordance to Good Clinical Practice (IHC) recommendations and to the most recent version (2001) of Helsinki declaration on human rights; it has received approval of the Ethics committee of CHC, Liège, Belgium (October 2001).

2. Material and methods

Patients aged over 18 years suffering from an histologically confirmed colorectal adenocarcinoma, metastatic or in locoregional relapse, were eligible for the study under the following conditions: at least one measurable lesion (RECIST criteria); a performance status less than 2; a life expectancy of at least 12 weeks; sufficient haematological, hepatic or renal functions; also possibility of an easy follow-up.

This was a first- or second-line treatment for advanced disease; patients having finished their adjuvant treatment less than 6 months ago could also be eligible. On the contrary, no previous CPT 11 administration was accepted.

After having given their informed consent, patients received every 2 weeks the following treatment (Fig. 1).

- at day 1: CPT 11 in chronomodulated infusion from 2 to 8 a.m. (peak at 5 a.m.);
- at days 2–5: an associative infusional chronotherapy with 5FU (700 mg/m^2 per day) and FOL (300 mg/m^2 per day – racemic form or 150 mg/m^2 per day – l-form) infused from 10 p.m. to 10 a.m. (peak at 4 a.m.) and carboplatin (40 mg/m^2 per day) infused from 10 a.m. to 10 p.m. (peak at 4 p.m..

In the phase I part of the study, three cohorts of patients, based on CPT11 doses, were foreseen (cohort 1: 120 mg/m^2; cohort 2: 160 mg/m^2 and cohort 3: 180 mg/m^2). According to recommendations for phase I studies, a minimum of three to four cases per cohort was required. In case of absence of significant dose limiting toxicity (DLT) event (grade 4 haematological or any grade ¾ non haematological toxicity) during the first two courses, next patients could be treated at the superior level. If the third level could be obtained with significant tumoral activity ($\geq$ 50% response rate), then the study could be pursued as a phase II trial up to 25 evaluable cases.

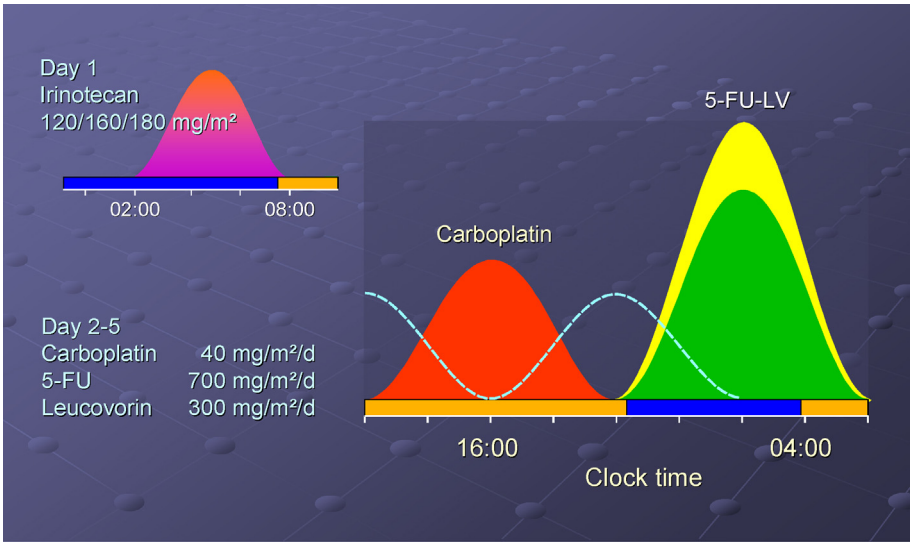

Fig. 1. Schedule of chronomodulated intravenous infusion of 5 FU, folinic acid, carboplatin and irinotecan. The local time in hours is plotted against the relative drug delivery rate. The chronopump automatically delivers drug according to schedule (day 1: CPT11; days 2-5: 5 FU, FOL and Carboplatin).