Oral fluoropyrimidines in colorectal cancer : A door open to the future ?

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Abstract

Since its first use 40 years ago, 5-fluorouracil (5-FU) has become an unquestionable component of colorectal cancer treatment. It is also now well established that infusional 5-FU administration, in combination with leucovorin, is associated with better tolerance and at least equal efficacy than bolus administration. However, requiring catheter and infusion pumps, infusional 5-FU administration is costly, rather inconvenient for patients and potentially associated with morbidity, initiating subsequent oral chemotherapy development. To address intravenous 5-FU related issues, oral fluoropyrimidines have been developed such as capecitabine, preferentially converted to 5-FU into tumour cells, and UFT, able of bypassing intestinal dihydropyrimidine deshydrogenase. We discuss in this article current oral fluoropyrimidines achievements in colorectal cancer management. (Acta gastroenterol. belg., **2004**, 67, **331-333**).

Key words : colorectal neoplasms, treatment, fluorouracil, oral administration.

Since its introduction, more than 40 years ago, 5-fluorouracil (5-FU) has become an important component of standard therapies of a wide variety of tumours, among which colorectal cancer (1). As a monotherapy, 5-FU achieved response rate of approximately 10% and a median survival time of 10 to 14 months in colorectal cancer (CRC) (2,3). Strategies developed to improve efficacy and convenience include : biochemical modulation, prolonged infusion of the drug, and oral administration.

Although higher response rates were observed with biomodulation, (23% vs. 11% for 5-FU with leucovorin) and prolonged infusion time (22% vs. 14%), median survivals were not improved and did not exceed 12 months (2, 4-6).

The development of oral chemotherapies has been driven with the hope of making chemotherapy more comfortable and better tolerated by avoiding the need for IV injection and unnecessary hospitalisation. Toxicity of 5-FU is mainly due to the lack of selectivity of the drug for tumour cells and also to its phosphorylation in the intestine. Absorption of an oral formulation of 5-FU is unpredictable and oral 5-FU pro-drugs have been developed to address that problem. Several drugs have been studied among which capecitabine and UFT, an oral combination of tegafur and uracil, a dihydropyrimidine deshydrogenase (DPD) inhibitor.

Capecitabine is characterized by a high, predictable oral bioavailability, and by a preferential conversion to 5-FU in neoplastic tissues due to the high activity of the enzyme thymidine phosphorylase (TP) in tumour cells compared to normal tissue (4). Based on phase I trials, the standard administration schedule for capecitabine, when used as a single agent, is 2,500 mg/m^2 given as a divided dose twice a day for 14 days, followed by a one week rest period (5). Capecitabine has shown manifest activity in a variety of tumours, including colorectal cancer (6-9). However, in metastatic colorectal cancer, grade 3 hand-foot syndrome occurred in 15% of the patients, and grade 3/4 diarrhoea in up to 9% of them (10). Three prospective randomised phase III trials have since then also demonstrated that capecitabine has a significantly superior tumour response rate (24.8% versus 15.5%), an equivalent time to disease progression (5.2 versus 4.7 months) and a similar overall survival (13.2 versus 12.1 months) compared to bolus 5-FU/LV. The majority of adverse events associated with capecitabine were considered as mild to moderate in severity, with a medium-low incidence of alopecia, stomatitis, diarrhoea, nausea and myelosuppression. However, severe hand-foot syndrome (HFS) occurred more frequently with capecitabine than with 5-FU/LV (16.2% versus 0.3%) (11-13).

As for UFT, uracil competitively blocks the actions of DPD, allowing tegafur absorption and therefore, increasing its bioavailibility. UFT metabolism however involves P450 enzymes interfering therefore potentially with other medications. It also requires leucovorin administration. Two prospective randomised studies, comparing UFT (300mg/m^2/day) plus LV with IV bolus 5-FU/LV, demonstrated similar results in both groups in terms of objective response and median time to progression (9.5%, 3.4 months) (14,15). UFT was also associated with no significant HFS, less myelosuppression and less stomatitis/mucositis than parenteral 5-FU. Altogether, these five prospective randomised studies comparing oral versus parenteral fluoropyrimidines led to the same conclusions : efficacy at least equal, with potential better toxicity profile for oral drugs compared to IV bolus 5-FU. Nevertheless, that conclusion applies only to bolus IV 5-FU, and not to infusional IV 5-FU schedules, which might be less toxic.

Treatment is now increasingly governed not only by concern for efficacy, but also by patient quality of life. Intravenous infusion requires hospital or clinic attendance, which is not without psychological impact on the

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patient. It also implies a non-negligible risk of complications from catheterisation. On the other hand, oral therapies offer a home-based treatment, more convenient and comfortable, allowing patients to continue daily activities and avoiding frequent hospital visits, IV lines or pumps problems (16,17). A study investigated the patient preference for oral UFT/LV versus IV 5-FU/LV chemotherapy in metastatic colorectal cancer. The authors established that most patients (84%) were in favour of oral UFT, since they experienced less stomatitis and diarrhoea, could take their medication home, and preferred pill to injection (18). However, patients do not wish to give up efficacy for the comfort of oral therapy (16).

Another aspect to consider is economic. Cost of chemotherapy depends upon a variety of factors, including clinical visits, laboratory tests and drug itself. If oral fluoropyrimidines are more expensive than IV 5-FU, their use implies less side-expenses. This advantage might be maintained even when oral pro-drugs are combined with IV administered drugs. Pharmaco-economic comparisons between capecitabine and bolus 5-FU/LV, as well as between XELOX (capecitabine plus oxaliplatin) and FOLFOX (infusional 5-FU/LV plus oxaliplatin) showed medical cost savings in groups using capecitabine. Chu and colleagues demonstrated that the main cutback was not due to chemotherapy acquisition and administration but adverse events management (six times greater for FOLFOX group) (19). These results indirectly confirm capecitabine safer toxicity profile. Wiklund *et al.* (20) even specified that capecitabine regimen could also cutback twice on time costs (waiting for the treatment, receiving the treatment and travelling), compared to bolus 5-FU/LV. Inconvenience can however be encountered with oral drugs, including toxicity (HFS, diarrhoea), drug interactions (role of intestinal cytochrome P 3A4 and P-glycoprotein), erratic intestinal absorption, responsible for the inter- and intra-patient variability in bio-availability of the drugs (21-23), and patient compliance with a treatment associated with potential toxic effects.

Bi-therapies are currently considered as the best option in advanced colorectal cancer (24-27). Several trials testing combination therapies between oral agents and new IV drugs such as oxaliplatin or irinotecan are currently ongoing. Preliminary data, showed promising results, with response rates varying between 40 and 50% and manageable toxicities (28-32).

The role of oral treatments goes far beyond the 5-FU approach. Many targeted therapies are given orally (33,34). Preliminary data suggested they could have a major impact on patient survival (35,36). The exact place of these agents remains to be settled, combined with standard IV therapies (37), alone (36) or combined together (38) to improve the response rate as well as the quality and duration of responses. It may be expected that demonstration of a significant activity of oral targeted therapies will also boost up the development of oral traditional cytotoxic drugs. Although much work remains to be done, we can already anticipate that the oral route will be extensively investigated in the upcoming years and that it will represent a significant step forward in the treatment of cancer in terms of activity and/or patient convenience and thus, quality of life.

Bibliography

1. HEIDELBERGER C.N., DANNENBERG P.B. Fluorinated pyrimidines, a new class of tumor-inhibitory compounds. *Nature*, 1957, **179** : 663-666.
2. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer : evidence in terms of response rate. Advanced Colorectal Cancer Meta-Analysis Project. *J. Clin. Oncol.*, 1992, **10** : 896-903.
3. KOHNE CH., SCHOFFSKI P., WILKE H., KAUFER C., ANDREESEN R., OHL U., KLAASEN U., WESTERHAUSEN M, HIDDEMANN W., SCHOTT G., HARSTICK A., BADE J., HORSTER A., SCHUBERT U., HECKER H., DORKEN B., SCHMOLL H.J. Effective biomodulation by leucovorin of high-dose infusion fluorouracil given as a weekly 24-hour infusion : results of a randomized trial in patients with advanced colorectal cancer. *J. Clin. Oncol.*, 1998, **16** : 418-426.
4. MIWA M., URA M., NISHIDA M., SAWADA N., ISHIKAWA T., MORI K., SHIMMA N., UMEDA I., ISHITSUKA H. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur. J. Cancer*, 1998, **34** : 1274-1281.
5. MACKEAN M., PLANTING A., TWELVES C., SCHELLENS J., ALLMAN D., OSTERWALDER B., REIGNER B., GRIFFIN T., KAYE S., VERWEIJ J. Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. *J. Clin. Oncol.*, 1998, **16** : 2977-2985.
6. O'REILLY S.M., MOISEYENKO V., TALBOT D.C., GORDON R.J., GRIFFIN T., OSTERWALDER B. A randomized phase II study of Xeloda (capecitabine) vs paclitaxel in breast cancer patients failing previous anthracycline therapy. *Proc. Am. Soc. Clin. Oncol.*, 1998, **17** : 627a.
7. BLUM J.L., JONES S.E., BUZDAR A.U., LORUSSO P.M., KUTER I., VOGEL C., OSTERWALDER B., BURGER H.U., BROWN C.S., GRIFFIN T. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J. Clin. Oncol.*, 1999, **17** : 485-493.
8. LOZANO R., PATT Y., HASSAN M., FROME A., VAUTHEY J., ELLIS L., SCHNIRER I., BROWN T., ABBRUZZESE J., WOLFF R., CHARNSANGAVEJ C. Oral capecitabine (Xeloda) for the treatment of hepatobiliary cancers (hepatocellular carcinoma, cholangiocarcinoma and gallbladder cancer). *Proc. Am. Soc. Clin. Oncol.*, 2000, **19** : 1025a.
9. KOIZUMI W. TT : A phase II study of capecitabine (Xeloda™) in patients with advanced/metastatic gastric carcinoma. *Proc. Am. Soc. Clin. Oncol.*, 2001, **20** : 2320a.
10. VAN CUTSEM E., FINDLAY M., OSTERWALDER B., KOCHA W., DALLEY D., PAZDUR R., CASSIDY J., DIRIX L., TWELVES C., ALLMAN D., SEITZ J.F., SCHOLMERICH J., BURGER H.U., VERWEIJ J. Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer : results of a randomized phase II study. *J. Clin. Oncol.*, 2000, **18** : 1337-1345.
11. TWELVES C., BOYER M., FINDLAY M., CASSIDY J., WEITZEL C., BARKER C., OSTERWALDER B., JAMIESON C., HIEKE K. Capecitabine (Xeloda) improves medical resource use compared with 5-fluorouracil plus leucovorin in a phase III trial conducted in patients with advanced colorectal carcinoma. *Eur. J. Cancer*, 2001, **37** : 597-604.
12. VAN CUTSEM E., TWELVES C., CASSIDY J., ALLMAN D., BAJETTA E., BOYER M., BUGAT R., FINDLAY M., FRINGS S., JAHN M., MCKENDRICK J., OSTERWALDER B., PEREZ-MANGA G., ROSSO R., ROUGIER P., SCHMIEGEL W.H., SEITZ J.F., THOMPSON P., VIEITEZ J.M., WEITZEL C., HARPER P. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer : results of a large phase III study. *J. Clin. Oncol.*, 2001, **19** : 4097-4106.
13. HOFF P.M., ANSARI R., BATIST G., COX J., KOCHA W., KUPERMINC M., MAROUN J., WALDE D., WEAVER C., HARRISON E., BURGER H.U., OSTERWALDER B., WONG A.O., WONG R. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer : results of a randomized phase III study. *J. Clin. Oncol.*, 2001, **19** : 2282-2292.

14. PAZDUR R., DOUILLARD J.Y., SKILLINGS J.R., EISENBERG P.D., DAVIDSON N., HARPER P., VINCENT M.D., LEMBERSKY B.C., BENNER S.E. Multicenter phase III study of 5-fluorouracil (5-FU) or UFT in combination with leucovorin (LV) in patients with metastatic colorectal cancer. *Proc. Am. Soc. Clin. Oncol.*, 1999, **18** : 263a.
15. CARMICHAEL J., POPIELA T., RADSTONE D., FALK S., BORNER M., OZA A., SKOVSGAARD T., MUNIER S., MARTIN C. Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J. Clin. Oncol.*, 2002, **20** : 3617-3627.
16. LIU G., FRANSSEN E., FITCH M.I., WARNER E. Patient preferences for oral versus intravenous palliative chemotherapy. *J. Clin. Oncol.*, 1997, **15** : 110-115.
17. PAYNE S.A A study of quality of life in cancer patients receiving palliative chemotherapy. *Soc. Sci. Med.*, 1992, **35** : 1505-1509.
18. BORNER M.M., SCHOFFSKI P., DE WIT R., CAPONIGRO F., COMELLA G., SULKES A., GREIM G., PETERS G.J., VAN DER BORN K., WANDERS J., DE BOER R.F., MARTIN C., FUMOLEAU P. Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin : a randomised crossover trial in advanced colorectal cancer. *Eur. J. Cancer*, 2002, **38** : 349-358.
19. CHU E. D.-R.E., MARSHALL J., TABERNERO J., TWELVES C., BARAN R., VENO A. Economic analysis of potential medical cost savings of XELOX (capecitabine and oxaliplatin combination) in metastatic colorectal cancer (MCRC). *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 269.
20. WIKLUND T.A. PM : Pharmacoeconomic comparison of capecitabine vs. intravenous 5-FU/leucovorin (Mayo protocol) in colorectal cancer (CRC) in Finland. *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 530.
21. BAKER S.D., KHOR S.P., ADJEI A.A., DOUCETTE M., SPECTOR T., DONEHOWER R.C., GROCHOW L.B., SARTORIUS S.E., NOE D.A., HOHNEKER J.A., ROWINSKY E.K. Pharmacokinetic, oral bioavailability, and safety study of fluorouracil in patients treated with 776C85, an inactivator of dihydropyrimidine dehydrogenase. *J. Clin. Oncol.*, 1996, **14** : 3085-3096.
22. WACHER V.J., WU C.Y., BENET L.Z. Overlapping substrate specificities and tissue distribution of cytochrome P450 3A and P-glycoprotein : implications for drug delivery and activity in cancer chemotherapy. *Mol. Carcinog.*, 1995, **13** : 129-134.
23. LOWN K.S., KOLARS J.C., THUMMEL K.E., BARNETT J.L., KUNZE K.L., WRIGHTON S.A., WATKINS P.B. Interpatient heterogeneity in expression of CYP3A4 and CYP3A5 in small bowel. Lack of prediction by the erythromycin breath test. *Drug Metab. Dispos.*, 1994, **22** : 947-955.
24. DOUILLARD J.Y., CUNNINGHAM D., ROTH A.D., NAVARRO M., JAMES R.D., KARASEK P., JANDIK P., IVESON T., CARMICHAEL J., ALAKL M., GRUIA G., AWAD L., ROUGIER P. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer : a multicentre randomised trial. *Lancet*, 2001, **355** : 1041-1047.
25. SALTZ L.B., COX J.V., BLANKE C., ROSEN L.S., FEHRENBACHER L., MOORE M.J., MAROUN J.A., ACKLAND S.P., LOCKER P.K., PIROTTA N., ELFRING G.L., MILLER L.L. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N. Engl. J. Med.*, 2000, **343** : 905-914.
26. DE GRAMONT A., FIGER A., SEYMOUR M., HOMERIN M., HMISSI A., CASSIDY J., BONI C., CORTES-FUNES H., CERVANTES A., FREYER G., PAPAMICHAEL D., LE BAIL N., LOUVET C., HENDLER D., DE BRAUD F., WILSON C., MORVAN F., BONETTI A. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J. Clin. Oncol.*, 2000, **18** : 2938-2947.
27. GIACCHETTI S., PERPOINT B., ZIDANI R., LE BAIL N., FAGGIUOLO R., FOCAN C., CHOLLET P., LLORY J.F., LETOURNEAU Y., COUDERT B., BERTHEAUT-CVITKOVIC F., LARREGAIN-FOURNIER D., LE ROL A., WALTER S., ADAM R., MISSET J.L., LÉVI F. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J. Clin. Oncol.*, 2000, **18** : 136-147.
28. GROTHEY A. J.K., KELLNER O., CONSTANTIN C., DITTRICH G., KROENING H., MANTOVANI L., SCHLICHTING C., FORSTBAUER H., SCHMO H.J. Randomized phase II trial of capecitabine plus irinotecan (CapIri) vs capecitabine plus oxaliplatin (CapOx) as first-line therapy of advanced colorectal cancer (ACRC). *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 255.
29. PFEIFFER P. H.P., JENS H.A. Short-time infusion of oxaliplatin in combination with capecitabine in patients with advanced colorectal cancer. *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 360.
30. BORNER M.M. D.D., POPESCU R., WERNLI M., SALETTI P., RAUCH D., HERRMANN R., KOEBERLE D., HONEGGER H., ROTH A. A randomized phase II trial of capecitabine (CAP) and two different schedules of irinotecan (IRI) in first-line treatment of metastatic colorectal cancer (MCC). *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 266.
31. GOLD P.J. G.T., DHAMI M., ANDRIA M., FISCHER D., CHEN Y.M., SAMID D., MEROPOL N. Capecitabine and irinotecan as 1st line therapy for patients with metastatic colorectal cancer : Phase II study preliminary results. *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 1158.
32. PATT Y.Z. L.E., LEIBMANN J., MILLER W., LEE F.C., KEISER W., SALVATORE J., DIAMANDIDIS D., ECKHARDT S.G., JAVLE M., JUSTICE G.R. Capecitabine plus irinotecan for chemotherapy-naïve patients with metastatic colorectal cancer (MCRC) : US multicenter phase II trial. *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 281.
33. TEWES M., SCHLEUCHER N., ACHTERRATH W., WILKE H.J., FRINGS S., SEEBER S., HARSTRICK A., RUSTUM Y.M., VANHOEFER U. Capecitabine and irinotecan as first-line chemotherapy in patients with metastatic colorectal cancer : results of an extended phase I study dagger. *Ann. Oncol.*, 2003, **14** : 1442-1448.
34. ZEULI M., NARDONI C., PINO M.S., GAMUCCI T., GABRIELE A., FERRARESI V., GIANNARELLI D., COGNETTI F. Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer. *Ann. Oncol.*, 2003, **14** :1378-1382.
35. BELANGER M. J.C., GERMOND C., BERGER M.S. A phase II, open-label, multicenter study of GW572016 in patients with metastatic colorectal cancer refractory to 5-FU5-FU in combination with irinotecan and/or oxaliplatin. *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 244.
36. HANAUSKE A., DIAZ-RUBIO E., CASSIDY J., ZINGEL D., SASTRE J., JONES R.J., ALFONSO R., BRENNSCHEIDT U., FEYEREISLOVA A., TWELVES C. Erlotinib HCL in combination with FOLFOX4 in patients with solid tumors. *Proc. Am. Assoc. Am. Oncol.*, 2003, **22** : 197.
37. CUNNINGHAM D. H.Y., SIENA S., KHAYAT D., BLEIBERG H., SANTORO A., BETS A., MUESER M., HARSTRICK A., VAN CUTSEM E. Cetuximab (C225) alone or in combination with irinotecan (CPT-11) in patients with epidermal growth factor receptor (EGFR)-positive, irinotecan-refractory metastatic colorectal cancer (MCRC). *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 252.
38. GIANTONIO B.J. L.D., O'DWYER P.J., MEROPOL N.J., CATALANO P.J., BENSON A.B. Bevacizumab (anti-VEGF) plus IFL (irinotecan, fluorouracil, leucovorin) as front-line therapy for advanced colorectal cancer (advCRC) : Results from the Eastern Cooperative Oncology Group (ECOG) Study E2200. *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 255.
39. KABBINAVAR F., HURWITZ H.I., FEHRENBACHER L., MEROPOL N.J., NOVOTNY W.F., LIEBERMAN G., GRIFFING S., BERGSLAND E. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J. Clin. Oncol.*, 2003, **21** : 60-65.
40. FINN R., WILSON C., SANDERS J., COOK A., OLSON T., GLASPY P., TCHEKMEDJIAN N., PEGRAM M.D., BRITTEN C., SLAMON D.J. Targeting the epidermal growth factor receptor (EGFR) and HER-2 with OSI-774 and trastuzumab, respectively, in HER-2 overexpressing human breast cancer cell lines results in a therapeutic advantage in vitro. *Proc. Am. Soc. Clin. Oncol.*, 2003, **22** : 940.