Piotr J Wysocki[1], Łukasz Kwinta[1], Paweł Potocki[1], Kamil Konopka[1], Joanna Streb[1], Marek Z Wojtukiewicz[2], Barbara Radecka[3, 4], Piotr Tomczak[5], Michał Jarząb[6], Andrzej Kawecki[7], Maciej Krzakowski[7]

[1]Department of Oncology, Jagiellonian University *Collegium Medicum*, Krakow, Poland
[2]Department of Oncology, Medical University of Bialystok, Cancer Center of Bialystok, Poland
[3]Opole Cancer Center T. Koszarowski in Opole, Poland
[4]Institute of Medical Sciences, University of Opole, Poland
[5]Department of Oncology, Poznan University of Medical Sciences, Poland
[6]Maria Skłodowska-Curie National Research Institute of Oncology, Branch in Gliwice, Poland
[7]Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Systemic treatment of patients with solid tumors during the COVID-19 (SARS-CoV-2) pandemic — comprehensive recommendations of the Polish Society of Clinical Oncology

Introduction

The COVID-19 (SARS-CoV-2) pandemic has become a reality and there is an increasing number of people infected and dead from COVID-19 day by day in Europe. At the time of publication of this study, there were already one million new cases and over 50,000 deaths reported worldwide, and 2,700 and 51 in Poland, respectively [1]. The rapidly increasing burden on healthcare systems may soon be unbearable even for the best organized and funded ones. There is no doubt that in Poland, similarly to all countries, there are many unknowns regarding the duration of the pandemic, the dynamics of the increase in the number of patients requiring hospitalization or intensive care and the possibility of organizational support of rapidly growing health care needs. Over the past month, many hospitals in our country have been turned into so-called uniform infectious hospitals, being de facto closed for patients with diseases other than COVID-19. More and more cancer centers and units are limiting their activities due to staff infections or mandatory quarantine. Unfortunately, this situation leads to a growing problem of limited or complete lack of access to oncological treatment. For many patients diagnosed with malignant diseases, such a situation of indefinite duration may be tantamount to taking away chances for cure or a sharp deterioration in prognosis. There is no doubt that many patients without systemic anticancer treatment will have much worse prognosis than the vast majority of people infected with SARS-CoV-2. Cancer patients require special measures to protect them from infection and to establish diagnose early because the combination of both diseases is particularly unfavorable, not only due to the risk of infection-related death, but also considering, how difficulty is oncological treatment of a SARS-CoV-2 positive individual for the patients, as well as, healthcare system.

In response to the current situation and to safeguard the quality and continuity of therapy for cancer patients, the Polish Society of Clinical Oncology (PTOK, Polskie Towarzystwo Onkologii Klinicznej) has developed preliminary recommendations for oncologists [2]. Due to the huge number of questions and requests for more detailed recommendations regarding specific clinical situations, PTOK has developed specific therapeutic recommendations. We would like to highlight that

Address for correspondence:

Prof. dr hab. n. med. Piotr J. Wysocki
Katedra i Klinika Onkologii, Uniwersytet Jagielloński — *Collegium Medicum*, Kraków
e-mail: piotr.wysocki@uj.edu.pl

Translation: dr n. med. Dariusz Stencel

Oncology in Clinical Practice 2020, Vol. 16, No. 2, 41–51
DOI: 10.5603/OCP.2020.0012

ISSN 2450–1654

this study does not apply to haemato-oncological and pediatric patients for whom the development of specific treatment recommendations is the responsibility of relevant societies.

COVID-19 in adults with solid tumors

It is widely known that elderly people with comorbidities represent the population at highest risk of complications and death due to SARS-CoV-2 infection [3]. Since the majority (> 60%) of cancer are diagnosed after the age of 65, and in Poland currently there are about a million people diagnosed with cancer (including a large group undergoing active treatment), there is no doubt that this is a special risk population. Available information on the course of COVID-19 in cancer patients is very limited and based on 2 publications including a total of 46 patients [4, 5]. In the most recent publication Liang et al. analyzed the data of 1590 patients with COVID-19 and 18 (1%) patients in the group had a history of cancer; this percentage was over 3 times higher than in the general Chinese population (0.29%). The majority of patients included in the analysis were people during post-treatment follow-up, while 6 patients underwent active systemic therapy (2 — targeted therapy of lung cancer, 2 — chemotherapy of lung cancer, 1 — immunotherapy of clear cell carcinoma, 1 — complementary systemic treatment of breast cancer of non-specified type). Serious complications associated with COVID-19 were observed much more frequently in the cancer group than in the general population (39% *vs.* 8%), however, cancer patients were older (mean age — 63.1 *vs.* 48.7 years) and were more often smokers (22% against 7%). In lung cancer patients who underwent chemotherapy or surgery within a month before the diagnosis of COVID-19, serious complications were more frequent than in patients during long-term follow-up (75% *vs.* 43% respectively). Based on logistic regression model it was shown that the risk of serious complications of COVID-19 was greater for people with positive oncological history (OR = 5.39) than with chronic obstructive pulmonary disease (COPD; OR = 3.39), diabetes (OR = 2.2) and hypertension (OR = 1.87). Zhang et al. analyzed a group of 28 patients with solid tumors diagnosed with COVID-19 and treated in three hospitals in Wuhan. The most common cancers in the analyzed population were lung cancer (25%), esophageal cancer (14.3%) and breast cancer (10.7%), and every third patient had stage IV disease. All patients had previous systemic treatment and 21% of them received therapy within 14 days prior to COVID-19 diagnosis (11% chemotherapy, 7% targeted therapy, 4% radiotherapy, 4% immunotherapy). In most patients, COVID-19 symptoms appeared while at home, and in 29% of patients this diagnosis was made during hospitalization. The most common symptoms were fever and cough (> 80% of patients). Severe complications of COVID-19 were observed in the majority (70%) of patients with generalized cancer and in 44% of patients with stage I–III. COVID-19 mortality in the analyzed patient population was 28.6%, which is almost 10 times higher than in the general Chinese population [6]. Multifactorial analysis indicated a four times higher risk of serious complications in patients who underwent oncological treatment within 14 days before the diagnosis of COVID-19 (HR = 4.079; 95% CI 1.086–15.332) [5].

As available literature is still scarce, it is difficult to draw unequivocal conclusions about the risk of severe course of COVID-19 in patients with cancer. However, it seems that higher risk group includes patients with generalized cancer during active oncological treatment. Nevertheless, it is difficult to say whether the location of the cancer, disease stage, or the type of anti-cancer treatment used is more important. In Liang et al. analysis there were no complications observed in the only patient (52 years) treated for breast cancer or in 3 patients treated for lung cancer (patients aged 55 and 58 years undergoing targeted therapy; 47-year-old patient undergoing chemotherapy). On the other hand, serious complications were observed in a 63-year-old patient receiving palliative chemotherapy for lung cancer and, surprisingly, in a 58-year-old patient undergoing immunotherapy for clear cell carcinoma [4].

Very limited scientific data does not allow to draw definitive conclusions regarding the principles of management in patients diagnosed with cancer in the context of the SARS-CoV-2 infection risk. There is no doubt, however, that the age of the patients, comorbidities, and anti-cancer treatment may increase the risk of serious complications and death during COVID-19.

Therefore, depending on the general condition of the patient, the nature of the planned or ongoing anti-cancer treatment and the clinical stage of disease, the principles of management during the SARS-CoV-2 pandemic should be differentiated.

Recommendations for systemic oncological treatment

Systemic treatment of cancer patients may be either radical (preoperative or postoperative treatment, chemotherapy alone in the case of chemo-sensitive tumors, chemotherapy in combination with irradiation) or palliative. We believe that it is essential to strive to maintain the recommended intensity of radical treatment. Each time, if it is not possible to continue the systemic treatment already introduced with a radical intention, the patient must be urgently transferred to

another functioning clinical oncology center in a given province in order to continue treatment. The list of such centers is available through voivodship clinical oncology consultants. In case of palliative therapy, care should be taken not to remarkably deteriorate the patient's chances of maintaining disease control, while reducing the exposure to infectious agents; achieving this goal may require modification of the regimen, dosage or the drug used.

Preoperative treatment

The decision of a multidisciplinary board to initiate preoperative treatment always takes into account the planned date of surgery. For patients with breast cancer, when the goal of preoperative treatment is to perform breast-conserving surgery (especially in postmenopausal women [7]), it is possible to consider postponing the start of preoperative chemotherapy for several weeks and more widely use preoperative hormone therapy (postmenopausal patients). In patients with primarily operable tumors in whom preoperative chemotherapy has no proven effect on improving prognosis, surgery should be performed first, followed by systemic adjuvant treatment. On the other hand, in all patients with significant local advancement of the disease, when the goal of neoadjuvant treatment is to achieve the possibility of surgery or radical radiation therapy, the procedure should be started without undue delay. In patients undergoing preoperative chemotherapy, when significant (many weeks) delay of surgery is expected, it is recommended to consider 1–2 additional cycles of chemotherapy according to the last used regimen. It should be ensured that there are no absolute contraindications for continuing chemotherapy (current tolerance, cumulative toxicity). If there are any doubts related to the possible "extension" of preoperative treatment, this situation could be consulted with team of consultants from the Department of Oncology, JU-CM, Krakow (chemioterapia@su.krakow.pl). Proposals for the management of pre/perioperative treatment are presented in Table 1.

Postoperative treatment

In majority of patients the initiation of systemic adjuvant treatment can be postponed and started within 2 (in justified cases — 3) months after surgery. The exception are patients with very high risk of recurrence (e.g. significant local stage, triple-negative breast cancer). In justified clinical situations, adjuvant treatment may be replaced by close observation. In patients with hormone-dependent breast cancer (especially with low malignancy grade [G1] and/or low proliferative index [Ki67 < 30%] or with types of better prognosis), where the potential benefit of chemotherapy may be small, adjuvant hormone therapy alone should be considered. If there any some doubts regarding the possibility/legitimacy of resigning from complementary chemotherapy, it is possible to consult patients with the consulting team of the Department of Oncology, JU-CM in Krakow (chemioterapia@su.krakow.pl). Proposals for modification of adjuvant treatment are included in Table 1.

Palliative treatment

Unlike therapy with radical intention, palliative systemic treatment, especially in the later lines, commonly based on less powerful evidence from large randomized clinical trials or meta-analyses. This treatment consists mainly of available in a given indication and active cytotoxic drugs used alone or in combination. In most cases, the way of conducting long-term, multi-stage palliative treatment is based on available literature data with relatively low scientific credibility and the own experience of individual oncological centers. As the duration and extent of the SARS-CoV-2 pandemic are indefinite, there is impossible to predict how long the implementation of exceptional rules for managing cancer patients will be necessary. In this context, the most questions regarding optimal management regard patients requiring chronic cancer therapy. There is no doubt that long-term suspension of systemic treatment increases the risk of disease progression, which may result in a significant deterioration of performance status and functional capacity of organs. It is therefore important to be aware that the long-term deterioration of oncological care during a pandemic can significantly worsen patients prognosis, to an unpredictable extent.

For the above reasons, PTOK's statement regarding the modification of palliative treatment, in the situation of complete uncertainty as to the scale and duration of the epidemic threat, is an attempt to find optimal solutions that allow in the several months to ensure the maximum possible safety of the patient and disease control.

Proposed modifications of systemic treatment with palliative intention

— Chemotherapy
- asymptomatic patients with good disease control and no risk of organ "crisis" — the possibility of discontinuing chemotherapy ("therapeutic holidays"), reducing the intensity of therapy (extending the intervals between courses by 50–100%) or implementing systemic treatment using available oral drugs (including metronomically used) should be considered;
- patients with deep or long-lasting remission during maintenance chemotherapy — periodic discontinuation of treatment should be considered;

Table 1. Modification of systemic therapy regimens in radical treatment

	Management options	Comment
Esophageal cancer	Perioperative treatment	
	Preferred CROSS protocol without modification (5 cycles of PXL 50 mg/m^2 + CBDCA AUC 2; all cycles q1w) — least exposure to other patients [8] For adenocarcinomas of the lower esophagus consider perioperative chemotherapy without radiation (as in gastric cancer)	CROSS protocol: a total of 5 + 23 RT fractions For comparison, the PF scheme is associated with greater exposure to contact with other patients. PF scheme: a total of 8–10 days of inpatient chemotherapy + 23–28 RT fractions
Gastric cancer	Perioperative treatment	
	FLOT (4 cycles before and after surgery: DXL 50 mg/m^2; OXA 85 mg/m^2; leucovorin 200 mg/m^2; 5-FU 2600 mg/m^2) q2w — preferred option CAPOX (3 cycles before and after surgery: OXA 85 mg/m^2; capecitabine 2000 mg/m^2 d1–14 or 1330 mg/m^2 d1–21)	FLOT regimen: a total of 16 days of inpatient chemotherapy — the preferred option with higher efficiency (the possibility of halving the length of hospitalization by using a home infusion device for long 5-FU infusions) CAPOX regimen: a total of 6 outpatient chemotherapy — a less effective option, dedicated to patients with reduced performance status, to consider in patients with good performance status when no hospital beds and infusors are available and there is no possibility to redirect the patient to another center No data on the efficacy of the FLOT regimen equivalent with capecitabine (only data on acceptable safety and activity in metastatic disease in phase I and phase II studies) — such modification is not recommended [9] Consider a larger number of cycles in the preoperative period at the expense of the postoperative (e.g. 6 × FLOT → resection → 2 × FLOT) —- with the option of giving the entire treatment before surgery when a timely operation is not possible
Pancreatic cancer	Adjuvant chemotherapy	
	mFOLFIRINOX (12 cycles IRI 150 mg/m^2; OXA 85 mg/m^2; leucovorin 400 mg/m^2; 5-FU 2400 mg/m^2) q2w — preferred option — keep the assumed dosage intensity [10] Gemcitabine (1000 mg/m^2) ± capecitabine (1650 mg/m^2) d1, 8 every 21 days	mFOLFIRINOX is the regimen of the highest effectiveness, preferred in patients in good performance status (PS) (it is possible to halve the length of hospitalization by using a home infusors device for long 5-FU infusions) GEM-CAP regimen is the second choice option in patients in good PS when no hospital beds and infusors are available and there is no possibility to redirect the patient to another center In 2 retrospective studies, the benefit of adjuvant therapy was still shown despite its implementation > 12 weeks after resection [11, 12] consider delaying the start of adjuvant treatment for 4 months after resection, especially in patients with slow recovery
HCC	Non-surgical treatment	
	Embolization of the hepatic artery alone seems no less effective than chemoembolization or radioembolization — an option when appropriate preparations are not available [13]	If definitive treatment (resection, embolization) is not available during the epidemic — sorafenib (400 mg bid) as a bridging option, preventing progression to the resumption of planned surgeries
Bile duct cancer	Adjuvant chemotherapy	
	Capecitabine (8 cycles 2500 mg/m^2; d1–14; q3w) — in case of good tolerance of the first 2 cycles — option of dispensing the medicine for 2–3 cycles and tolerance control via telemedicine	In patients with abnormal kidney function (CrCl 50–30 mL/min) — the capecitabine dose must be reduced to 75%, for CrCl < 30 mL/min — do not use capecitabine

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Table 1. cont. Modification of systemic therapy regimens in radical treatment

	Management options	Comment
Colon cancer	Adjuvant chemotherapy	
	Shift from the Mayo regimen (5-FU bolus) to capecitabine, also in combination with radiotherapy in rectal cancer [14]. It is possible to dispense the medicine for the entire 5 weeks at once in case of combined radiochemotherapy Do not use radiochemotherapy with oxaliplatin in rectal cancer. This is more toxic and its beneficial effect on OS has not been proven [15] Adjuvant chemotherapy with capecitabine (8 cycles 2500 mg/m^2; d1–14; q3w) — in case of good tolerance of the first 2 cycles — option of dispensing the medicine for 2–3 cycles and tolerance control via telemedicine In patients pT3 N1 consider only four XELOX cycles [16, 17]	The Mayo regimen is more toxic and generates more visits than treatment with capecitabine Serious complications will affect no more than 20% of patients taking capecitabine [18] In the stage, II consider only observation, except the patients for extremely poor prognosis (T4N0) In patients with abnormal kidney function (CrCl 50–30 mL/min) — the capecitabine dose must be reduced to 75%, for CrCl < 30 mL/min — do not use capecitabine
Breast cancer	Adjuvant chemotherapy	
	Luminal HER2-negative • intermediate risk — 4 × TC (docetaxel 75 mg/m^2 + cyclophosphamide 600 mg/m^2* q3w) [19, 20] • high risk [21, 22] — **4 × ddAC** (q2w) → 4 × docetaxel 75–100 mg/m^2* (q3w)** — 4 × docetaxel 75–100 mg/m^2* (q3w) → 4 × ddAC** (q2w) HER2-positive • **6 × TCH (docetaxel 75 mg/m^2 + carboplatin AUC6 + trastuzumab)* q3w** [23] • 4 × ddAC** (q2w) → 4 × docetaxel 75–100 mg/m^2* + trastuzumab (q3w) [22, 24] Triple-negative breast cancer (TNBC) • **4 × ddAC** (q2w) → 12 × paclitaxel 80 mg/m^2* (q1w)***** [22, 25]	PREDICT tool (https://breast.predict.nhs.uk/) allows you to estimate the benefit of chemotherapy in the context of overall survival. Considering the benefit against the risk of distant complications, it seems that the benefit up to 3–4 percentage point (p.p.) does not justify the use of chemotherapy, in the case of intermediate risk the benefit is usually 4–6 p.p., and at high risk the estimated benefit of chemotherapy exceeds 7 p.p. For patients with pN0–pN1 stage with a complex tumor phenotype (especially G2, with low or medium hormone sensitivity, borderline Ki67 10–40% or an unusual phenotype, e.g. G1 with high Ki67) optimal risk estimation is obtained using the Magee calculator (https://path.upmc.edu/onlineTools/MageeEquations.html). It captures the percentage of Ki67 in tumor meshwork, the degree of differentiation with the score breakdown to nuclear pleomorphism, mitotic index and tubular structure (3–9 points, where 3–5 points correspond to G1, 6–7 points corresponds to G2, 8–9 points corresponds G3, Nottingham system according to Scarff-Bloom-Richardson modified by Elston-Ellis). Magee allows an approximate estimation of the Recurrence Score, which can be obtained using the Oncotype DX genomic test. In case of values < 11 points patients can be safely withdrawn from chemotherapy. In turn, the result > 25 points indicate high risk and is an indication for chemotherapy Patients with ≥ pN2 stage — always belong to the highrisk group and must receive chemotherapy For all triple-negative and high-risk HER2-positive and HER2-negative cancers (≥ pN2), adjuvant chemotherapy should be started within 30 days of surgery Adjuvant treatment regimens recommended for use in preoperative chemotherapy are marked in bold In case of high-risk, HER2-positive breast cancer adding pertuzumab to preoperative treatment is recommended If paclitaxel 80 mg/m^2 cannot be used weekly, docetaxel 100 mg/m^2 every 3 weeks should be given (+ long-acting growth factor [granulocyte-colony stimulating factor, G-CSF]) The adding of carboplatin to standard preoperative chemotherapy in patients with triple-negative breast cancer increases the likelihood of a pathological complete response (pCR) regardless of harbouring *BRCA1/2* mutation. However, this approach increases the toxicity of chemotherapy and should be reserved only for patients with significant local advancement

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Table 1. cont. Modification of systemic therapy regimens in radical treatment

Lung cancer	Adjuvant chemotherapy	
	Modified regimen PN: cisplatin 75–80 mg/m^2 + vinorelbine 25–30 mg/m^2 d1 + vinorelbine (tab) 60 mg/m^2 d8 — q3w [26] Sequential radiochemotherapy (locally advanced stage) wit regimen PN: cisplatin 75–80 mg/m^2 + vinorelbine 25–30 mg/m^2 d1 + vinorelbine (tab) 60 mg/m^2 d8 — q3w	In case of contraindications to the use of cisplatin as part of adjuvant postoperative chemotherapy, replacement by carboplatin is not recommended and patient should be only closely monitored. No literature data support any benefit of carboplatin in the adjuvant setting in patients with non-small cell lung cancer Vinorelbine tablets can be dispensed on day 1
Gynecological cancers	Preoperative treatment	
	There are no data on the possibility to modify the recommended adjuvant treatment regimens in ovarian and endometrial cancer	
Bladder cancer	Pre- or postoperative treatment	
	4 AMVAC courses — methotrexate 30 mg/m^2, vinblastine 3 mg/m^2, doxorubicin 30 mg/m^2 cisplatin 70 mg/m^2 (4-hours infusion)** d1 — cycle repeated every 14 days [27]	AMVAC chemotherapy (accelerated MVAC) reserved for patients in good general condition (so-called fit for chemotherapy). Preferred preoperative treatment. In case of any doubts regarding the possibility of using postoperative chemotherapy — leave patients under observation
Upper urinary tract cancer	Adjuvant chemotherapy	
	4 courses with cisplatin 70 mg/m^2 + gemcitabine 1000 mg/m^2 d1, 8 every 21 days	In patients with GFR ≥ 30 and < 50 mL/min — carboplatin may be used [28] In case of any doubts regarding the possibility of administering full 4 courses — leave patients under observation If there is a need to extend the intervals between courses — the treatment should be discontinued [28]

*Short-acting growth factor (G-CSF); **long-acting growth factor (G-CSF); q1w — every week; q2w — every 2 weeks; q3w — every 3 weeks; bid — 2 times a day

- patients requiring maintenance of continuous systemic treatment (organ "crisis" threat, symptoms, recently started treatment) receiving chemotherapy based on regimens administered at 3-week intervals — treatment should be continued with the chosen regimen;
- patients receiving weekly regimens — it is recommended to modify to 2- or 3-weekly regimens (increase the dose of the drug) or to modify to doublet regimen used every 2–3 weeks. Examples of weekly regimens modifications are presented in Table 2;
- In selected patients, with satisfactory tolerability and efficacy of oral chemotherapy, drugs can be dispensed on more than one treatment cycle. The prerequisite for this is the possibilit to perform adequate blood tests in the district outpatient clinic, and phone verification of results and subjective tolerance of therapy at the beginning of each course.

— Molecularly targeted treatment
  - patients taking oral molecularly targeted drugs with good previous treatment tolerance — dispensing medication for a maximum of 6 months provided that they maintain regular remote contact with the attending physician and that there is the possibility of blood tests at the place of residence;
  - patients receiving intravenous molecularly targeted drugs (mainly monoclonal antibodies) — the need to maintain therapy with the possibility of reducing its intensity according to Table 3.

— Hormonotherapy — it is necessary to continue hormone therapy in accordance with standards, it is not recommended to stop or delay the administration of drugs regardless of the form of their use (oral, intramuscular, subcutaneous). In the case of gonadoliberin analogues — patients should receive injections outside the oncological centers.

Table 2. Exemplary modifications of chemotherapy regimens in palliative treatment

Regimen	Proposed modification
Paclitaxel 80 mg/m^2 weekly	Paclitaxel 120 mg/m^2 every 2 weeks [29]
Gemcitabine 1000 mg/m^2 d1, 8 every 21 days Gemcitabine 1000 mg/m^2 d1, 8, 15 every 28 days	Gemcitabine 1250 mg/m^2 every 2 weeks *Gemcitabine 1000 mg/m^2 every 2 weeks if there is a problem in maintaining the earlier dosage*
Cisplatin 25–30 mg/m^2 weekly	Cisplatin 50 mg/m^2 every 2 weeks Cisplatin 75 mg/m^2 every 3 weeks
Cisplatin 25 mg/m^2 + gemcitabine 1000 mg/m^2 d1, 8 every 21 days	Cisplatin 35 mg/m^2 + gemcitabine 1250 mg/m^2 every 2 weeks
Cisplatin 70 mg/m^2 d1 + gemcitabine 1000 mg/m^2 d1, 8, 15 every 28 days	
Vinorelbine 25 mg/m^2 *i.v.* or 60–80 mg/m^2 weekly	Vinorelbine 50 mg *p.o.* (Monday, Wednesday, Friday) [30] or 30 mg *p.o.* every 2nd day (in the elderly) — cycles every 2–3 weeks [31, 32]
Carboplatin 2 AUC *i.v.* weekly	Carboplatin 5–6 IV AUC every 3 weeks
Capecitabine dosage d1–14 every 21 days	Capecitabine — continuous mode (66% of the standard daily dose for 14/21 cycle) visits every 6 weeks

Table 3. Optimization of intravenous targeted therapies use

Breast cancer	Docetaxel + trastuzumab + pertuzumab	Pertuzumab + trastuzumab — after 6 courses with docetaxel — dosing at intervals of up to 6 weeks [33, 34] (no need for loading doses)
	Trastuzumab + chemotherapy (different drugs)	Trastuzumab (up to every 6 weeks) + monotherapy or combinations of metronomically used drugs [35]
	Trastuzumab emtansine	Intervals up to every 6 weeks [36]
Ovarian cancer	Paclitaxel + carboplatin + bevacizumab	Recommended intervals up to every 4 weeks — *no clear data on the possibility of using longer intervals* [37, 38]
Colon cancer	FOLFOX + panitumumab FOLFIRI + cetuximab	Intervals up to every 4 weeks [39, 40]. In patients with an objective response (according to the provisions of the drug program) — interruption of the treatment or chemotherapy alone (without anti-EGFR) — FOLFIRI/FOLFOX (up to every 5 weeks), alternatively capecitabine alone. *The use of monotherapy with anti-EGFR antibodies — is less active than the combination of anti-EGFR antibody with 5-FU/LV* [41]
	FOLFIRI/FOLFOX + bevacizumab	Courses every 4 weeks. *The use of monotherapy with anti-VEGF antibodies — is less active than combination of anti-EGFR antibody with 5-FU/LV* [42]
	FOLFIRI + aflibercept	Courses every 4 weeks [43]
Gastric cancer	Capecitabine/5FU + cisplatin + trastuzumab	Use of trastuzumab at intervals of up to 6 weeks + capecitabine monotherapy [44]
Renal cancer	Temsirolimus	There is no conclusive data on the possibility of delay — intervals of up to 2 weeks may be considered [45–47]

— Immunotherapy with immune checkpoint inhibitors
  - in patients with complete response lasting at least 24 months — treatment interruption and observation;
  - in patients with objective response lasting for more than 6 months to consider a maximum 2-fold extension of the intervals between courses;
  - patients with stabilization or deepening response — continuation of treatment according to the standards.

If there are any doubts regarding the possibility of dose modification, it is possible to contact the consulting team of the Department of Oncology, JU-CM in Krakow (chemioterapia@su.krakow.pl).

Neutropenic fever in the course of cancer treatment

Due to the fact that symptomatic SARS-CoV-2 infection manifests with high fever, it is difficult to distin-

guish the first symptoms of COVID-19 from neutropenic fever without performing diagnostic tests. According to current recommendations, patients with suspected COVID-19 (at least one of the symptoms: **fever,** cough, shortness of breath) should be isolated in properly equipped rooms (sluice room, personal protective equipment, pulse oximeter, thermometer, access to medical gases, resuscitation kit)) and then subjected to further diagnostics [9]. There is no doubt that in the current situation every patient with symptoms suggestive of COVID-19 (also with only "classic" neutropenic fever) can seriously disrupt the functioning of the entire healthcare unit and disorganize the work of medical staff. Therefore, in order to minimize the risk of neutropenic fevers in patients undergoing chemotherapy, it is recommended to use prophylactically G-CSF for the duration of the COVID-19 (SARS-CoV-2) pandemic:

— in all patients receiving chemotherapy at intermediate risk (10–20%) of neutropenic fever;
— in all patients receiving chemotherapy, who had episode of neutropenia grade 3 according to CTC-AE (< 1000/mm^3) during the current regimen.

Corticosteroids in premedication and treatment of complications

Corticosteroids in clinical oncology are most often used to prevent the side effects of chemotherapy (nausea, vomiting, anaphylactic reactions) or targeted drugs (prevention of mineralocorticoid excess syndrome during abiraterone acetate therapy). These drugs are also sometimes necessary to maximize the anti-cancer effect (prednisone with docetaxel in the treatment of castration-resistant prostate cancer or multi-drug hematology regimens. In recent years, corticosteroids have also become the key medicines used to neutralize the autoimmune complications of immunotherapy with immune checkpoint inhibitors, which often are life-threatening. However, since corticosteroids have a strong immunosuppressive effect, a lot of controversies has arisen about the safety of these drugs in the context of COVID-19.

Available literature data indicate that **there are no significant risks associated with the use of corticosteroids in patients infected with SARS**. These drugs were widely used during the SARS-CoV and MERS-CoV epidemics [48, 49]. In a retrospective analysis of 401 critically ill patients diagnosed with SARS-CoV infection, corticosteroids reduced mortality and hospitalization time, without increasing the risk of secondary infections and other complications [50]. Available publications covering patients with MERS-CoV, SARS-CoV and RSV infections indicate that corticosteroids may delay the time of virus elimination from the body and induce typical complications, but have a beneficial effect on reducing the inflammatory process and lung tissue damage [48, 51]. WHO guidelines do not recommend routine use of corticosteroids in all patients diagnosed with COVID-19 [52]. According to current recommendations in patients with SARS-CoV-2 infection requiring corticosteroids (inhaled or systemic) their administration should not be interrupted, but dose reduction may be considered [53]. Therefore, corticosteroids in cancer patients without SARS-CoV-2 infection should be used in accordance with medical practice.

Patients with dyspnea without other clinical signs of infection

Patients reporting with dyspnea, which was not present before the pandemic onset, require extended diagnostics. If there are no other clinical symptoms suggestive of an infectious background, a chest CT scan should be performed and a SARS-CoV-2 test should be considered in accordance with current Chief Sanitary Inspector (Główny Inspektor Sanitarny, GIS) guidelines and the standards of health care unit. When radiological features suggesting interstitial pneumonia are present or difficult to differentiate from interstitial tumor involvement, a SARS-CoV-2 infection diagnostic should be performed and the patient should be isolated. In a patient without evident radiological symptoms, it is also important to urgently exclude the risk of pulmonary embolism.

Reuse of personal protective equipment

An essential element of health care during an epidemic is adequate protection of both staff and patients against secondary infection. Currently, all healthcare providers in the world are facing the problem of insufficient supplies of single-use personal protective equipment, and this problem especially applies to FFP2 and FFP3 masks. However, there are some possibilities for multiple use of protective masks through their appropriate disinfection. Such approach is usually contrary to the characteristics of the discussed medical products and based on low-class evidence. In the current epidemiological situation, however, it may be the only alternative that allows securing medical staff during patient care.

Protective mask is defined as a filtering protective mask in the FFP2 or FFP3 class (in the US terminology N95 and N99, respectively). According to the current guidelines, protective masks are disposable medical devices that should be exchanged between each individual contact with patient and attempts to reuse or disinfect them are possible only in exceptional situations, in accordance with internal hospital recommendations.

Prolonged use is defined as the use of one protective mask without removing it between subsequent patients, assuming that all patients are infected with one

pathogen. The maximum duration of use is difficult to determine — experience shows that FFP2 and FFP3 protective masks can be used for approx. 8 hours. This time is also preferred when protective masks are reused.

Decontamination of protective masks in the FFP2 and FFP3 class is not allowed in standard situations and can only be used in emergency situations after it has been approved by the personnel responsible for the epidemiological policy. Data on the possibility of decontamination of protective masks are based on the assessment of their protective properties against pathogens other than SARS-CoV-2. Available data confirm that a temperature of 70 degrees applied for 30 minutes is an effective method of destroying previously tested forms of SARS-coronavirus [54]. It is also important, that viruses survival time on external surfaces is limited and, depending on the material, ranges from 4–72 hours.

Any method used can have a negative effect on both the protective properties and structure of the mask, which can lead to leakage, therefore, a leak test should be carried out after every wearing a mask. The reuse of masks is associated with an increased risk of infection in case of a decrease in filtration efficiency or incomplete decontamination.

Based on the data on virus survival, it is possible to reuse the face mask by staff after a downtime of 5 days. In this situation, each employee exposed to the virus receives 5 masks signed with their name, each of which is used for 1 day, and then stored in a paper bag for 5 days. If there are not enough masks, it is possible to consider one of the decontamination methods (Table 4).

Based on the available data, the method of heating the mask for 30 minutes in the oven air heated to 70–75°C or use of UV disinfection for 30 minutes can be considered as a preferred method in conditions of limited availability of specialized equipment.

Summary

The recommendations of the Polish Society of Clinical Oncology and their brief summary (Table 5), in the absence of adequate, strong scientific evidence for management during COVID-19 (SARS-CoV-2) pandemic, reflects the authors' opinions. The PTOK position and help offered by the consultancy team of the Oncology Department of the Jagiellonian University-Collegium Medicum in Krakow are aimed at supporting decision-making clinical oncologists in this extremely complicated situation in which they find themselves.

As doctors, we must remember that our own and our colleagues' safety is a critical factor in the possibility of providing continuous care to our patients. As clinical oncologists, in many cases coordinating and binding oncological treatment, we may be forced in this extraordinary situation to make extraordinary decisions, extraordinary commitment, extraordinary effort. At the same time, we must remember that we have in our hands the fate of the patients, in whom we cannot miss the chance to be completely cured, as well as of patients with advanced disease, in whom our decisions should not worsen the prognosis.

Table 4. Methods of decontamination of FFP2 and FFP3 masks

Decontamination method [55–57]	Filtration efficiency/ /safe number of decontamination	Comment
Methods recommended by the CDC (Centers for Disease Control and Prevention) [58]		
Vaporous hydrogen peroxide (VHP)	High/20	Adequate infrastructure is needed
UV (sterilization chamber, 0.5–1.8 J/cm^2), 30 minutes	High/10	Adequate infrastructure is needed
Moist heat sterilization (min. temp. 60° C and 80% relative humidity), 15–30 minutes	High	Adequate infrastructure is needed
Other methods		
Hot air (oven), 70–75°C, 30 minutes	High/20	Risk of mask deformation (depending on the material used)
Steam > 160°C	High/3	A significant decrease in effectiveness after 5 procedures
75% alcohol, wetting and drying	Ineffective	The method should not be used
Chlorine containing solution, 5 minutes	Ineffective	The method should not be used
Gamma radiation (25 cGy)	No data	Risk of loss of tightness, access to the cyclotron necessary
Microwaves (microwave oven)	No data	All tested masks melted during the procedure

Table 5. PTOK recommendations in the context of the SARS-CoV-2 pandemic — summary

1. Recommendations for the management of systemic antitumor treatment during the COVID-19 (SARS-CoV-2) pandemic are not based on the results of prospective studies and to the greatest extent include observations regarding the management of other infections and expert opinions.
2. The most important element of the management is to prevent the spread of infection according to typical principles recommended in epidemic emergencies.
3. Systemic anti-cancer treatment should be carried out according to generally accepted principles.
4. Systemic treatment according to generally accepted principles should also include dealing with complications.
5. Systemic treatment according to generally accepted principles should be particularly observed in case of treatment with a radical intention.
6. Interrupting or abandonment of continued systemic treatment with a radical intention in a COVID-19 (SARS-CoV-2) pandemic situation is not scientifically justified.
7. Initiation of systemic adjuvant treatment may be replaced by close observation in strictly justified clinical situations. The use of one of the available methods or shortening the duration of the entire treatment should be considered.
8. Palliative systemic anti-cancer treatment should be continued, and it is possible to modify the regimens and doses depending on individual situations.
9. Modifications of palliative systemic anti-cancer treatment may include wider use of oral medications or metronomic treatment.
10. Preventive use of antiviral drugs has no scientific justification.
11. Granulopoietins prophylaxis during an epidemic emergency should be used in patients at intermediate risk of neutropenic fever.
12. Every patient with suspected COVID-19 before admission to the oncology center should have SARS-CoV-2 infection excluded in accordance with the applicable recommendations of the Chief Sanitary Inspectorate and the Ministry of Health.

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