SPANDIDOS PUBLICATIONS

ONCOLOGY REPORTS 43: 1719-1728, 2020

Oral therapies in digestive oncology (Review)

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Received May 27, 2019; Accepted December 13, 2019

DOI: 10.3892/or.2020.7555

Abstract. Targeted therapy and oral chemotherapy indications are increasing in the realm of digestive oncology. Oral intake of cancer agents is sometimes compulsory (no i.v. equivalent) or is preferred by the patient or the physician. Although oral chemotherapy facilitates the treatment of oncology patients, the treatment diversity, risk of pharmaceutical interactions and monitoring of side effects are potentially challenging and need to be fully acknowledged by the physician. We offer here a literature review of the indications, doses, side effects and monitoring of every oral therapy indicated in Digestive Oncology. We suggest a prescription algorithm including therapeutic education by the physician or a trained nurse, and pharmaceutical counseling.

Contents

1. Introduction

The indications for the use of oral therapies in the field of digestive oncology are increasing. Whether oral chemotherapy or targeted therapies, their use is favored by patients. Adherence to treatment is directly linked with the patient's understanding, the ability to remember the information provided by the physician, treatment length and psychological distress (1). A good coordination between oncologists, general practitioners, pharmacists and nurses is essential, information about drug monitoring and management of the side effects has to be widely distributed. Drug and food interactions have to be known by the oncologist. We herein propose an updated review of the literature about oral therapies in digestive oncology and a short reminder of how to use them and to manage their side effects.

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Key words: oral therapy, cancer, digestive oncology, pharmaceutical counselling, therapeutic education

2. Oral chemotherapy

Capecitabine. Capecitabine is an antimetabolite, an oral prodrug of 5-fluorouracil (5-FU), which is metabolized to 5'-deoxy-5-fluorocytidine, 5'-deoxy-5-fluouridine and 5 fluorouracil by cytidine deaminase and thymidine phosphorylase. Capecitabine is a uracil-based nucleic acid analog that inhibits thymidylate synthase, resulting in inhibition of DNA synthesis and RNA damage. It has been shown that 5-FU concentrations after capecitabine intake are higher in colorectal tumors than levels in healthy tissue, due to cytidine deaminase and thymidine phosphorylase concentrations in these tumors (2).

A systematic screening for dihydropyrimidine dehydrogenase (DPD) deficiency is recommended before any administration of 5-FU-based chemotherapy (3).

Capecitabine is administered orally, twice a day, in a divided dose 12 h apart, 30 min after a meal. Tablets come in 2 doses; 150 and 500 mg.

In a neoadjuvant setting, capecitabine is indicated in association with radiotherapy. The standard neoadjuvant CAP50 regimen is recommended in rectal T3-4M0 cancer (4), with a dose of concomitant capecitabine 800 mg/m^2 twice daily, 5 days per week.

In adjuvant situations, capecitabine is applied in monotherapy with a 1250 mg/m^2 dose twice daily, 14 days/21 after complete resection of a cholangiocarcinoma, as shown in the recent BILCAP study (5). Capecitabine monotherapy can be discussed in adjuvant therapy for stage II colorectal cancer (CRC), or in stage III after 70 years of age (6). In association with oxaliplatin, capecitabine is administered at the dose of 1,000 mg/m^2 twice daily, 14 days/21 in adjuvant for stage II/III CRC, for 3 or 6 months, as shown in the IDEA study (7). In association with gemcitabine after surgery for pancreatic adenocarcinoma, capecitabine is administered at the dose of 1,660 mg/m^2 daily, 21 days/28 (ESPAC-4 study) (8).

In metastatic situations, capecitabine can replace intravenous 5-FU in monotherapy, doublet, or triplet with targeted therapy (9). Capecitabine is preferentially used in maintenance

therapy in association with bevacizumab in CRC (10). In pancreatic neuroendocrine tumors (NETs), administration of capecitabine at a dosage of 750 mg/m^2 twice daily from day 1 to 14 and temozolomide at 200 mg/m^2 once daily from day 10 to 14 every 28 days was found to be associated with durable response rate (11).

Oncologists and pharmacists have to be aware of drug interactions, and the most common is in regards to warfarin, which is prohibited during capecitabine treatment (12). It has also been shown that proton pump inhibitors (PPIs) negatively affect capecitabine efficacy, by modifying gastric pH leading to altered absorption (13). The use of PPIs must be withdrawn when possible.

Toxicity associated with capecitabine is described in nearly 80% of patients (14), and up to 40% grade III. Nausea and vomiting from 3 to 35% is observed depending on the studies (5,6,9,15,16), mucositis is observed in 2 to 22% of cases, diarrhea up to 30%, hand and foot syndrome, 17% and hematologic toxicity less than 10%. Cardiac toxicity is described at a range of 3 to 6%, and its incidence increases with the presence of underlying cardiopathy. The incidence of toxicity and grade depends on the dose, combination therapy and the DPD status.

Systematic education for hand and foot syndrome management, mucositis management and treatment for digestive side effects must be provided at initial capecitabine prescription.

TAS 102. TAS-102 is an orally administered combination of a thymidine-based nucleic acid analogue, trifluridine and a thymidine phosphorylase inhibitor, tipiracil. Tipiracil improves the bioavailability of trifluridine by inhibiting its catabolism by thymidine phosphorylase.

The only indication validated to this day was for refractory metastatic CRC after oxaliplatin and 5 FU-based chemotherapy and irinotecan and 5 FU-based chemotherapy (targeted therapies included). TAS-102 was administered at a dose of 35 mg/m^2 twice a day, 5 days a week, with 2 days of rest for 2 weeks followed by a 14-day rest period. Overall survival was 7.1 months (vs. 5.3 months in the placebo group; P<0.001) (17).

Toxicity was found to be mainly hematologic, with 38% of ≥grade III neutropenia, with 4% febrile neutropenia. Mild nausea (grade I-II) and vomiting have been described in 48 and 28% of cases, respectively (17).

Temozolomide. Temozolomide is an oral alkylating agent indicated for the treatment of neuroendocrine pancreatic carcinoma, in association with capecitabine. Temozolomide is an alkylating agent prodrug, delivering a methyl group to purine bases of DNA. DNA alkylation induces cell cycle arrest at G2/M phase of mitosis eventually leading to apoptosis (18).

The indication for temozolomide in the treatment of pancreatic NETs was studied by Strosberg *et al* (11). The regimen consisted of oral capecitabine at 750 mg/m^2 twice a day for 14 days (days 1-14) and oral temozolomide at 200 mg/m^2 once a day at bedtime for 5 days (days 10-14) every 28 days. The dose was adapted in the case of renal insufficiency. Median progression-free survival was 18 months.

The first prospective randomized study was presented this year (ASCO) (19) comparing temozolomide alone vs. temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine carcinoma, in progression after targeted therapy or somatostatin analogues. Progression-free survival was 22.7 months in the temozolomide+capecitabine group vs. 14.4 months in the temozolomide group (P=0.023). Overall survival was not reached in the bi-chemotherapy group, vs. 38 months in the temozolomide group (P=0.012). Predictive value of MGMT status for temozolomide response was studied in pancreatic NETs. Combination therapy induced more side effects (44%), with 13% grade III or more neutropenia. Digestive side effects were present in 8% of cases.

3. Targeted therapies

Sorafenib. Sorafenib is an oral multikinase inhibitor of the vascular endothelial growth factor receptor (VEGFR), the platelet-derived growth factor receptor (PDGFR) and Raf kinase. Sorafenib inhibits tumor cell proliferation and angiogenesis (20).

Sorafenib is indicated in the first-line treatment of advanced HCC (21) at the dose of 400 mg twice daily. It is recommended to take sorafenib as far away as possible from meal-times or with a low-fat diet for better absorption. No adaptation is necessary in case of renal dysfunction. In case of cirrhosis, sorafenib is indicated in the case of Child A score. In a study by Llovet *et al* (21) enrolling 602 patients with advanced HCC without previous systemic treatment, the median overall survival of the patients was 10.7 months in the sorafenib group vs. 7.9 months in the placebo group (P<0.001). Toxicity described in the sorafenib group included diarrhea (55%), weight loss (30.9%), anorexia (28.6%), hand and foot syndrome (21.2%), vomiting (14.8%) and alopecia (14.1%). A treatment discontinuation was necessary in 31.6% of the patients due to these side effects.

Lenvatinib. Lenvatinib is a multikinase inhibitor, targeting VEGF receptors 1-3, fibroblast growth factor (FGF) receptors 1-4, PDGF receptor α, RET and KIT. Lenvatinib is indicated in τηε first-line treatment for unresectable or metastatic hepatocellular carcinoma (22). The recommended dose is 12 mg/day for body weight ≥60 kg or 8 mg/day for <60 kg. Kudo *et al* (22) enrolled 1,492 unresectable hepatocellular carcinoma patients randomly assigned to lenvatinib or sorafenib as first-line treatment. The median survival time for lenvatinib was 13.6 months (95% CI, 12.1-14.9), not inferior to sorafenib [(12.3 months, 10.4-13.9), HR 0.93, 95% CI, 0.79-1.06]. The most common any-grade adverse events for lenvatinib were fatigue (30%, grade ≥3: 4%), hypertension (42%, grade ≥3: 23%), diarrhea (39%; grade ≥3: 4%), anorexia (34%, grade ≥3: 5%), decreased weight (31%, grade ≥3: 8%). A similar tolerance profile was observed in an elderly population (23).

Regorafenib. Regorafenib is an oral multikinase inhibitor which targets angiogenic, stromal and oncogenic tyrosine kinase receptors. Inhibition of angiogenesis is accomplished by inhibition of VEGF, fibroblast growth factor (FGF) and PDGF receptors. Inhibition of metastatic invasion was found to be due to the inhibition of VEGFR2 and VEGFR3. Oncogenic inhibition was found to be induced by inhibition of the MAP kinase pathway. Regorafenib was administered at a dose of 160 mg daily, in the morning (4x40 mg) associated with a low-fat breakfast, during 3 weeks over a 4-week cycle (24).

Table I. Oral therapies in digestive oncology: indications, dose, side effects and surveillance.

Name	Indications	Dose and treatment intake modalities	Side effects	% ≥grade 3	Surveillance
Capecitabine	CRC, esophageal, gastric, biliary tract cancer, NETs	Monotherapy 1,250 mg/m^2 twice a day; 14 days/21	Nausea, vomiting, diarrhea, mucitis, hand foot syndrome, cardiac toxicity	40	Clinical monitoring Biological monitoring before each cycle
TAS 102	CRC ≥3rd line	35 mg/m^2 J1-J5 and J8-J12 J1=J28	Neutropenia	38	Biological monitoring before each cycle
Temozolomide	In association with capecitabine; pancreatic NETs	Capecitabine 750 mg/m^2 2x/day (days 1-14), Temozolomide 200 mg/m2/day (days 10-14) J1=J28	Neutropenia	13	Biological monitoring before each cycle; Renal function adaptation
Sorafenib	Advanced HCC	400 mg twice daily	Hand foot syndrome	8	Clinical monitoring and biological surv/4 weeks
			Diarrhea	8	
			Fatigue	3	
			Weight loss	2	
Lenvatinib	Advanced HCC	12 mg/day for ≥60 kg or 8 mg/day for <60 kg	Fatigue	4	Clinical monitoring and biological surv/4 weeks
			Hypertension	23	
			Diarrhea	4	
			Anorexia	5	
			Decreased weight	8	
Regorafenib	Metastatic CCR after 5-FU, oxaliplatin, irinotecan, targeted therapy Advanced HCC after sorafenib	160 mg daily 3 weeks/4	Hand foot syndrome	17	Clinical, biological monitoring (phosphoremia, BCC, hepatic) every 15 days.
			Fatigue	10	
			Diarrhoea	36.7	
			Hypertension	36.7	
			Rash	29.6	
Cabozantinib	Advanced HCC after sorafenib	60 mg daily	Hand-foot syndrome	17	Clinical monitoring, biology monitoring (phosphoremia, BCC, glycemia, hepatic) every 15 days
			Hypertension	16	
			Increased ALT	12	
			Fatigue	10	
			Diarrhea	10	
Sunitinib	Advanced pancreatic well-differentiated NETs	37.5 mg daily	Neutropenia	12	Clinical monitoring, biological monitoring BCC, ionogram, (renal function) Proteinury/6 weeks Cardiac ultrasonography/3 months
			Hypertension	10	
			Hand foot syndrome	6	
			Diarrhea	5	
			Fatigue	5	
			Abdominal pain	5	
			Thrombocytopenia	4	
			Stomatitis	4	

Table I. Continued.

Name	Indications	Dose and treatment intake modalities	Side effects	% ≥grade 3	Surveillance
Capecitabine	CRC, esophageal, gastric,	Monotherapy	Nausea, vomiting, diarrhea, mucitis,	40	Clinical monitoring
Everolimus	Advanced progressive well-differentiated NETs	10 mg daily	Stomatitis	9	Clinical monitoring, biological monitoring (BCC, glycemia, cholesterol, triglycerides) at 15 days and once a month, HBA1C/3 months
			Anemia	6	
			Hyperglycemia	5	
			Diarrhea	7	
			Infections	7	
			Fatigue	3	
			Non-infectious pneumopathy	8 to 12	
Imatinib	Adjuvant in high-risk GI stromal tumors or first-line metastatic GI stromal tumors	400 mg daily, 800 mg in case of *KIT* exon 9 mutation or failure at the dose of 400 mg	Fatigue	2	Clinical monitoring, biological monitoring (BCC once a week/1 month, twice a month during 3 months and once every 3 months; ionogram, renal and hepatic function once a month/3 months and/3 months)
			Neutropenia	3	
			Edema	2	
			Gastrointestinal		

CRC, colorectal cancer; NET, neuroendocrine tumors; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; GI, gastrointestinal.

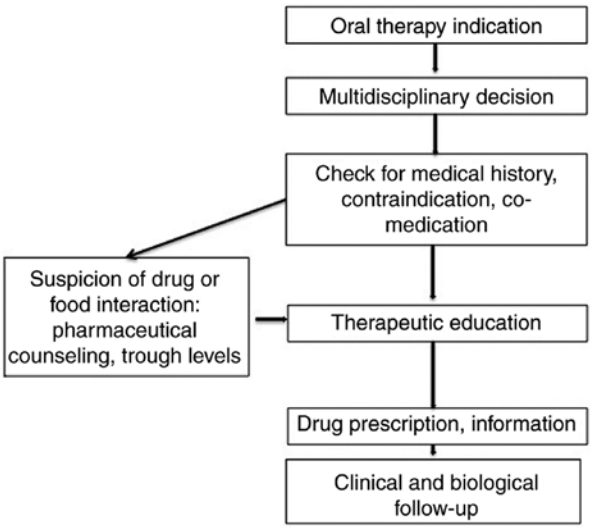

Figure 1. Proposition of an algorithm for the initiation of oral therapy in digestive oncology.

Regorafenib is indicated for patients with metastatic CRC previously treated with fluoropyrimidine-based chemotherapy, anti-VEGF or anti-EGFR therapy. The CORRECT study (25) included 760 metastatic CRC PS 0 or 1 patients after failure of fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and anti-EGFR therapy of RAS wild-type tumors. They received either placebo or regorafenib at 160 mg per day. The median overall survival was 6.4 months in the regorafenib group vs. 5 months in the placebo group (HR=0.77, 95% CI, 0.64-0.94).

A multicentric randomized phase II study was carried out and enrolled 123 metastatic CRC patients treated with regorafenib; randomized between a dose-escalation strategy (starting dose 80 mg/day taken orally with weekly escalation, per 40 mg increment, to 160 mg/day regorafenib) vs. a standard dose strategy (160 mg/day) (26). A comparable anti-tumoral activity was observed, with lower incidence of adverse events in the 'dose escalation strategy' group. This strategy is due to be implemented in clinical practice.

Regorafenib is also indicated in advanced HCC after sorafenib treatment. The RESORCE study (27) randomized 573 HCC (Child A) patients between best supportive care or regorafenib 160 mg daily 3 weeks/4. Patients had to have tolerated sorafenib at least 400 mg/day for at least 20 of the last 28 days of treatment. Regorafenib improved overall survival: 10.6 vs. 7.8 months (HR=0.63, 95% CI 0.50-0.79).

Regorafenib is also indicated in metastatic or unresectable gastrointestinal (GI) stromal tumors after intolerance or failure of imatinib and sunitinib (28), with a dose of 160 mg per day 3 weeks/4. The median progression-free survival vs. placebo was 4.8 vs. 0.9 months (P<0.001).

In the CORRECT study (25) the most common adverse events of grade III or higher were hand-foot syndrome (18%), asthenia (10%), diarrhea (36.7%), hypertension (36.7%), rash or desquamation (29.6%). In the RESORCE study (27), at least grade III or higher adverse events consisted of hypertension (15%), hand-foot syndrome (13%), asthenia (9%) and diarrhea (3%).

Biological monitoring during regorafenib treatment includes phosphoremia, blood cell count (cytopenia) and hepatic biology. Regorafenib is forbidden in case of recent (<6 months) arterial thrombosis.

Cabozantinib. Cabozantinib is a tyrosine kinase inhibitor which targets VEGF1, VEGF2, VEGF3, hepatocyte growth factor receptor (MET) and AXL receptor tyrosine kinase (AXL), which are implicated in the progression of HCC and the development of resistance to sorafenib. Inhibition of VEGFR and c-MET decreases resistance of VEGFR inhibitor via c-Met axis (29).

Cabozantinib is indicated for the treatment of non-resectable HCC after progression with sorafenib. A randomized double-blind phase III trial recruited 707 HCC patients after progression with sorafenib. The patients received either cabozantinib 60 mg once daily or placebo (30). The median overall survival was longer with cabozantinib, 10.2 months vs. 8 months (HR for death 0.76, 95% CI, 0.63-0.92, P=0.005). Principal grade III or higher adverse events included palmar-plantar-erythrodysesthesia (17%), arterial hypertension (16%), increased alanine aminotransferase (ALT) (12%), fatigue (10%) and diarrhea (10%).

Biological monitoring for this agent includes testing for blood cell count, hepatic biology, TSH, glycemia and electrolytes.

Sunitinib. Sunitinib is a multi-targeted tyrosine kinase inhibitor indicated for the treatment of advanced well-differentiated pancreatic neuroendocrine carcinoma. Sunitinib has been identified as an inhibitor of VEGFR1, VEGFR2, VEGFR3, KIT proto-oncogene, receptor tyrosine kinase (KIT), proto-oncogene tyrosine-protein kinase receptor Ret (RET) and PDGFRA. The recommended dose is 37.5 mg daily continuously (31).

A phase III randomized trial of sunitinib treatment vs. a placebo included 171 patients who had progressive pancreatic well-differentiated neuroendocrine carcinoma (32). The median progression-free survival was 11.4 months in the sunitinib group vs. 5.5 months for the placebo group (HR for progression or death 0.42, IC 95% 0.26-0.66, P<0.001). The HR for death was 0.41 (IC 95% 0.19 to 0.89, P=0.02).

Sunitinib is also indicated for the treatment of metastatic or unresectable GI stromal tumors, after imatinib resistance or intolerance (32,33). The recommended dose is 50 mg per day for 4 weeks/6, but a dose of 37.5 mg per day continuously showed an acceptable toxicity profile and similar efficiency in a non-randomized phase II study (33).

Grade III or greater adverse events included neutropenia (12%), hypertension (10%), palmar-plantar-erythrodysesthesia (6%), diarrhea (5%), fatigue (5%), abdominal pain (5%), stomatitis (4%) and thrombocytopenia (4%) (32,33).

A transthoracic ultrasonography is recommended before treatment initiation and every 3 months, due to a possible decreased left ventricular ejection fraction (LVEF). Urine analysis (protein) is recommended every 6 weeks. Co-medication with P450 cytochrome treatments must be monitored (34).

Everolimus. Everolimus is a selective mammalian target of rapamycin (mTOR) inhibitor. Everolimus inhibits tumor cell

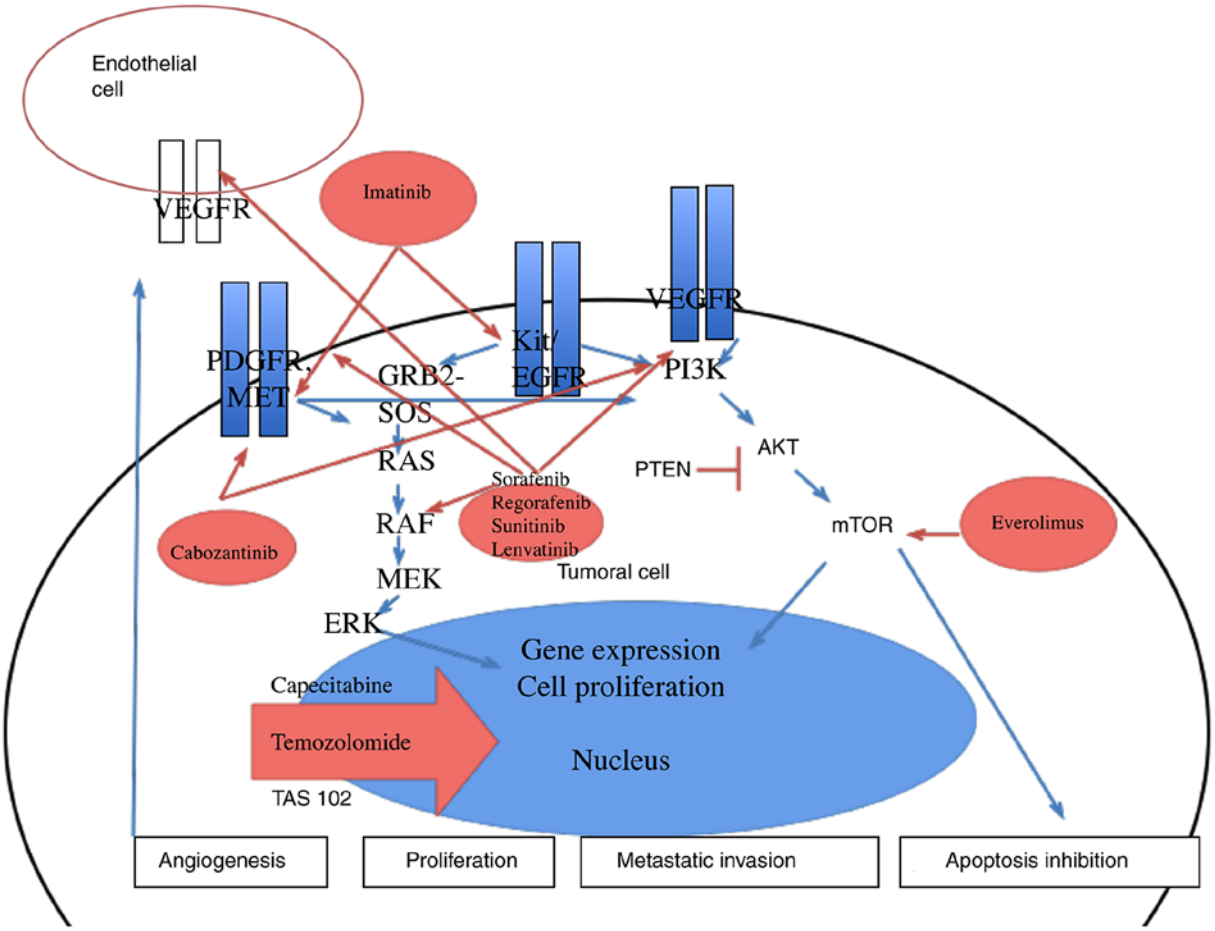

Figure 2. Simplified pathway of tumor proliferation and the mechanisms of action of oral therapeutic agents for digestive oncology. VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; MET, hepatocyte growth factor receptor; GRB2, growth factor receptor bound protein 2; SOS, SOS Ras/Rac guanine nucleotide exchange factor; PTEN, phosphatase and tensin homolog; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin.

growth as well as that of endothelial cells and fibroblasts. Everolimus is indicated for the treatment of advanced and progressive well-differentiated digestive neuroendocrine tumors (35-37). The dose recommended is 10 mg per day continuously.

In the RADIANT-3 study (37), 410 patients with advanced low-grade or intermediate-grade pancreatic progressive neuroendocrine tumors were randomized between an everolimus 10 mg/day group and a placebo group. The median progression-free survival was 11 months in the everolimus group vs. 4.6 months in the placebo group (P<0.001).

In the RADIANT-4 study (36), 302 patients with advanced progressive well-differentiated neuroendocrine tumors of pulmonary or gastrointestinal origin were enrolled, and randomized between an everolimus 10 mg per day group and a placebo group. The median progression-free survival was 11 months in the everolimus group vs. 3.9 months in the placebo group (P<0.00001) and no significance in overall survival.

Grade 3 or 4 events with everolimus included anemia (6%), hyperglycemia (5%), stomatitis (9%), diarrhea (7%), infections (7%) and fatigue (3%). A non-infectious pneumopathy was observed in 12% of cases; therefore, a systematic clinical investigation for dyspnea, auscultation and pulmonary evaluation on TDM is recommended (36,37). A systematic follow-up of metabolic disorders induced by everolimus should be performed at day 15, and then once a month (38).

Additionally there is a high risk of toxicity linked with the association of inhibitors of p450 cytochrome, which could lead to a dose reduction and should justify a close watch (39).

Imatinib mesylate. Imatinib is a tyrosine kinase inhibitor targeting BCR-ABL tyrosine kinase and stem cell factor receptor, encoded by the proto-oncogene c-Kit, and PDGFR. Competitive inhibition at the ATP-binding site of BCR-ABL tyrosine kinase leads to inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction. Imatinib also inhibits the receptor PDGFR and KIT (40). The recommended dose is 400 to 800 mg once daily during a meal.

Imatinib is indicated as an adjuvant therapy for high risk stromal tumors or in cases of metastatic stromal tumors.

In an adjuvant situation, a phase III randomized trial (41) included patients who underwent surgery for a gastrointestinal stromal tumor of at least 3 cm, and who were randomized between a placebo (N=354) and imatinib 400 mg per day (N=359) daily group, for 1 year after tumor resection. At 1 year, imatinib significantly improved the recurrence-free survival of the imatinib group compared with the placebo group [HR=0.35 (0.22-0.53), P<0.0001]. In the imatinib group,

grade III or IV adverse events occurred in 30.9% of the cases. Grade III edema was noted in 2%, grade III or IV neutropenia in 3% and grade III or IV fatigue in 2% of the cases.

A secondary analysis concerning the function of tumor genotype was performed (42), confirming that *KIT* exon 11 mutation was associated with the significantly improved prognosis in the imatinib treatment, contrary to exon 9 mutation or wild-type genotype. Imatinib did not benefit patients with a PDGFRA mutation type D 842V of exon 18.

Joensuu *et al* (43) assessed adjuvant therapy with imatinib for 1 to 3 years in 400 patients with operable GI stromal tumors with a high risk of recurrence (size, mitosis, tumoral breach). Recurrence-free survival was 66% in the 3-year treatment group vs. 48% in the 1-year treatment group (P<0.0001). After 5 years, the overall survival was 93 vs. 87% (P=0.032), in favor of the 3-year treatment. A 3-year treatment was also recommended in adjuvant therapy for high-recurrence risk stromal tumors.

Imatinib is recommended for cases of metastatic GI stromal tumors (44,45). In cases with *KIT* exon 9 mutation, a higher dose of 800 mg per day is recommended, as well as in the event of progression at the dose of 400 mg per day (46).

Table I provides a summary of drug indications, dose, principal side effects and monitoring.

4. Practical aspects

Initiating oral therapy. Similar to every treatment in oncology, the prescription must follow a multidisciplinary decision. Before initiating oral therapy, medical history of the patient must be known by the clinician, as well as co-medications. Therapeutic education for the treatment's modalities and side effects is essential, completed by the physician or specially trained oncology nurses (47). Patients therefore tend to handle side effects and critical situations better.

Pharmaceutical counseling is suggested (48), to alert the patient to the importance of compliance with therapy, as well as for interactions with concomitant medication and food. Treatment trough levels should be assessed in the case of a suspicion of pharmaceutical interactions, primary treatment failure, before dose optimization (Fig. 1).

Fig. 1 illustrates the proposition of a decisional pathway for initiating oral therapy in digestive oncology. A multidisciplinary decision must lead to the initial prescription, with an assessment of the patient's medical history co-medication or contraindications. Pharmaceutical counseling can be useful in these cases. Therapeutic education and clinical close follow-up must be organized.

Fig. 2 summarizes the oral therapies used in digestive oncology, the simplified pathway of tumoral proliferation and the mechanisms of action of the various oral therapies. As cytotoxic therapies are mainly mitosis inhibitors, targeted therapies such as multikinase inhibitors act on pathways related to cell proliferation, angiogenesis, and metastatic invasion.

Selection of personalized therapy. The therapeutic choice is sometimes difficult, as in some clinical situations there are no head-to-head clinical trials. As an example, in the treatment of refractory metastatic CRC, regorafenib or TAS 102 are both approved (17,25). Moreover, patient preferences, medical history and tolerance to previous medication must be taken into account.

A retrospective study of 550 Japanese patients (49) observed no difference in overall survival between patients receiving regorafenib or TAS 102. In a subgroup analysis, a significant interaction with age was observed; regorafenib treatment showed favorable survival in patients aged <65 years (HR 1.29, 95% CI 0.98-1.69); and TAS 102 showed favorable survival in patients aged >65 years (HR 0.78; 95% CI 0.59-1.03). Tolerance of side effects and adherence to treatment must be taken into account in interpretation of such retrospective results.

An observational study enrolled 469 patients treated with TAS 102 and 311 treated with regorafenib for metastatic CRC, aiming to describe real-world adherence to treatment (50). Patients treated with TAS 102 had higher compliance to treatment, better persistence and lower risk of discontinuation than patients treated with regorafenib (HR 0.76, P=0.006).

A dose optimization (ReDOS study) (26) with regorafenib could be a way to strengthen treatment continuation and lower incidence of adverse events.

Main adverse events management

Nausea and vomiting. Up to 80% of patients receiving chemotherapy experience nausea or vomiting. Preventive treatment is important and is currently used in i.v. chemotherapy; depending on the emetogenical potential of agents (high emetic risk, >90%; moderate risk, 30-90%; low risk, 10-30%; minimal risk, <10%). The ESMO guidelines recently classified oral therapies by their emetic potential, based upon a full course of therapy and not a single dose (51). For example, imatinib and temozolomide were classified as moderately emetogenic. Capecitabine, everolimus, regorafenib and sunitinib were classified as having low emetic risk, and sorafenib as having minimal risk. For low or minimal risk there is no recommendation for an anti-emetic prophylaxis (51). Metoclopramide or a setron (granisetron, odansetron) can be prescribed in the case of delayed nausea. In the case of refractory nausea or vomiting, dexamethasone and olanzapine (10 mg orally for 3 days) is available (51).

Diarrhea. Treatment-related diarrhea is described as a frequent side effect with capecitabine and tyrosine kinase inhibitors. Its severity is assessed by the number of bowel movements, a need of hospitalization and the effects on activities of self-care. In mild-to-moderate diarrhea, a simple treatment with oral hydration, dietary modifications (fibers decreased) and loperamide (4 mg to start and then 2 mg after each loose stool) is recommended. In the case of severe diarrhea hospitalization can be necessary for an i.v. hydroelectrolytic supplementation, stool bacteriological examination, discussing CT scan or endoscopic explorations. Somatostatin and budesonide have shown to be effective for refractory i.v. chemotherapy-induced diarrhea (52).

Hand and foot syndrome. Severe hand and foot syndrome, often occurring in patients treated with multikinase inhibitors or capecitabine can be painful and interfere with normal daily activities. Supportive measures must be initiated as soon as the symptoms appear. To relieve inflammation, the application of cold packs, the use of moisturizing creams, topical preparations containing vasoconstrictor (eg. phenylephrine), astringents, anesthetics or dermocorticoids can be used (53).

In hyperkeratosis, keratolytic agents such as urea-based cream are useful. Hydrocolloid or alginate dressing may be used to protect pressure points and aid healing. Treatment discontinuation should be discussed in case of toxicity≥grade 2.

Mucositis. Oral mucositis can be painful and affect nutritional intake, oral treatment intake and quality of life. Oral decontamination by brushing with a soft toothbrush, flossing and the use of sodium bicarbonate rinses are the first step in treatment (54). Pain control with the use of viscous lidocaine, which can be mixed with equal volumes of soothing covering agents such as kaopectate may provide short-term relief. Treatment of an associated candidosis infection with fluconazole can be helpful. Nutritional support and treatment discontinuation should be discussed in the case of severe mucositis.

5. Conclusions

Various oral therapies can be prescribed in digestive oncology. Classic chemotherapies such as capecitabine, TAS 102 and temozolomide are often well known by physicians, from their prescription modalities to the monitoring of the side effects. However, targeted therapies and the risk of drug or food interactions and their specific side effects are challenging. In neuroendocrine tumors as well as in stromal tumors, drug exposure spreads over an extended period of time. Therefore, dealing with side effects and drug interactions is a common occurrence and digestive oncologists should be able to know how to handle them. A multidisciplinary association with the pharmacist and a trained nurse should be developed.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

CPK was involved in the conception and design of the research, drafting and revision of the review. SD, LJP and JL were involved in acquisition and analysis of the work, and drafting of the manuscript. SC, CB and RC carried out the interpretation of the data for the review and revision of the manuscript. All authors contributed to the literature review and gathering of the data and information. All authors read and approved the final manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Patient consent for publication

Not applicable.

Competing interests

CPK, SD, LJP, JL, SC and CB declare no competing interest. RC acts as consultant or speaker for Bayer, Amgen, Novartis, Servier, Ipsen, Keocyt, AAA, Roche, and Merck.

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