Cancer in the time of COVID-19: expert opinion on how to adapt current practice

To the Editor:

The susceptibility of cancer patients to the adverse outcomes of viral infections is well known from past experiences: influenza increases the risk of hospital admission with respiratory distress four times, and the risk of death 10 times, compared with patients without cancer [1]. This risk is particularly elevated in patients with neutropenia or lymphopenia, which is often the case in patients treated with chemotherapy. In Wuhan, China, 1% of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported to suffer from cancer, which is more than three times the incidence of cancer in the Chinese population in 2015 [2]. In addition, in 39% of cancer patients (compared with 8% of patients without cancer), transfer to the intensive care unit was necessary, with their illness deteriorating more rapidly (13 *versus* 43 days to severe event) [2]. Chemotherapy or surgery <1 month before was an important risk factor (OR 5.34, p=0.0026).

There is no doubt that patients with lung cancer or mesothelioma, who are often older and with concurrent obstructive or restrictive lung disease, are even more at risk of an unfavourable outcome where there is infection with SARS-CoV-2. Therefore, we have to reconsider our current clinical practice, in order to limit time in hospital, promote telemedicine, avoid unnecessary contact with medical personnel and reduce severe neutropenia.

The British Thoracic Society (BTS) recently published recommendations on coronavirus disease 2019 (COVID-19) and lung cancer/mesothelioma [3], and the French Haut Conseil de la Santé Publique (HCSP) published on cancer in general [4, 5]. This letter describes the viewpoint of the authors on these general recommendations (not always in agreement!) and tries to translate them into practical advice for clinicians (note: some may not be feasible due to reimbursement issues), starting with the current standard care. In all patients, we suggest video consultation is used as much as possible instead of face-to-face consultation [3, 5].

Recommendations for the treatment of small-cell lung cancer

Stages I–III

- Standard care in most patients is chemoradiotherapy with four cycles of cisplatin/etoposide as the preferred chemotherapy regimen.
- Replacing intravenous with oral etoposide to reduce the time in hospital should be weighed against its lower biological availability and variable pharmacodynamics in a curative setting [6].
- In patients with stage I small-cell lung cancer surgical resection of the tumour, followed by adjuvant chemotherapy (four cycles of cisplatin/etoposide), is indicated.
- In selected patients, accelerated hyperfractionation of radiotherapy (twice daily) remains an option to decrease the number of hospital visits.

Stage IV or not eligible for chemoradiotherapy

- Palliative chemotherapy with platinum/etoposide is recommended.
- Replacing intravenous with oral etoposide to reduce time in hospital may be considered, providing attention is given to its lower biological availability and variable pharmacodynamics [6].
- In patients with increased risk of febrile neutropenia (FN), dose reduction may be an alternative to primary prophylactic use of granulocyte colony-stimulating factor (G-CSF) in all patients, given the palliative setting [7].

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Our current thoracic oncology practice could/should be adapted to the COVID-19 pandemic by reducing time in hospital and patient contacts with healthcare workers, whilst maintaining quality of care. This letter offers expert advice on how to do so. https://bit.ly/2JR2IoT

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- Given the limited improvement in overall survival and the need for tri-weekly clinic visits during the maintenance phase, the addition of a checkpoint inhibitor (atezolizumab or durvalumab) can be omitted.
- The indication for second-line systemic therapy should be reviewed with extra care. In platinum-sensitive relapse, rechallenge with first-line chemotherapy is recommended. In platinum-refractory relapse, oral topotecan is the preferred regimen. Cyclophosphamide/doxorubicin/vincristine is not recommended as an alternative to topotecan in view of the need to hospitalise the patient.
- Any third-line chemotherapy should be considered only in fit patients with low risk of complications.

Recommendations for the treatment of nonsmall-cell lung cancer

Surgery

- Consider delaying surgery for ⩽3 months in small tumours that appear not to grow fast; follow-up of growth rate with chest CT is recommended [3].
- Consider stereotactic radiotherapy as an alternative in patients who are marginally fit for surgery, due to comorbidity or limited pulmonary reserve [3].
- Minimal invasive approaches are preferred over thoracotomy to limit time in hospital [3].

Adjuvant chemotherapy

- Adjuvant chemotherapy in stage II and III and in some patients with high-risk stage IB leads to 5% improvement in 5-year survival and is therefore recommended.
- In elderly patients with significant comorbidity or decreased performance (Eastern Cooperative Oncology Group (ECOG) performance score (PS) ⩾2), the possible benefits of adjuvant chemotherapy may be outweighed by the increased risk of complications. Consider omitting adjuvant chemotherapy or stopping early (*e.g.* after three cycles) [3].
- Consider administering cisplatin/docetaxel to limit time in hospital, as it avoids day 8 administration of gemcitabine or vinorelbine, and has equivalent efficacy. In non-squamous nonsmall cell lung cancer (NSCLC), cisplatin/pemetrexed is an equally efficacious alternative [8].
- In patients with an activating epidermal growth factor receptor (EGFR) mutation, consider a 1-year course of daily oral EGFR tyrosine kinase inhibitor (TKI) as an alternative to adjuvant chemotherapy (currently no phase 3 evidence of superiority available).

Radiotherapy

- Consider delaying curative radiotherapy for small tumours that appear not to grow fast; follow-up of growth rate with chest computed tomography is recommended [3].

Concurrent chemoradiotherapy

- Consider administering cisplatin/pemetrexed instead of cisplatin/etoposide, or weekly carboplatin/paclitaxel in non-squamous NSCLC to limit time in hospital [9].
- Consider administering adjuvant durvalumab at a dose of 20 $mg \cdot kg^{-1}$ every 4 weeks instead of 10 $mg \cdot kg^{-1}$ every 2 weeks to limit time in hospital. Phase 1b data have not shown an increase in adverse events [3, 10]

Systemic therapy

- Evaluate the indication for palliative chemotherapy, immunotherapy or both with extra care in elderly patients or patients with significant comorbidity, decreased performance (ECOG PS ⩾2), social isolation, decubitus, urinary catheters, *etc.*, especially in second or further lines [3].
- Consider delaying chemotherapy or immunotherapy in patients who are asymptomatic and have indolent disease [3].
- The usual recommendations for chemotherapy, immunotherapy and targeted therapy apply.
- In patients with an increased risk of FN, dose reduction might be an alternative to primary prophylactic use of G-CSF in all patients, given the palliative setting [7].
- Keep in mind that pneumonitis may also be drug-induced (*e.g.* chemotherapy, TKIs) or immune-mediated (checkpoint inhibitors).
- Tri-weekly chemotherapy is preferred over weekly regimens (*e.g.* docetaxel) to limit time in hospital [4].
- Consider limiting palliative chemotherapy to four cycles and omitting pemetrexed maintenance therapy [3].

- In patients who have >50% programmed death-ligand 1 (PD-L1) expression, first-line pembrolizumab monotherapy is preferred over pembrolizumab plus chemotherapy [3].
- Consider administering nivolumab at a dose of 480 mg every 4 weeks instead of 240 mg every 2 weeks to limit time in hospital [3, 11].
- Immunotherapy as second-line is preferred over chemotherapy in patients who did not receive immunotherapy as first-line.
- Where there is a lack of response to immunotherapy or significant toxicity, early discontinuation should be considered.
- Third-line chemotherapy is not advisable [3].
- Consider evaluating the response to immunotherapy or TKI less often in clinically stable patients.

Supportive therapy/other

- Advance care planning should be discussed with all patients in order to avoid admission to hospital [3].
- Do not resuscitate status should be available for all stage IV patients.
- Patients receiving denosumab or low-molecular weight heparin should be taught to self-administer [3].
- Patients receiving denosumab should not routinely consult a dentist before starting.
- Avoid transfusion of blood or platelets by using dose reduction or early discontinuation of chemotherapy in palliative patients.

Recommendations for the treatment of malignant pleural mesothelioma

- Where there is early stage disease in a fit patient, evaluate for multimodality treatment including surgery (preferably extended pleurectomy/decortication) and chemotherapy.
- Palliative chemotherapy with four cycles of platinum/pemetrexed is recommended in all other cases of ECOG PS 0-1 patients.
- Evaluate the indication for palliative chemotherapy with extra care in elderly patients, patients with significant comorbidity or poorer performance (ECOG PS $\geqslant$2).
- Consider delaying chemotherapy in patients who are asymptomatic [3].
- Pemetrexed maintenance therapy is not recommended due to lack of efficiency data.
- Be reluctant with second-line chemotherapy with either vinorelbine, gemcitabine or doxorubicin.
- A home-managed indwelling pleural catheter is preferred over procedures that require a clinic visit [3].

Recommendations for treatment of thymic epithelial tumours

- Platinum/etoposide is preferred over more haematotoxic regimens such as ADOC (cisplatin/doxorubicin/vincristine/cyclophosphamide), CAP (cyclophosphamide/doxorubicin/cisplatin) or VIP (etoposide/ifosfamide/cisplatin).

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