Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Oncology 32 (2020) 490–492

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

Looking a Gift Horse in the Mouth: Observations on NHS England's Interim Guidance on Pembrolizumab in Head and Neck Squamous Cell Cancer

K.J. Harrington [*†], S.A. Bhide [*†], M.D. Forster [‡], J.S. Good [§], L. Gunn [*†], A. Kong [¶], A.A. Melcher [*†], R. Metcalf [||], P. Nenclares [*†], K.L. Newbold [*†], C.M. Nutting [*†], R. Prestwich [**], J.J. Sacco [††‡‡], H. Soliman [*], K.H. Wong [*]

[*] *Head and Neck Unit, The Royal Marsden NHS Foundation Trust, London, UK*
[†] *Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK*
[‡] *University College London Hospital, London, UK*
[§] *Queen Elizabeth Hospital, Birmingham, UK*
[¶] *King's College, London, UK*
[||] *Experimental Cancer Medicine Team, The Christie NHS Foundation Trust, Manchester, UK*
[**] *Leeds Cancer Centre, St James's Hospital, Leeds, UK*
[††] *The Clatterbridge Cancer Centre, Liverpool, UK*
[‡‡] *The University of Liverpool, Liverpool, UK*

Received 21 May 2020; accepted 21 May 2020

The novel severe acute respiratory syndrome coronavirus-2 (n-SARS-CoV2) that causes COVID-19 has played havoc with normal medical care. Patients with or suspected of having cancer have experienced significant knock-on effects on referral, investigation, diagnosis, treatment and follow-up. Those with relapsed and/or metastatic disease who should be receiving palliative systemic anti-cancer therapy (SACT) have been particularly affected.

Physicians have had to tell their patients, often via remote consultations in which the nuances of the doctor/patient interaction are lost, that their treatment with chemotherapy and/or immunotherapy will be withheld, deferred, suspended or withdrawn, even when this may result in worse cancer-specific outcomes. National Institute for Health and Care Excellence (NICE) guideline-161 (NG-161) on prioritising SACT ranks all patients receiving palliative intravenous chemotherapy in categories 4, 5 and 6 (with 6 ranking as the lowest priority) [1]. Consequently, many oncology units across the UK have eschewed palliative SACT because of concerns relating to increased risks of adverse outcomes of COVID-19 in patients with disseminated cancers, especially when compounded by iatrogenic immunosuppression (or immunomodulation); the need to facilitate self-isolation of vulnerable groups and avoid repeat hospital visits during which patients might contract and spread n-SARS-CoV2; the potential challenges of the optimal management of toxicities in hospitals overwhelmed by COVID-19; and, in the early stages of planning the National Health Service (NHS) response, the perceived need to concentrate available medical resources on treating the anticipated 'tidal wave' of COVID-19 patients.

As the first wave of COVID-19 passes, NHS England is trying to ensure that patients can still receive anti-cancer treatment, while simultaneously optimising the use of NHS resources and continuing to protect patients and staff from infection. To help achieve these objectives, NHS England is offering alternative cancer therapies, where clinically indicated, to meet patients' needs, reduce hospital admissions, increase self-treatment at home and avoid myelosuppressive therapies. In brief, under NG-161, many patients who might otherwise receive chemotherapy will now be offered immunotherapy or targeted agents for indications not yet approved in the UK [2]. This seems a laudable, well-intentioned approach and offers patients access to new drugs ahead of formal NICE appraisal. What could possibly be wrong with such an apparent win–win proposition?

First, it is possible that NG-161's basic premise – summarised briefly as immunotherapy good, chemotherapy bad – may be, at best, simplistic and, at worst, completely wrong.

Author for correspondence: K.J. Harrington, Head of Division of Radiotherapy and Imaging, The Institute of Cancer Research, London SW3 6JB, UK.
E-mail address: Kevin.Harrington@icr.ac.uk (K.J. Harrington).

https://doi.org/10.1016/j.clon.2020.05.016

Preliminary data from series including relatively small numbers of cancer patients reported that recent SACT was associated with a significant adverse influence on the outcome of COVID-19 [3–6]. However, these early reports may have significantly overstated the risks of SACT based on small numbers of at-risk patients. In fact, virtually real-time UK data [7] suggest that patients receiving cytotoxic chemotherapy within 4 weeks of a COVID-19 diagnosis have a lower odds ratio for death, probably because such patients are younger and fitter than the general population (UKCCMP, personal communication). Importantly, especially relating to NG-161's provisions, emerging data show that the risks of immunotherapy and chemotherapy may be equivalent. Moreover, there are no reliable data on the magnitude of risk of n-SARS-CoV2 infection when attending hospitals for the appointments needed for anti-cancer treatment, relative to remaining at home in self-isolation, and no true understanding of the impact of the suboptimal management of toxicities due to limited NHS resources or disinclination to use high-dose steroids (for immunotherapy complications).

Even if we accept the underlying assumption that immunotherapy is inherently less risky than chemotherapy, its use might expose some to risks of inferior cancer-specific outcomes. Such concerns are raised by the recent partnership agreement between NHS England and Merck, Sharp & Dohme Ltd (MSD), under the auspices of NG-161, to supply pembrolizumab to replace the current standard chemotherapy-based regimens as first-line treatment for metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express programmed death ligand-1 (PD-L1) at a combined positive score (CPS) $\geq$ 1 [8]. The agreement permits the use of pembrolizumab in England, but only as monotherapy and for an initial 3 months, as per the interim treatment changes document attached to NG-161. This position temporarily, and partially, reverses NICE's rejection, in 2019, of pembrolizumab as first-line single-agent or combination therapy for relapsed HNSCC – a decision based on what many regard as rather idiosyncratic grounds [8]. Regrettably, this earlier rejection of pembrolizumab means that there is a lack of infrastructure and training of pathologists to conduct PD-L1-CPS immunohistochemical tests for patients with HNSCC. The current COVID-19 crisis presents significant logistical obstacles to disseminating these capabilities across the UK. Therefore, even where using single-agent pembrolizumab (SAP) under NG-161 may be optimal, there may be protracted delays in obtaining the PD-L1 test result.

Although US Food and Drug Administration (FDA), Japanese and European Medicine Agency (EMA) licences authorise SAP for HNSCC in the conditions covered in NG-161, it is important to stress that, in these jurisdictions, treating physicians can also select the combination of pembrolizumab plus chemotherapy (for all-comers per FDA/Japanese approvals and in PD-L1-CPS $\geq$ 1 for EMA approval) in line with the pivotal KEYNOTE-048 trial [9]. The availability of both SAP and pembrolizumab-chemotherapy combination allows experienced oncologists to select appropriate treatment for their patients based on factors such as CPS value, bulk, tempo and site of disease (locoregional versus systemic), threat to critical structures (airway/swallowing apparatus/vasculature), presence or absence of symptoms and performance status. Regrettably, the NHS England–MSD agreement does not cover the use of pembrolizumab in combination with platin/5-fluorouracil-based chemotherapy. As discussed below, NG-161's decision to supply SAP as the only alternative to either no treatment (in most units) or standard-of-care chemotherapy (in a minority of units) presents significant challenges, as well as opportunities.

Regulatory authorities generally base decisions on drug approval on overall survival data derived from randomised studies, such as KEYNOTE-048 [10]. In this regard, SAP was superior to the EXTREME regimen for the PD-L1-CPS $\geq$ 1 population, with a median overall survival of 12.3 versus 10.3 months. However, most of the benefit was driven by about 45% of the population with PD-L1-CPS $\geq$ 20 with a median overall survival of 14.9 versus 10.7 months. The current absence of published data [9] specifically for patients with PD-L1-CPS 1–19 leaves clinicians in a quandary when applying NG-161 to these individuals.

In the current context of exceptional access to SAP and its short-term goal of aiming to reduce hospital admissions and the number of patients on myelosuppressive therapies over the course of 'an initial 3 months', oncologists may regard objective response rates and progression-free survival data as better guides when deciding whether to offer patients SAP during the COVID-19 outbreak. Indeed, the response to treatment and avoidance of progression are recognised as indicators of the likelihood of deriving clinical gain from systemic therapy [11]. In this regard, the objective response rates to SAP were 19% for PD-L1-CPS $\geq$ 1 and 23% for PD-L1-CPS $\geq$ 20 compared with 35–36% for EXTREME regimen arms in KEYNOTE-048 (and about 20% for platin/5-fluorouracil in the original EXTREME study) [12]. When comparing SAP with the EXTREME regimen, progression-free survival data reveal non-significantly worse outcomes for immunotherapy (median 3.2 versus 5.0 months for PD-L1-CPS $\geq$ 1, median 3.4 versus 5.3 months for PD-L1-CPS $\geq$ 20). Furthermore, the overall survival data reveal that, for both PD-L1-CPS $\geq$ 1 and $\geq$20, the survival curves cross at about 7–8 months – with the SAP curve below the EXTREME chemotherapy curve in the initial treatment period. Therefore, some patients, especially those with CPS 1–19, may be harmed by using SAP rather than chemotherapy.

In the absence of specific information for the PD-L1-CPS 1–19 group, we believe that NG-161 represents an essentially unscientific 'one-size fits all' solution to the challenge of first-line management decisions for patients with metastatic/unresectable recurrent HNSCC during the COVID-19 outbreak. Rather than blithely accepting SAP, we urge clinicians to look this particular gift horse carefully in the mouth as they make the complex decisions that their patients need. We believe they should consider the following options:

- For patients with PD-L1-CPS $\geq$ 20 and relatively asymptomatic/paucisymptomatic and non-bulky disease, offering SAP seems to be uncontroversial

and may well deliver benefit with modest adverse effects.

- For patients with PD-L1-CPS $\geq$ 20 and symptomatic or bulky (especially locoregional) disease, SAP may be appropriate but consideration should also be given to platin/5-fluorouracil-based chemotherapy (where available) or even palliative irradiation/re-irradiation.
- For patients with PD-L1-CPS 1–19 with asymptomatic/paucisymptomatic and non-bulky disease, SAP under close clinical observation is a reasonable option. Alternatively, watchful waiting with regular telephone follow-up and repeated imaging (e.g. 6-weekly computed tomography scans) may safely allow treatment deferral until later in the course of the outbreak when greater data availability on the consequences of SACT on COVID-19 outcomes will allow physicians to make informed choices with their patients.
- The group of patients with PD-L1-CPS 1–19, with disease needing rapid commencement of SACT, presents the most difficult decisions. Here, there are three main options: (i) withhold all treatment because of concerns about patients contracting and spreading COVID-19 during repeat hospital visits; (ii) commence platin/5-fluorouracil-based chemotherapy (where possible); and (iii) commence SAP under NG-161 in units where chemotherapy is not possible. In the first situation, the patient, their family and the clinician are left in limbo, observing and supervising symptomatic deterioration, disease progression and, ultimately, the patient's death. In situations (ii) and (iii), clinicians must explain the considerable uncertainty about excess risks of chemotherapy/immunotherapy on the clinical course of COVID-19. Where SAP is used, clinicians must also explain that there are concerns that a minority of patients may experience rapid disease progression and worse survival outcomes relative to the underlying HNSCC. As an alternative, we urge NHS England to revisit its judgement and approve pembrolizumab in combination with chemotherapy for these patients.

Although COVID-19 may be in decline, the spectre of recrudescence will remain for months; and ongoing restrictions to our ways of working and living are inevitable. Although we welcome and support NHS England's current initiative to facilitate anti-cancer treatments, there is a clear need for careful consideration of recommendations made, by necessity, in haste. Although we highlight the case of pembrolizumab in HNSCC, the principles involved will probably apply to other clinical scenarios, particularly in the context of an incomplete and evolving understanding of risk/benefit for cancer treatments in the context of COVID-19.

Conflicts of Interest

K.J. Harrington discloses membership of MSD's Global Scientific Advisory Committee for head and neck cancer and has received research grant income, speaker's fees and honoraria for Advisory Board membership from MSD. All fees were paid to The Institute of Cancer Research. M.D. Forster has received research grant income, speaker's fees and honoraria for Advisory Board membership from MSD. J.J. Sacco has received speaker's fees, travel and conference expenses, and honoraria for Advisory Board membership from MSD. A. Kong has received travel and conference expenses, and honoraria for Advisory Board membership from MSD.

References

[1] https://www.nice.org.uk/guidance/ng161/chapter/6-Prioritising-systemic-anticancer-treatments.
[2] https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381.
[3] Liang W, Guan W, Chen R, Wang W, Li J, Xu K, *et al*. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;21:335–337.
[4] Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, *et al*. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020:36383–36393. pii: S0923-7534(20).
[5] Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol* 2020:e200980. https://doi.org/10.1001/jamaoncol.2020.0980.
[6] Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, *et al*. Patients with cancer appear more vulnerable to SARS-COV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov* 2020. https://doi.org/10.1158/2159-8290.CD-20-0422. pii: CD-20-0422.
[7] The UK Coronavirus Cancer Monitoring Project Team. The UK Coronavirus Cancer Monitoring Project: protecting patients with cancer in the era of COVID-19. *Lancet Oncol* 2020;21(5):622–624.
[8] https://ecancer.org/en/news/17193-pembrolizumab-rejected-by-nice-as-a-first-line-treatment-for-advanced-head-and-neck-cancer.
[9] https://www.nice.org.uk/guidance/indevelopment/gid-ta10181.
[10] Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro Jr G, *et al*. KEYNOTE-048 Investigators. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 2019;394:1915–1928.
[11] Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? *J Clin Oncol* 2012;30:1030–1033.
[12] Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, *et al*. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116–1127.