editorials

Cancer Treatment Adaptations in the COVID-19 Era

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The coronavirus disease 2019 (COVID-19) pandemic may set a point of no return in our way to understanding public health. The reality of our world was turned upside down, and in the best scenario, many lessons were and will be learned to prevent future critical circumstances. Patients with cancer and their families were not prepared to think about some of the questions that we are facing now: Is it convenient to proceed with the treatment that was planned? Should it be changed? Is it safe to go to the doctor's office? What extra protection measures should be taken? We, the attending physicians, were not prepared either. Patients with cancer were observed to have a higher risk of severe events caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Although those suffering from solid tumors represent a heterogeneous population, long-term immunosuppressive therapies may be associated with a higher risk of severe complications. Regarding planned treatments, some evidence-based decisions could be approached in particular cases to reduce a patient's exposure to coronavirus without compromising effectivity, especially in regions with a greater prevalence of this pandemic disease.

Adapt Treatment Regimens to Reduce Patient Visits

Current evidence supports that treatment regimens can be adapted in many cases, favoring oral drugs, shorter administration times, or larger intervals between doses.

In the treatment of advanced colorectal carcinoma, as well as in the adjuvant setting, CAPOX (3-week schedule of capecitabine and oxaliplatin) is at least as effective (2-week schedule of 5-fluorouracil continuous infusion, leucovorine and oxaliplatin) (2-week schedule with continuous infusion).[2,3] Analogously, in advanced squamous head and neck cancer, TPEX regimen (4-5 hour infusion of docetaxel, cisplatin and cetuximab) was associated with similar outcomes compared with the standard EXTREME (4-day infusion of cetuximab, 5-fluorouracil and cisplatin).[4]

Correspondingly, no significant differences were obtained in disease-free survival (DFS) and overall survival (OS) when weekly paclitaxel was compared with an every-3-weeks docetaxel schedule given after the standard doxorubicin-cyclophosphamide regimen in the adjuvant treatment of breast cancer.[5] However, it should be noted that a higher incidence of neutropenia was observed in patients who received docetaxel.

Two recent phase III randomized trials (ICON-8 [ClinicalTrials.gov identifier: NCT01654146] and MITO-7 [ClinicalTrials.gov identifier: NCT00660842]) showed similar efficacy when carboplatin plus paclitaxel given once per week was compared with every-3-weeks schema in first-line treatment of advanced ovarian cancer.[6,7] Furthermore, in the ICON-8 study, patients assigned to the 3-week group had less neutropenia than those allocated to weekly chemotherapy.

These examples are supported by evidence and represent less complex possibilities that could be safely adapted in our current critical situation.

Some tumor models may offer the possibility of de-escalating treatment regimens before disease progression. To illustrate this, we highlight that the OPTIMOX1 trial (ClinicalTrials.gov identifier: NCT01023633) showed that for patients with previously untreated advanced colorectal cancer, oxaliplatin can be discontinued after 6 cycles of FOLFOX without compromising efficacy.[8] A similar finding was obtained in the randomized phase II PRODIGE 35-PANOPTIMOX trial (ClinicalTrials.gov identifier: NCT02352337), which compared standard 6-month FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) treatment, 4 months of FOLFIRINOX followed by maintenance with LV5FU2, and a regimen that alternated gemcitabine and FOLFIRI (5-fluorouracil, leucovorin and irinotecan) in the first-line treatment of metastatic pancreatic cancer.[9] No significant differences were appreciated in progression-free survival (PFS). In both scenarios, it is also reasonable to recommend capecitabine after completing 6 cycles of FOLFOX or 4 months of FOLFIRINOX, respectively, to encourage outpatient management of cancer treatment.

When possible, other common therapies used in the cancer field can be administered subcutaneously out of the hospital. Longer intervals may be preferred, such as goserelin 10.8 mg every 12 weeks, or leuprolide 45 mg every 6 months. For some treatments, it is possible to switch from intravenous to subcutaneous administration according to availability, including trastuzumab and denosumab. Furthermore, the possibility of prescribing immunotherapy with extended dosage intervals should also be considered. In this

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context, the recent European Commission's approval of pembrolizumab every 6 weeks could be a valuable approach.[10]

Reduce Treatment Duration

Despite being statistically inferior, the clinical impact of reducing duration of adjuvant trastuzumab was low in some randomized clinical trials. For instance, in the phase III randomized Short-HER trial (ClinicalTrials.gov identifier: NCT00629278), which compared the adjuvant treatment of trastuzumab for 9 weeks versus standard 12-month treatment, 5-year DFS was 85% and 88%, respectively.[11] On the other hand, the randomized phase III PERSEPHONE trial (ClinicalTrials.gov identifier: NCT00712140) established the noninferiority of a 6-month regimen compared with standard (4-year DFS, 89.4% *v* 89.8%, respectively).[12] Some limitations of this trial were widely discussed, such as only 15% of the included population had undergone neoadjuvant treatment, the high number of low-risk included patients, and suboptimal treatment schemes used for adjuvant treatment. Having analyzed these observations, it is reasonable that in a low-risk patient, adjuvant trastuzumab can be stopped before 1 year.

A similar conclusion could be obtained from immunotherapy publications. Recently, Betof Warner et al[13] showed in a retrospective series that among 102 patients with advanced melanoma who achieved a complete response (CR) with immunotherapy, 72 discontinued treatment as a result of a suspected CR. Among complete responders, 72.1% did not require additional treatment for 3 years. In advanced non–small-cell lung cancer immunotherapy, duration ranges from up to 2 years to disease progression in phase III trials. However, the optimal treatment duration remains unknown, because a deeper response was associated with longer PFS and OS.[14] We need to highlight that there is insufficient evidence to generalize these recommendations. Hence, every decision should be carefully discussed with the patients.

Consider Not Prescribing Treatment or Delaying Treatment Initiation

The typical assessment of risk and benefit of prescribing adjuvant therapy has been altered by the pandemic; it is crucial to critically balance decisions before indicating treatment. Regarding adjuvant treatment of renal cell carcinoma, it could be argued that although provocative DFS increases have been shown, significant differences in OS have not been achieved.[15] However, it should be noted that in some trials data are still immature. In soft tissue sarcomas, large randomized trials failed to show benefit of adjuvant chemotherapy after tumor resection, and, only by meta-analysis, a 14% reduction in the hazard of death was obtained (absolute OS benefit of 5.1%).[16]

Timing of treatment initiation is another factor to bear in mind. Standard adjuvant therapy for curative scenarios, supported by a proven relapse risk reduction, should not be delayed. However, under current critical circumstances, an intentional delay from definitive surgery to initiation of adjuvant chemotherapy may be an option in high endemic areas. An uncompromised relapse-free survival and OS were observed if treatment is postponed for up to 8-12 weeks in patients with early-stage breast cancer and 8 weeks in colon cancer.[17,18,19]

On the other hand, in many advanced tumor models, there are not substantially beneficial treatment options in second, third, or later lines. This could be the case for many patients with advanced cervical carcinoma, biliary duct cancer, and glioblastoma. Cancer therapy in these situations should be carefully individualized and discussed with the patient. Moreover, some patients with advanced cancer can be followed expectantly before initiating systemic therapy, such as indolent oligometastatic slow progressive renal cell carcinomas, well-differentiated neuroendocrine and thyroid tumors, and adenoid cystic carcinomas. However, it cannot be ignored that some scenarios required immediate active treatment even in critical public health situations, such as for germ cell tumors.

Carefully reviewing potential benefits and analyzing the evidence that supports cancer treatment becomes crucial in times when any visit that could be avoided may benefit our patients. All efforts should be oriented to preserve minimum risk of COVID-19 infection without reducing the efficacy of oncology treatments. In that way, therapy must be considered in a careful case-by-case discussion between patients and physicians. The role of virtual tumor boards is fundamental. Finally, multiple aspects have to be carefully considered, including a patient's cancer risk for relapse or progression, goals of therapy, other patient comorbidities, and the impact of coronavirus transmission in the local community.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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