Abstract. To overcome 5-Fluorouracil (5FU) infusion-related problems, oral 5FU precursors and inhibitors of 5FU degradation have been developed. Capecitabine is one of these new oral fluoropyrimidines. Capecitabine treatment of advanced colorectal carcinoma, when compared to 5FU, results in superior response rates (26.6% versus 17.9%, p=0.013), equivalent times to progression and survival, and improved safety, including less stomatitis and myelosuppression. The benefits are principally derived from the avoidance of hospital visits for intravenous drug administration, less expensive drug therapy for the treatment of toxic side-effects, and fewer treatment-related hospitalisations required during the course of therapy for adverse drug reactions. In this review, the use of capecitabine, alone or in association with other drugs, in neoadjuvant, adjuvant and metastatic settings, was analysed in a selected group of elderly patients (≥70 years old) affected by colorectal cancer.

The incidence of colorectal cancer (CRC) is approximately 650,000 cases per year worldwide, of which 30,000 occur in Italy (1). In patients over 85 years old, CRC constitutes one-third of all neoplasms; 65-71% of patients with rectal cancer are aged 65 years or older (2), of which only 24% received any additional therapy (radio- or chemotherapy) following surgery, compared to 44% of those under 60 years. Even if age-related differences in the metabolism of chemo-therapeutic agents are present, these differences are not clinically significant for many drugs if the older patients are in good health (3). Chronological age is an imperfect surrogate for physiological age, so, neither comorbidity nor treatment toxicity nor short natural life expectancy appear to justify the lack of additional therapy offered to the elderly; more often non-medical factors are the principal limit. The only way to improve the treatment for this category of patients is to find a schedule or drugs which can be easily administered.

5-Fluorouracil (5FU) has been studied more than other drugs because it has been the only efficacious treatment for locally advanced and/or metastatic colorectal cancer for 40 years. Changes in the schedule of administration have shown that biochemical modulation or continuous infusion (c.i.) were associated with a response rate (RR), but not an overall survival (OS), better than bolus administration (pathological complete remission, pCR, of 67% versus 10%) (4-6). When randomised trials also involved elderly patients, no significant relationship was observed between age and the efficacy of treatment. The incidence of toxic effects was not increased among patients ≥70 years old (7).

However, recently, oral drugs (e.g., capecitabine) have been introduced. Capecitabine, an oral fluoropyrimidine, was initially administered only to younger patients, then, due to its efficacy and low toxicity rate, was also administered to elderly patients. Here, the few clinical trials designed for capecitabine in the treatment of locally advanced and/or metastatic CRC are examined and the existing data supporting its use, alone or in association with other drugs, in elderly patients are reviewed.

Mechanism of Action

Capecitabine is an antimitabolite, belonging to the fluoropyrimidine carbamate class; it causes cell injury via RNA- and DNA-related mechanisms. The drug is, in fact, metabolised in tumour cells and in the liver by carboxyesterase, cytidine deaminase and thymidine phosphorylase (present in the liver and in tumours) to 5FU. 5FU is metabolized to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). FdUMP and the folate co-factor N5-10-methylene-tetrahydrofolate bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from
2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Moreover, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error interferes with RNA processing and protein synthesis.

Capecitabine metabolisation to 5FU permits more prolonged cell exposure to the drug but lower plasma concentrations and, consequently, lower toxicity (hand-foot syndrome, HFS, diarrhoea, vomiting and mucositis) than 5FU. Capecitabine mimics the c.i. action of 5FU with the advantage (or disadvantage in the elderly because of risk of dosing errors) of oral administration (taking the medication with food which decreases the rate of absorption with minor decreases in the AUC of 5-FUDR(floxuridine) and 5FU), also enabling a fine control of the dosing (8). Capecitabine is rapidly absorbed after oral administration, with peak blood levels at 1.5 h and peak 5FU levels in about 2 h. The pharmacology of capecitabine is not significantly affected by gender, race, performance status, body surface area, albumin or hepatic dysfunction. The pharmacokinetics are largely dose-proportional. Over 70% of its metabolites are excreted by the kidney, so it is contra-indicated in patients with severe renal impairment (creatinine clearance below 30 ml/min) and should be given at doses reduced to 75% to patients with moderate renal impairment (creatinine clearance 30-50 ml/min). Faecal excretion is minimal (2.6%). The drug or its metabolites are distributed in the intestinal mucosa, plasma, liver and other tissues. It is still unknown whether this drug crosses the blood-brain barrier.

While capecitabine has been shown to be tolerated by fit elderly patients, information on the dosing and scheduling for patients with impaired organ function is not available. In combination with docetaxel, patients >60 years old experience more toxicity. Elderly patients may also experience a greater incidence of gastrointestinal grade 3/4 events.

The possible side-effects include cardiovascular oedema (5%), EKG changes/arrhythmias (rare), ischaemic infarction (rare), HFS (53%; severe 17%; commonly referred to as palmar-plantar erythrodysesthesia, characterised by numbness, dysesthesia or paresthesia, tingling, painless or painful swelling, erythema, desquamation, blistering and severe pain of the hands and/or feet), dermatitis (24%), alopecia (6%), photosensitivity/nail disorder, skin discoloration (7%), diarrhoea (49%; severe 14%), nausea (38%; severe 3%), vomiting (23%; severe 3%), stomatitis (25%; severe 2%), constipation (7%), anorexia (20%), abdominal pain (17%), haematological anaemia (grades 3 and 4: 2%), neutropenia (grades 3 and 4: 3%), hepatic hyperbilirubinemia (grades 3 and 4: 23%), neurological paresthesia (9%), dizziness (5%) and sensory disturbance (6%) (Table I).

Three dose-finding studies with oral capecitabine added to a fixed dose of radiation were reported (9-11). One study used a continuous schedule of capecitabine (9) and the other two a 5-day-per-week regimen (10, 11). The first study identified the maximum tolerated dose (MTD) of

Table I. Side-effects, possible treatment and characteristics.

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Diarrhoea</td>
<td>1. Anti-diarrhoeal therapy (e.g., loperamide).</td>
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<td></td>
<td>2. Close monitoring (if severe) and fluid and electrolyte replacement for dehydration as indicated.</td>
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<td></td>
<td>3. Capecitabine held and the dose reduced after recovery.</td>
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<tr>
<td></td>
<td>Older patients (&gt;65 years) may be more at risk of grades 3 or 4 diarrhoea compared to younger patients. No dose adjustment for the starting dose is required, but patients should be closely monitored and dose modification should be performed.</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>1. Dosage interruption/adjustment.</td>
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<tr>
<td>(hand-foot syndrome)</td>
<td>2. Topical emollients (e.g., hand creams, udder balm) or oral pyridoxine therapy.</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1. No dose adjustment, but caution (more frequent in patients with hepatic metastases).</td>
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<tr>
<td>Cardiac toxicity</td>
<td>The risk may be increased in older patients with prior coronary artery disease.</td>
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<tr>
<td>Coagulopathy</td>
<td>Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants, such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating the drug therapy and, in a few cases, within one month after stopping it. Patients taking coumarin derivative anticoagulants concomitantly with capecitabine (especially elderly patients) should be monitored regularly for alterations in their coagulation parameters (PT or INR).</td>
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No separate studies have been conducted to examine the effect of age on the pharmacokinetics of capecitabine and its metabolites.
continuous capecitabine to be 1000 mg/m² twice daily every day (9); the recommended dose for phase II studies was capecitabine 825 mg/m² twice daily every day plus standard radiotherapy (12). In the other two trials, the recommended dose for phase II studies was 900 mg/m² twice daily with pCR up to 31% (13-15).

At present, capecitabine is approved as first-line treatment for metastatic CRC, as adjuvant treatment for stage III colon cancer and, in combination with docetaxel, for advanced or metastatic breast cancer after prior anthracyclines. The Public Health Agency of Canada approved its use in advanced or metastatic breast cancer after the failure of standard therapy (including taxanes).

**Clinical Trials**

a) **Neoadjuvant treatment:** Data regarding the effects of capecitabine in the neoadjuvant treatment of elderly patients have been extrapolated from studies on patients of different ages (9-16). Specific trials on patients over 70 years old do not exist.

b) **Adjuvant treatment:** Again, specific data on capecitabine administration only to patients over 70 years old does not exist (17, 18).

c) **Metastatic disease treatment:** Only in metastatic disease have trials specifically designed for elderly patients been reported.

To determine the tolerability of capecitabine in patients ≥70 years old with advanced CRC, 51 patients, who were considered ineligible for combination chemotherapy, received oral capecitabine 1,250 mg/m² twice daily on days 1 to 14 every 3 weeks (19). Patients with a creatinine clearance of 30 to 50 ml/min received a dose of 950 mg/m² twice daily. The overall RR was 24% (95% CI, 15% to 41%), including 4% complete remission (CR) and 20% partial remission (PR). Disease control (CR + PR + stable disease (SD)) was achieved in 67% of patients. The median time to progression (TTP) and OS were 7 months (95% CI, 6.4 to 9.5 months) and 11 months (95% CI, 8.6 to 13.3 months), respectively. Of the 35 patients evaluated for clinical benefit response, 14 (40%; 95% CI, 24% to 58%) showed clinical benefit. Capecitabine was well tolerated. Treatment-related grades 3 and 4 adverse events were observed in only six patients (12%) and the most common events were diarrhoea, HFS and thrombocytopenia. One patient (2%) had an episode of angina, but no treatment-related deaths were reported. The results suggest that capecitabine is effective and well tolerated in elderly patients with advanced CRC who are considered ineligible for combination chemotherapy.

Three randomised studies, comparing capecitabine to the Mayo Clinic regimen (5FU bolus), reported a better RR (p<0.0002) in the first group of patients (20-22). There were no significant differences for median TTP (p=0.72) or median survival time (MST) (p=0.974) in either regimen. Toxicity was significantly lower in the first group than in the latter (p<0.001), regardless of patient age.

Van Cutsem’s phase III trial (23), involving 602 patients, demonstrated that capecitabine 1250 mg/m² administered twice daily, on days 1 to 14 every 3 weeks, had at least equivalent efficacy when compared with the Mayo Clinic regimen (RR of 18.9% versus 15%; median TTP of 5.2 versus 4.7 months, p=0.65). The MST was 13.2 and 12.1 months, respectively (p=0.33). The toxicity profiles of both treatments were typical of fluoropyrimidines, however, capecitabine led to a significantly lower incidence (p<0.0001) of grade 3-4 stomatitis, neutropenia and alopecia and a higher incidence of grade 3 HFS (p<0.0001). On the basis of these results, it was concluded that capecitabine monotherapy provided advantages compared with bolus 5FU/leucovorin (LV), including a favourable toxicity profile and the convenience of an oral drug (more appealing for elderly patients, enabling convenient out-patient therapy) (24).

In a prospective trial (25) with capecitabine 2500 mg/m²/day as a first-line therapy, administered on days 1 to 14, every 3 weeks, to 51 patients aged ≥70 years, the RR was 25% and the median TTP was 7.9 months. No significant difference in grade 3-4 toxicities between the general population and the population over 80 years of age was noted. Even in this case, the therapy was well tolerated and the oral administration was preferred to intravenous regimens.

Considering the improved outcomes with capecitabine versus bolus 5-FU/LV in overall trial populations and in patients aged ≥70 years, and because capecitabine/oxaliplatin (XELOX) is a safe and active combination for the first-line treatment of metastatic CRC, Twelves et al. (26) compared data from older and younger patients treated with first-line XELOX. Oxaliplatin 130 mg/m² was administered intravenously on day 1 followed by oral capecitabine 1000 mg/m² twice daily for 14 days every 3 weeks. The median age of the overall population (N=96) was 64 years (range, 34-79 years), including 52 younger patients (<65 years of age) and 44 older patients (≥65 years of age). The XELOX regimen had a similar high activity in both groups, with a RR of 58% (95% CI, 43%-71%) and 52% (95% CI, 37%-68%) in the younger and older patients, respectively. In addition, the TTP and OS were similar in both groups (p>0.5 for both outcomes). The XELOX regimen also had a favourable safety profile, with no clinically relevant differences between older and younger patients. The overall incidence of adverse events (including grade 3/4), dose reductions and withdrawals because of adverse events were similar in both groups. In the context of an aging population, XELOX provided a highly effective and tolerable first-line treatment for patients with metastatic colorectal cancer (27) (Table II).
was planned at 100 mg/m², while capecitabine was planned in the first cycle; in the second cycle, oxaliplatin at 2500 mg/m² (per day) on the third cycle. The treatment consisted of oxaliplatin 50 mg/m² daily (days 1, 8, 15, 22) and capecitabine 1000 mg/m² twice daily for 14 days every 3 weeks. All patients were evaluable for toxicity and 26 for response. Five PR (19.2%), nine SD (34.6%) and twelve PD (46.2%) were observed; three patients underwent surgical resection of their relapsing disease (hepatic) which led to CR; the median TTP was 6.1 months and the OS was 14.2 months. Toxicity was very low: grade 1/2 peripheral neuropathy in eleven patients (40%), grade 1/2 nausea-vomiting in five patients (18%), grade 1/2 neutropenia in seven patients (26%) and grade 1/2 anaemia in ten patients (35%). In one case the treatment was interrupted for toxicity (neuropathy grade 3 after one course). This regimen was feasible, active and very safe in elderly patients; no life-threatening toxicities were registered.

In a phase III study, 399 patients (median age 65, range 32-86) were randomised to receive either FUFOX (196 patients: 5FU 2000 mg/m² 24-h infusion, folinic acid 500 mg/m², oxaliplatin 50 mg/m² days 1, 8, 15, 22; every 5 weeks) or CAPOX (203 patients: capecitabine 1000 mg/m² bid days 1-14, oxaliplatin 70 mg/m² days 1 and 8; every 3 weeks) (31). Based on 154 observed events, the median TTP was 8 months in the FUFOX arm and 7.5 months in the CAPOX arm, p=0.47 (hazard ratio (1.13) 95%CI: 0.82-1.55). The RR were approximately 49% and 44%, respectively, while grade 3-4 toxicities were similar in both groups. The results of this study showed, for the first time, that CAPOX has a comparable efficacy and toxicity profile to FUFOX in the first-line treatment of advanced CRC; the data on the elderly patients were retrospectively extrapolated.

In a second-line CRC study (after first-line therapy with FOLFIRI (oxaliplatin 180 mg/m² on day 1 and 5FU 600 mg/m² bolus on days 1 and 2, 5FU 600 mg/m² 22-h c.i. days 1 and 2, LV 100 mg/m² 2-h infusion on day 1) in 16 cases, group A; FOLFIRI (CPT11 180 mg/m² on day 1, 5FU 600 mg/m² bolus days 1 and 2, 5FU 600 mg/m² 22-h c.i. days 1 and 2, LV 100 mg/m² 2-h infusion day 1) in four cases, group B; and 5-FU/LV/MTX in six cases, group C); 26 patients received the second-line XELIRI regimen (irinotecan or CPT11 150 mg/m² on day 1 and capecitabine 750 mg/m² twice daily on days 1-15, respectively) (32). There was evidence of clinical...
control (PR+SD) in 50% of group A, 50% of group B and 20% of group C. The most common grade 3 side-effects were diarrhoea (40%), nausea and vomiting (20%) and HFS (10%). Grade 3-4 neutropenia was seen in 40% of patients. No treatment-related deaths were reported. Eight out of 24 evaluable patients (33%) showed a response to treatment and control of the disease (PR+SD) was observed in 15 cases (63%; nine group A, one group B, five group C). The median TTP was 5.5 months and the OS was 11.5 months. XELIRI is also active and well tolerated in patients pretreated with FOLFOX4. Capecitabine should replace 5FU in combination with CPT11 as second-line therapy to obtain an effective, safe and well-accepted opportunity for pretreated elderly patients (33). Studies with capecitabine plus CPT11 (CPT11 250 mg/m² on day 1 and capecitabine 1000 mg/m² twice daily on days 1-15, respectively, every 3 weeks or CPT11 200 mg/m² on days 1 and capecitabine 750 mg/m² twice daily on days 1-15, in patients ≥65 years) (XELIRI) as a first-line therapy (34) reported grade 3-4 toxicities in 26% of patients and disease control (SD+CR+PR) in 84% of them. The TTP and OS were 6.1 and 15.6 months, respectively. In this case as well, data on elderly patients were not precisely stated.

Conclusion

Capecitabine single-agent therapy could be an important therapeutic option in elderly patients who are ineligible for combination therapy, either in the adjuvant (17, 18), neoadjuvant (35) or palliative settings (23, 27). The lack of high-grade haematological or non-haematological toxicities, the avoidance of infusional adversities and good compliance, render capecitabine a suitable option for elderly patients, though care must be taken in the case of previous cardiopathy or coagulopathy (36, 37). Moreover, the availability of a new biological therapy, which has already shown promising activity and good tolerability in combination with 5FU in advanced CRC and with capecitabine in different cancers, might be expected to improve the outcomes without increasing toxicity in this selected category of patients.

The lack of prospective adjuvant or neoadjuvant trials specific for colon- and/or rectal cancer in elderly patients suggests that further studies on capecitabine in future phase II-III clinical trials could be significant.

References


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