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Systemic Treatment of Patients With Gastrointestinal Cancers During the COVID-19 Outbreak: COVID-19-adapted Recommendations of the National Cancer Institute of Milan

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Abstract

The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak poses a major challenge in the treatment decision-making of patients with cancer, who may be at higher risk of developing a severe and deadly SARS-CoV-2 infection compared with the general population. The health care emergency is forcing the reshaping of the daily assessment between risks and benefits expected from the administration of immune-suppressive and potentially toxic treatments.To guide our clinical decisions at the National Cancer Institute of Milan (Lombardy region, the epicenter of the outbreak in Italy), we formulated Coronavirus-adapted institutional recommendations for the systemic treatment of patients with gastrointestinal cancers. Here, we describe how our daily clinical practice has changed due to the pandemic outbreak, with the aim of providing useful suggestions for physicians that are facing the same challenges worldwide.

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Introduction

In December 2019, Chinese authorities firstly reported a cluster of cases of severe pneumonia in Wuhan (Hubei province). The newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was deemed responsible for coronavirus disease 2019 (COVID-19) and the pandemic outbreak. This highly infectious disease is usually associated with flu-like symptoms but may rapidly evolve to severe interstitial pneumonia and even death, particularly in older patients with comorbidities, including cancer. As of April 4, 2020 Italian authorities reported 124,632 SARS-CoV2 confirmed cases and 15,362 deaths, thus representing the highest number of COVID-19-related deaths in the world.[1]

A Chinese single-institution cohort study showed that patients with cancer may be at higher risk of SARS-CoV-2 infection compared with the general population,[2] and a nationwide study associated a history of cancer with higher risk of severe events, defined as intensive care unit admission, invasive ventilation, or death.[3] Additionally, because nosocomial transmission was identified in up to 41.3% of hospitalized patients,[4] hospital admissions or

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repeated clinic visits clearly represent a crucial source of contagion. On top of their disease, patients with cancer face several threats related to their frequent hospital accesses: the presence of cancer-related and treatment-related immune suppression and coexisting comorbidities.

The risk of hospital transmission of SARS-CoV-2 may be reduced, thanks to the screening of patients and staff and by minimizing face-to-face interactions.[5] Furthermore, Hanna et al provided a general framework to prioritize the use of systemic chemotherapy or radiotherapy during this global emergency, taking into account the magnitude of treatment benefit and the potential negative impact of treatment delays/interruptions on outcomes.[6] However, there is no cancer-specific recommendation yet, particularly for curable disease, on how to choose less toxic or more easy-to-administer treatments without jeopardizing survival outcomes.

The National Cancer Institute of Milan (INT) is a comprehensive cancer center located in the Lombardy region, which accounts by itself for more than a half of the COVID-19-related deaths in Italy so far. In February 2020, INT faced the challenge of profoundly reorganizing its daily routine and procedures at an unprecedented pace to maintain its patients with cancer as safe as possible from COVID-19 and, at the same time, guarantee adequate levels of care. In few weeks, our Gastrointestinal Oncology Unit has elaborated Coronavirus-adapted treatment guidelines and regimens, measures for patient information and support and procedures for dynamic up- and downscaling of clinical activities and research.

Here, we describe how our daily clinical practice has changed due to the COVID-19 outbreak, with the aim of providing useful recommendations for physicians that are facing the same challenges worldwide.

Methods

Since the beginning of the Lombardy outbreak in February 2020, a Gastrointestinal Oncology task force drafted the new Coronavirus-adapted institutional guidelines for gastrointestinal cancers. The multidisciplinary panel also included an external consultant (C.C.), member of the steering committee of the Italian Association of Medical Oncology (AIOM) Guidelines and based in a less impacted Italian region, with the aim to minimize the potential bias related to physicians' stress condition and burnout.

Treatment decisions were discussed on an individual basis, and, whenever necessary, multidisciplinary meetings were held as routinely via video or call conference. Phone screening surveying patients' conditions, symptoms, latest radiologic evaluation, and contact with potential infected subjects was carried out on a daily basis.

Table 1 summarizes our recommendations according to disease subtype.

Gastric and Gastroesophageal Cancer

For perioperative or adjuvant chemotherapy of patients with locally advanced gastric or gastroesophageal junction adenocarcinoma, the choice of multimodality treatment over surgery alone was made after careful evaluation of each individual risk-benefit profile. First, microsatellite instability (MSI) testing was performed for all patients to avoid perioperative/adjuvant treatments in those with MSI-high, R0 resectable cancers.[7] Based on a multidisciplinary team assessment, preoperative chemotherapy was recommended only for patients with age $<$ 70 years and resectable high-risk disease. Oxaliplatin-based doublets were the treatment of choice for patients with node-positive disease assessed by both fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan and endoscopic ultrasonography and for selected patients with cT3N0 tumors with adverse prognostic features (ie, diffuse histotype) or technical risks of incomplete resection (ie, gastroesophageal junction cancers). FLOT (docetaxel, oxaliplatin, and fluorouracil/leucovorin) triplet chemotherapy, which is associated with increased survival at the cost of a higher risk of toxicity,[8] was recommended only for cT4 tumors and in those cases with unacceptable risk of positive (R1/R2) tumor margins. For patients with gastroesophageal junction adenocarcinoma, the use of neoadjuvant chemoradiation was discouraged even for Siewert 1 and 2 tumors. Regarding postoperative chemotherapy, we carefully assessed the patient's health condition and nutritional status after gastrectomy, and the choice between adjuvant single-agent fluoropyrimidines (capecitabine) or CAPOX (capecitabine plus oxaliplatin) was made based on pathologic stage and individual risk of relapse.[9,10]

For patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic gastric cancer (mGC), the most commonly used first-line chemotherapy regimens are represented by combinations of fluoropyrimidines and platinums, with or without a third chemotherapy agent. Given the limited overall survival advantage provided by triplet chemotherapy at the cost of significant toxicity, doublet regimens are usually preferred in the clinical practice. Moreover, the administration of cisplatin requires protracted hydration and may cause severe vomiting, nephrotoxicity, and grade 3 to 4 neutropenia worthy of hospital admissions or intravenous supportive treatments. Several studies demonstrated the non-inferiority of oxaliplatin compared with cisplatin as part of combination regimens.[11,12] Therefore, the choice of CAPOX regimen was preferred over FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin) thanks to its 3-weekly schedule and the oral administration of fluoropyrimidine, with no need for infusion pumps and central venous catheters.[11-13] For dysphagic patients needing nutritional support, initial treatment with FOLFOX infusional regimen was shifted to CAPOX as soon as the symptoms' resolution allowed it.

For patients with HER2-positive mGC, phase II non-randomized trials of trastuzumab added to standard CAPOX demonstrated an advantageous safety profile of this chemotherapy backbone and efficacy outcomes in line with those achieved with cisplatin-based regimens in the phase III ToGA registration trial.[14-16] Therefore, we selected CAPOX-trastuzumab for 6 cycles followed by maintenance with single-agent trastuzumab as the strategy of choice.

Even if irinotecan, taxanes, or the anti-vascular endothelial growth factor receptor 2 (VEGFR-2) monoclonal antibody ramucirumab represent evidence-based second-line treatment options,[17-19] the absolute survival benefit is quite limited and should be carefully evaluated based on the relevant toxicity risk and individual patients' life expectancy.[20] The optimal candidates for

Table 1 Summary of Coronavirus-adapted Institutional Guidelines at the National Cancer Institute of Milan, Lombardy Region, Italy

Gastric and gastroesophageal cancer	
Pre (peri)-operative treatment	*MSI-high cancer and R0 resectable or age > 70 years:* Not recommended *Node-positive or cT3N0 tumors with adverse prognostic/technical features:* CAPOX *cT4 stage or high-risk of R1/R2 resection:* FLOT *CRT for gastroesophageal junction cancers (including Siewert 1-2):* Not recommended
Adjuvant	*MSI-high cancer:* Not recommended *Based on pathologic stage and individual risk of relapse:* capecitabine CAPOX
First line	*HER2-negative:* CAPOX *HER2-positive:* CAPOX + trastuzumab for 6 cycles followed by trastuzumab maintenance
Second line	Paclitaxel + ramucirumab (modified biweekly regimen: mRAINBOW) *Ramucirumab contraindicated or not available:* Three-weekly irinotecan/docetaxel
>Third line	Not recommended
Pancreatic cancer	
Pre (peri)-operative treatment	*Resectable cancer:* Upfront resection *Borderline resectable cancer:* Multidisciplinary discussion (evaluating age, ECOG PS, comorbidities, and risk factors)
Adjuvant	*ECOG PS 0, < 70 years old patients, based on pathologic stage, individual risk of relapse/toxicity, and comorbidities:* Consider modified FOLFIRINOX (consider delaying treatment up to 12 weeks after surgery).
First line	Nab-paclitaxel + gemcitabine, biweekly *BRCA-mutated disease:* Oxaliplatin-based doublets with a stop-and-go approach Olaparib maintenance only if residual grade ≥ 2 neuropathy after oxaliplatin-based induction *ECOG PS ≥ 2 patients and/or extensive comorbidities:* Consider best supportive care alone
>Second line	Only in highly selected cases, ECOG PS 0-1
Biliary tract cancers	
Adjuvant	*Based on pathologic stage, individual risk of relapse/toxicity, and comorbidities:* Capecitabine (consider delaying treatment up to 16 weeks after surgery)
First line	*ECOG PS 0-1 patients:* CAPOX
>Second line	Only in highly selected cases, ECOG PS 0-1
Hepatocellular carcinoma	
First line	*Only in ECOG PS 0-1 and Child A:* sorafenib or lenvatinib
Second line	*Only in highly selected cases:* cabozantinib or regorafenib
Colorectal cancer	
Preoperative treatment (rectal cancer)	*For cT3b and/or cN+ tumors in the lower rectum and any cT4 tumors:* Long-course capecitabine-based chemoradiation *For all other locally advanced tumors:* Short-course radiotherapy
Adjuvant	Three-weekly capecitabine-based regimen preferred *Stage III MSS tumors:* pT3 and pN1: CAPOX for 3 months pT4N1 or anyTN2: CAPOX for 6 months

Table 1 Continued

First line	*Left-sided, RAS and BRAF wild-type, MSS and HER2-negative and age < 75 years:* FOLFOX + bi-weekly anti-EGFRs *Right-sided and/or RAS mutated and age <75 years:* CAPOX + bevacizumab *BRAF mutated, right-sided/KRAS mutated with high disease burden. AND age < 70 years:* Modified FOLFOXIRI + bevacizumab *Unfit or elderly patients:* Capecitabine ± bevacizumab Strongly consider treatment holidays following 4 to 6 months induction. Capecitabine-based maintenance in case of RECIST response and aggressive disease
Second line	FOLFIRI + bevacizumab *MSI-high:* Six-weekly pembrolizumab *BRAF mutated:* Bi-weekly cetuximab plus oral encorafenib
Third line	Bi-weekly anti-EGFR agents if not used in the first-line and only for left-sided, *RAS* and *BRAF* wild-type, HER2-negative tumors. Consider best supportive care or regorafenib with alternative schedules
Anal cancer	
Curative therapy	Capecitabine-based chemoradiation or radiotherapy alone for unfit patients
Palliative therapy	Carboplatin plus paclitaxel
Advanced neuroendocrine neoplasms	
First line	*Well differentiated GEP-NETs:* SSAs *Poorly differentiated NECs:* Carboplatin plus oral etoposide
Second line	*Well/moderately differentiated pNETs:* Sunitinib *Well-differentiated small intestinal NETs:* High-dose SSAs or PRRT *Poorly differentiated NECs:* Consider best supportive care or capecitabine + temozolomide

Abbreviations: CAPOX = capecitabine and oxaliplatin; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; FLOT = docetaxel, oxaliplatin, and fluorouracil/leucovorin; FOLFIRI = folinic acid, 5-fluorouracil, and irinotecan; FOLFIRINOX = folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; FOLFOX = folinic acid, 5-fluorouracil, and oxaliplatin; FOLFOXIRI = folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan; GEP-NET = gastroenteropancreatic neuroendocrine tumor; HER2 = human epidermal growth factor receptor 2; MSI = microsatellite instable; MSS = microsatellite stable; NEC = neuroendocrine carcinoma; NET = neuroendocrine tumor; PNET = pancreatic neuroendocrine tumor; PRRT = peptide receptor radionuclide therapy; RECIST = Response Evaluation Criteria in Solid Tumors; SSAs = somatostatin analogues.

second-line therapy may be identified based on Eastern Cooperative Oncology Group performance status (ECOG PS), tumor response to first-line treatment, and a first-line treatment-free interval of at least 3 months.[21] Noteworthy, the combination of weekly paclitaxel and ramucirumab achieved an unprecedented median overall survival (OS)[22] and is frequently used in several countries as the standard second-line treatment in absence of contraindications to anti-angiogenics. We selected the modified RAINBOW (mRAINBOW) bi-weekly simplified regimen (paclitaxel 110 mg/m^2 plus ramucirumab 8 mg/kg every 2 weeks) as our standard according to the MD Anderson study.[23] Whenever ramucirumab was contraindicated or not available, second-line chemotherapy consisted of 3-weekly courses of docetaxel or irinotecan (provided pharmacogenomic testing results were available).

Pancreatic Cancer

For patients with resectable pancreatic adenocarcinoma (PAC), we recommended upfront resection. For borderline resectable disease, neoadjuvant chemotherapy was indicated only after multidisciplinary discussion and careful evaluation of age, ECOG PS, comorbidities, and risk factors. Regarding postoperative treatments, given the survival advantage of adjuvant mFOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin),[24] this triplet regimen was recommended only for patients with ECOG PS 0 and age < 70 years—a more selected patient population compared with the pivotal study. Furthermore, we chose to delay the treatment start as much as possible and up to 12 weeks after resection.

As far as unresectable or metastatic PAC is concerned, the 2 standard first-line regimens are standard-dose FOLFIRINOX[25] and nab-paclitaxel plus gemcitabine.[26] Even in the absence of a randomized comparison between the 2 options, the toxicity profile of the triplet regimen is clearly worse[27] and may represent a challenge even for fit and younger patients. Therefore, we chose nab-paclitaxel plus gemcitabine as the preferred upfront regimen, with a modified bi-weekly schedule instead of the classical 3 weeks on/1 week off schedule.[28,29] When the triplet was deemed necessary (ie, for selected patients with locally advanced or borderline resectable disease), we used the modified FOLFIRINOX schedule that is commonly used in the adjuvant setting (irinotecan dose reduced to 150 mg/m^2 and omission of the 5-fluorouracil bolus), due to better tolerability.[30] For *BRCA*-mutated disease, our standard strategy was initial oxaliplatin-based doublet chemotherapy for at least 4 months followed by treatment breaks in case of disease control (stop-and-go approach). Maintenance treatment with oral olaparib was taken into account mostly for patients who had

platinum-induced neuropathy of grade 2 or more. For patients with an ECOG PS $\geq$ 2 and/or extensive comorbidities, we strongly advised best supportive care based on a home-delivery model.

Even if no standard second-line treatment is defined yet, there is evidence on effectiveness and manageable toxicity of such regimens defined according to what was given as first-line and ECOG PS.[31-33] However, given the very poor prognosis of metastatic PAC in this extremely palliative setting, we recommended that a second-line treatment was offered only to patients with a good ECOG PS and chemosensitive disease.

Biliary Tract Cancers and Hepatocellular Carcinoma

Although the only curative treatment for biliary tract cancer (BTC) is surgery, adjuvant oral capecitabine is recommended for patients with resected BTC based on the results of the BILCAP trial.[34] However, this study was criticized due to its failure to meet the primary endpoint (OS) in the intention-to-treat population, with a relapse rate as high as 60%. Considering such issues, we decided to: (1) delay treatment start as much as possible, giving the patient time to fully recover from surgery and (2) discuss each case according to the risk-benefit profile with regard to ECOG PS, age, comorbidities, and patients' preferences.

As far as metastatic or unresectable disease is concerned, the standard initial treatment for patients with a good ECOG PS is the combination of cisplatin and gemcitabine, which achieved superior OS compared with gemcitabine alone.[35] However, the schedule of the regimen by Valle et al (on days 1 and 8 every 21 days) requires multiple accesses to the hospital and abundant hydration and may cause relevant grade 3 to 4 toxicities, including hematologic ones.

The gemcitabine-based GEMOX (gemcitabine and oxaliplatin) regimen is considered a reasonable alternative and safer option, also when considering single-day courses given every 2 weeks.[36] Furthermore, CAPOX was non-inferior to GEMOX in terms of 6-month progression-free survival (PFS) rate in a recent phase III trial, with a better toxicity profile and less frequent hospital visits.[37] Therefore, CAPOX was recommended as the first-line treatment of choice for ECOG PS 0 to 1 patients with metastatic or unresectable BTC. For patients with liver-limited unresectable disease, we discussed, in a multidisciplinary setting, the chance for locoregional therapy (eg, yttrium-90 radioembolization), when feasible.[38] For patients with an ECOG PS $\geq$ 2 and/or extensive comorbidities, we strongly advised best supportive care based on a home-delivery model.

Regarding second-line treatment, the same considerations expressed for patients with PAC were valid.[39] For *IDH1*-mutated or *FGFR2* translocated intrahepatic cholangiocarcinoma, patients' access to orally administered selective inhibitors was recommended, whenever feasible.[40,41]

For patients with advanced and unresectable hepatocellular carcinoma (HCC), oral treatments were prescribed via web-based telemedicine and continued until symptomatic deterioration or radiologic progression, whichever occurred first. The tyrosine kinase inhibitors sorafenib or lenvatinib[42] were recommended in the first-line setting only in patients with ECOG PS 0 or 1 and Child-Pugh score A. Second-line treatment with cabozantinib[43] or regorafenib[44] was recommended only in highly selected patients with good prognostic features. Enrollment in clinical trials with immunotherapy agents was discouraged.

Colorectal Cancer

For patients undergoing adjuvant treatment for colon cancer, 3-weekly capecitabine-based regimens were preferred over biweekly infusional 5-fluoruracil-based schedules in order to limit the accesses to hospital. When oxaliplatin was indicated (mainly in the case of stage III MSS tumors), the limitation of treatment duration to 3 months was highly recommended in stage III low-risk (pT3 and pN1) tumors.[45]

In the same perspective, for locally advanced rectal cancer, the indication to neoadjuvant capecitabine-based long-course chemoradiation was carefully pondered and mainly applied to tumors arising in the lower rectum and staged $\geq$ cT3b and/or node-positive, or for cT4 cancers located in any part of the rectum. Short-course radiotherapy was preferred in all other cases of locally advanced rectal cancer.

In the metastatic setting, the impact of the first-line therapy is the most relevant, both on patients' long-term outcome and on the potential subsequent steps of treatment, including surgical and other locoregional approaches. The relative additional benefit from second and further lines of therapy is much less important, and their intent is definitely palliative in most of cases.

Therefore, when choosing of the "best" upfront treatment, every effort was made to limit toxicity while offering the most efficacious therapy to each individual patient. In patients unfit for a combination of chemotherapy, the opportunity to start a first-line regimen was properly evaluated and discussed, with capecitabine $\pm$ bevacizumab as the preferred option.

When an anti-epidermal growth factor receptor (EGFR) monoclonal antibody was chosen as first-line targeted agent (mainly in fit patients with a left-sided, *RAS* and *BRAF* wild-type, MSS, and HER2-negative tumors), it was combined with a 5-fluorouracil-based doublet. In the case of cetuximab, we used the bi-weekly schedule, now widely adopted in clinical trials and in the daily practice because of its equivalent efficacy and safety compared with the weekly schedule.[46]

With regard to the choice of the upfront chemotherapy, in fit patients, the triplet FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan) provides survival benefit as compared with both oxaliplatin- and irinotecan-based doublets at the price of increased gastrointestinal and hematologic toxicities.[47] The choice of this intensive and highly active regimen was suggested only for patients with aggressive cancers, such as those with *BRAF* mutation, or with right-sided primary tumor/*KRAS* mutation and high tumor burden, or whenever conversion to liver surgery was foreseen in borderline resectable liver metastases. Because in patients aged 70 to 75 years the risk of grade 3 and 4 diarrhea and neutropenia is increased, we carefully weighted the use of the triplet in this age subgroup.[48] To minimize the risk of neutropenia, the use of granulocyte-colony stimulating factor (G-CSF) as primary prophylaxis, which is not routinely recommended, was considered, as well as modified schedules of FOLFOXIRI, with reduced doses of 5-fluorouracil (2400 mg/m^2 instead of 3200 mg/m^2) and irinotecan (150 mg/m^2 instead of 165 mg/m^2).[46]

If an oxaliplatin-based doublet plus bevacizumab was chosen as an upfront option, the use of capecitabine instead of 5-fluorouracil was preferred to reduce the frequency of in-hospital infusional procedures.[49]

The duration of the induction therapy was limited to 4 to 6 months. If locoregional treatments were not pursuable, de-intensifying the treatment to maintenance with fluoropyrimidine and the biologic agent used during induction is generally recommended. However, because the actual benefit of maintenance with fluoropyrimidine and bevacizumab as compared with treatment holiday is modest,[50] whereas bevacizumab alone does not provide any advantage,[51] we suggested treatment breaks as a reasonable clinical option. With regard to anti-EGFRs, although continuing 5-fluorouracil with panitumumab improves PFS when compared with panitumumab alone,[52] the magnitude of benefit from maintenance as compared with treatment holiday has not been assessed yet. In general, in an effort to adequately assess the cost/effectiveness balance of each treatment choice, the opportunity to administer maintenance therapies was limited to patients with high tumor burden (when a rapid disease progression may deeply impair subsequent chances of therapy) and/or those who experienced objective response rather than disease stabilization in previous disease assessments.

With regard to second-line chemotherapy, minimizing toxicity was our primary aim, given the outbreak situation. As a consequence, if the inhibition of angiogenesis beyond progression was the preferred strategy, bevacizumab was chosen over aflibercept and ramucirumab owing to the increased incidence of gastrointestinal and hematologic chemotherapy-related adverse events observed with aflibercept[53] and the higher occurrence of neutropenia with ramucirumab.[54] In patients bearing *BRAF V600E*-mutated tumors, the combination of cetuximab and encorafenib was considered a valid option with manageable toxicity profile in the second and third line, based on results of the phase III BEACON trial.[55] Though in the absence of data in this specific setting, the bi-weekly schedule of cetuximab appears safe and therefore preferable.

Finally, in the patients who were chemorefractory, we carefully evaluated the option of best supportive care based on the assessment of individual patients' life expectancy[56] and comorbidities. Two guideline-recommended third-line oral therapies are available: the multikinase inhibitor regorafenib is associated with fatigue, hand and foot skin reaction, skin rash, hypertension, and aspartate aminotransferase/alanine aminotransferase elevation as the most frequent adverse events, whereas neutropenia and anaemia more frequently occur with the novel fluoropyrimidine trifluridine/tipiracil. Therefore, though the safety profile of trifluridine/tipiracil seems to affect patients' quality of life much less than regorafenib and thus its use is more frequently favored, in the frame of the COVID-19 outbreak, avoiding neutropenia and its consequences was regarded as of paramount importance, thus leading to widen the potential indications for the use of regorafenib. The registrative schedule (160 mg/daily 3 weeks on/1 week off) was not recommended, although other schedules of dose escalation, developed to reduce the toxicity burden, were implemented.[57]

Out of the frame of clinical trials, therapies supported by low levels of evidence (ie, anti-EGFR rechallenge or chemotherapy reintroduction, anti-HER2 strategies, alkylating agents in *MGMT* methylated tumors) were not administered.

Anal Cancer

Concomitant chemoradiation using 5-fluorouracil plus mitomycin is the standard approach for most patients with localized anal squamous cell carcinoma (ASCC) and is able to achieve long-term disease cure in up to 82% of patients. Even if randomized trials showed the superiority of chemoradiation over radiotherapy alone in terms of disease-free survival, local control, and colostomy-free survival, no OS differences were observed.[58] Thus, we considered radiation treatment alone in patients with lower risk of local relapse, such as those with cT1-2N0 disease. For patients with locally advanced disease, we weighed up the use of oral capecitabine as a radiosensitizer as a reasonable treatment alternative to infusional 5-fluorouracil.[59]

Finally, HIV-associated patients with ASCC are at higher risk of developing toxicities from chemoradiotherapy,[60] and, due to their comorbidities, have augmented risk of severe COVID-19. Hence, we carefully assessed a de-escalation of anticancer treatment in this peculiar and frail patient category, whereas patients not able to receive effective highly active antiretroviral therapy (HAART) or those with CD4+ cell counts less than 200/μL were treated with radiotherapy alone.

In the setting of metastatic disease, the combination of cisplatin plus 5-fluorouracil is regarded as the treatment of choice.[61] Nevertheless, the recent phase II InterAACT randomized trial of cisplatin plus 5-fluorouracil versus reduced-dose carboplatin plus weekly paclitaxel showed superior survival outcomes and reduced treatment-related toxicity in favor of the experimental arm.[62] Based on these data, the combination of carboplatin/paclitaxel has entered the clinical practice and was recommended at our hospital.

Gastroenteropancreatic Neuroendocrine Neoplasms

We recommended the use of somatostatin analogues (SSAs) as one of the mainstay treatments of well-differentiated gastoenteropancreatic neuroendocrine tumors (NETs).[63] Both octreotide and lanreotide have very low toxicity and may be administered at patients' homes. Notably, because lanreotide does not require reconstitution, it can be injected by a trained individual (either the patient or a trusted "partner") without concern of variability in drug preparation. High-dose SSAs were used after progression on standard doses. For small intestinal NETs, we recommended the standard second-line treatment with peptide receptor radionuclide therapy (PRRT) only after a careful patients' selection based on high ^{68}Ga-DOTATATE-PET-TC uptake, high tumor burden, or the presence of tumor-related symptoms, adequate bone marrow function, young age, and good ECOG PS. Of note, severe lymphopenia occurred in less than 10% of patients in the pivotal phase III study, and PRRT requires a short hospitalization every 8 weeks.[64]

In patients with advanced progressive G1-2 pancreatic NETs (pNETs), we chose to administer further therapy in case of symptomatic progression and to prefer sunitinib over everolimus due to the lower risk of immune suppression and interstitial pneumonia.[65,66]

For patients with advanced poorly differentiated gastroenteropancreatic neuroendocrine carcinomas (NEC G3-4), etoposide-platinum combinations are the most commonly used upfront regimens and are able to achieve high tumor response rates (30%-50%)[63,67] and potential symptom relief. Although the quality of the available evidence is relatively low, the Nordic NEC trial did not

show differences in terms of efficacy between cisplatin- versus carboplatin-based regimens. Therefore, we chose the short infusion of carboplatin plus 3 days of oral etoposide with granulocyte-stimulating factor support for up to 4 to 6 cycles. Second-line chemotherapy after platinum-containing regimens has not been established nor compared with best supportive care. Even if oxaliplatin- and irinotecan-based doublets showed some activity, temozolomide-based regimens showed a promising response rate.[68-70] Therefore, we chose CAPTEM (capecitabine plus temozolomide) as our reference second-line regimen to be adopted for fit patients with chemosensitive disease, thanks to its 4-weekly schedule and fully oral administration.

Microsatellite Instability-high Advanced Solid Tumors

"Universal" MSI testing was performed for all patients with advanced gastrointestinal adenocarcinomas, and, after failure of at least 1 prior treatment line, those with MSI-high cancers were treated as early as possible with off-label use of immune checkpoint inhibitors.[71] Our treatment of choice was the 6-weekly schedule of pembrolizumab at the flat dose of 400 mg, which was recently approved by the United States Food and Drug Administration (FDA) for several indications.[72]

Pharmacogenetic Testing

Pharmacogenetic testing for DYPD and UGT1A1 genotypes was recommended in all patients to personalize the starting dose of fluoropyrimidines and irinotecan, respectively, thus reducing the risk of hematologic and gastrointestinal toxicities.[73]

Maintenance of Central Venous Catheters

Routine maintenance of central venous catheters (CVCs), as well as the potential complication of such devices, are among the most common reasons for hospital accesses, particularly for patients with gastrointestinal cancers. Even if the standard schedule recommended by several guidelines is a 4-week locking with saline solution plus or minus heparin, delayed schedules (every 8 or 12 weeks) did not increase the risk of complications in 2 studies.[74,75] Based on these data, despite the absence of randomised trials, the delayed schedule of CVCs maintenance was recommended at our hospital.

Thromboprophylaxis

COVID-19 has been associated with a hypercoagulable state due to cytokine release syndrome,[76] together with prolonged bed rest and invasive ventilation, which may result in a higher risk of thromboembolic events and disseminated intravascular coagulation. Treatment with low molecular weight heparin (LWMH), namely enoxaparin administered at therapeutic dosages (1 mg/kg twice a day), has shown initial evidence of reducing mortality in hospitalized patients with COVID-19 and is recommended as a support treatment in these cases.

Also, it is well-recognized that patients with cancer are at major risk of thromboembolic events.[77] Of note, patients with gastrointestinal malignancies, especially advanced gastric and pancreatic cancers, are at the highest risk, so that thromboprophylaxis is almost universally recommended in these patients when an anticancer treatment is initiated.

Given these considerations, we recommended proper thromboprophylaxis for patients with advanced gastrointestinal cancers. As these patients are also at higher risk for bleeding complications,[78] LMWH should be considered as the preferred agent over direct oral anticoagulants in this phase.

Conclusions

The current COVID-19 pandemic represents an unprecedented challenge to our health care systems. As the Gastrointestinal Oncology Unit of a referral comprehensive cancer center, we were faced with the need of changing our day-by-day clinical practice to cope with the pandemic. Our adaption of standard-of-care treatment regimens was guided mainly by 2 needs: (1) to minimize the number of hospital visits and hospitalizations, and (2) to prevent anticancer treatment-induced complications of COVID-19. COVID-19 created a reality where we needed to decide almost immediately on what is important and what is of less importance, instead of making very careful decisions based on large trials and thoughtful discussions as we, like most oncologists, are used to doing. Therefore, even if we tried to set up a rigorous method, inevitably, most measures are based on educated assumptions and expert opinions, influenced or supported by extrapolated information.

Despite their limits, we hope that our guidelines might be of interest for gastrointestinal oncologists who are now beginning to face the outbreak all over the world.

Disclosure

F.Pi. received honoraria for speaker activities and participation in advisory boards from Sanofi SA, Amgen, Inc, Bayer AG, Merck-Serono, Roche, and Servier Laboratories. F.M. received honoraria from Servier Laboratories. M.N. received honoraria from EMD Serono. C.C. received honoraria for speaker activities and participation in advisory boards from Roche, Amgen, Inc, Bayer AG, and Servier Laboratories and research grants from Merck-Serono. S.P. received honoraria from Ipsen, Novartis, AAA, Pfizer, Italfarmaco. F.d.B. received honoraria for speaker activities and participation in advisory boards from Amgen, Inc, Roche, and Novartis International AG, EMD Serono. M.D.B. received honoraria for speaker activities and participation in advisory boards from Amgen, Inc, Roche, Eli Lilly and Company, Servier Laboratories. Incyte Corp, and Celgene Corporation. All other authors state that they have no conflicts of interest.

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