COVID-19 and systemic anticancer therapy: exploiting uncertainty

Gelderblom, H.; Veelken, H.; Stiggelbout, A.M.

surgical morbidity; however, this trend was not observed in the RAPIDO trial. The rates of anastomotic leak were also similar between the two treatment groups (five [1%] of 426 in the experimental group *vs* six [2%] of 400 in the standard of care group).

The PRODIGE 23 trial is the only other trial to our knowledge that has shown promising results with an improvement in disease-free survival (75·7% [95% CI 69·4–80·8] in the experimental group *vs* 68·5% [61·9–74·2] in the standard of care group; p=0·034) and metastases-free survival (78·8% [72·7–83·7] *vs* 71·1% [65·3–77·2]; p<0·02).[9] This trial assessed an induction chemotherapy regimen of six cycles of mFOLFIRINOX (modified leucovorin, flourouracil, irinotecan, and oxaliplatin) followed by a standard protocol of chemoradiotherapy, surgery, and adjuvant chemotherapy. Although this induction regimen was well tolerated in this trial setting, the generalised tolerability of mFOLFIRINOX in the population remains unknown.

The landscape of total neoadjuvant therapy for locally advanced rectal cancers looks promising, and the RAPIDO protocol is likely to be the new standard of care, especially in resource-limited settings and the current climate of the COVID-19 pandemic, when fewer visits to health-care centres are desirable. This treatment protocol is also likely to increase the number of patients being offered organ preservation with the watch and wait policy due to the increase in pathological complete response and likely subsequent increase in clinical complete response rate. However, whether or not this new treatment paradigm will have similar outcomes in a younger population with aggressive disease biology and increased preponderance of signet ring cell histology, as seen in the Indian subcontinent,[10] is unknown.

We declare no competing interests.

*Avanish Saklani, Diwakar Pandey, Swapnil Patel
saklaniap@tmc.gov.in

Division of Colorectal and Peritoneal Surface Oncology, Department of Surgical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai 400012, India

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COVID-19 and systemic anticancer therapy: exploiting uncertainty

The COVID-19 pandemic has not only disrupted lives, but has put health-care systems under considerable strain. The resource demands for the acute treatment of patients with COVID-19 had to be balanced against resources needed for regular care of patients with cancer during the peaks in COVID-19 incidence. Initially, there were concerns that patients with COVID-19 who were undergoing cancer treatment would have considerably increased mortality rates. Subsequently, cancer screening programmes were temporarily paused and cancer treatments were scaled down according to rapidly published guidelines.[1,2] The effect of reductions in treatments prescriptions on the prognosis of patients with cancer is not yet known, but the impact on patient concerns about their treatment and follow-up has been substantial. A survey of more than 5000 patients in the

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Netherlands has shown that even among patients who had no alterations to their treatment since the pandemic began, one in four patients reported being concerned or very concerned about potential consequences for their treatment or follow-up, with higher proportions reported in regions with incidence considered high enough to overwhelm health-care systems (>200 cases per 100 000 people).[3] The restrictions on face-to-face consultations will have added to this uncertainty. At present, a second wave of COVID-19 is being observed in many European countries, and thus uncertainty remains. Practical strategies for clinicians have been proposed, to employ in conversations with patients, caregivers, and family to address the uncertainty associated with their care.[4]

In *The Lancet Oncology*, James Clark and colleagues[5] analysed the impact of COVID-19 on systemic anticancer treatment registrations in England, immediately after lockdown and after new treatments were implemented to reduce patient risk, using registration data for systemic anticancer treatment for various oncological indications. A decrease in total registrations was observed immediately after the onset of the COVID-19 pandemic in April, 2020, when compared with the control period (September, 2019 to February, 2020; relative reduction 32%, absolute difference 4·2 SDs, p<0·0001), which was likely due to the reluctance of clinicians to expose patients to harm from oncology treatments, the fear of patients contracting COVID-19 in the hospital, a reduction in referrals and subsequent diagnoses, and reduced capacity of hospitals. The total number of registrations increased in May, 2020, but remained 10% lower than in the control period (absolute difference 1·3 SDs, p<0·0001) and in June, 2020, the number of registrations had increased by 15% when compared with the control period (absolute difference 1·9 SDs, p<0·0001). It is impossible to infer causality from these registration data, but the analyses of registrations between April and June, 2020, provide a convincing case for the conclusion that the quick recovery of systemic anticancer treatment prescriptions was attributable to treatments given temporary approval by the UK National Health Service.

Innovative strategies to decrease the burden of treatment for health-care systems were welcomed after the onset of the pandemic. The rapid implementation of newer anticancer treatments, possibly with a better risk–benefit ratio, as described by Clark and colleagues, seems reassuring, but also highlights some issues that require discussion. Refraining from neoadjuvant treatment with little survival benefit or palliative treatment that only extends life by a few months, as proposed by Clark and colleagues, should always be an option in a process of shared decision making, not only during a pandemic. However, the default introduction of less toxic but more expensive regimens should be carefully considered and balanced against the sustainability of a health-care system that is already under pressure.

Generally, in Europe, the European Society for Medical Oncology magnitude of clinical benefit scale[6] is adopted to guide the use of new anticancer drugs. Rapid availability for high priority indications based on this scale should not be delayed.[6] Late introduction of new and active medication might lead to loss of life-years in general.[7] Use of new expensive medications outside the registered indication (eg, for an earlier line of therapy), has the potential to cause harm. Nevertheless, the COVID-19 pandemic has lead to more thoughtful provision of toxic adjuvant and palliative regimens with only small benefits, and thus could provide a unique window of opportunity for assessing the effects of de-escalating systemic anticancer therapy, which might stimulate the development of more refined and less toxic treatments.[8] The decision on whether the benefits are worthwhile, considering not only the toxicity but also the burden of treatment and the long term side-effects, should always be shared with the patient during treatment consultations.[9,10]

The COVID-19 crisis has forced oncologists to make choices in unpredictable situations, and to limit treatments, especially in the non-curative setting.[2] This issue has lead to uncertainty among both clinicians and patients and their families, which should be recognised and discussed.[4] This pandemic might result in more careful evaluation of indications for treatment, and after the crisis has ended, to involve patients in decisions about these treatments.

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*Hans Gelderblom, Hendrik Veelken, *Anne M Stiggelbout*
a.m.stiggelbout@lumc.nl

Department of Medical Oncology (HG), Department of Hematology (HV), and Department of Biomedical Data Sciences (AMS), Leiden University Medical Center, Leiden 2300RC, Netherlands

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Results from the FeDeriCa trial: are we reducing the burden of breast cancer treatment?

Besides improving patients' outcome, decreasing the burden of cancer treatment is the most pertinent aim in breast cancer care today. In both respects, major advances have been achieved in the past 20 years, and HER2-positive breast cancer is one shining example. The introduction of monoclonal antibodies and, more recently, the antibody–drug conjugate trastuzumab–emtansine have gradually improved both pathological complete response rates and long-term outcomes in patients with early-stage disease as well as overall survival in the metastatic setting.[1–4] In addition, escalation of HER2-directed treatment allowed for the design of chemotherapy de-escalation trials in high-risk breast cancer subtypes.[5]

Although novel drugs and risk-adapted de-escalation strategies are clearly important, patients might also benefit from novel drug formulations that ease therapy administration. The neoadjuvant HannaH trial established subcutaneous trastuzumab as clinically equivalent to the antibody's conventional intravenous formulation.[6] Furthermore, the adjuvant phase 2 PrefHer study evaluated patients' preference with a crossover design and observed a greater satisfaction with the subcutaneous application route,[7] with time saving being by far the main reason for patient preference.[8] However, dual HER2 inhibition has supplanted single-agent trastuzumab in the majority of disease settings. Therefore, a combined subcutaneous administration of both antibodies in a single syringe appears to be meaningful, justifying approval by the US Food and Drug Administration in June, 2020. Still, the potential benefit of this formulation needs to be counterbalanced by the fact that biosimilar intravenous trastuzumab is currently available and pricing might be of equal (or greater) importance in many regions worldwide. Therefore, we must ask ourselves whether an innovative (more convenient) formulation is really justified in patients with HER2-positive disease.

In *The Lancet Oncology*, Antoinette Tan and colleagues report the first results from the prospective randomised, phase 3 FeDeriCa trial comparing combined subcutaneous administration of trastuzumab and pertuzumab with the conventional intravenous route of both antibodies in combination with chemotherapy as a component of neoadjuvant treatment.[9] Non-inferiority of cycle 7 pertuzumab serum trough concentration with the subcutaneous formulation was defined as the primary study endpoint, with pathological complete response and safety being key secondary endpoints. The study met its primary objective, as the geometric mean ratio of subcutaneous pertuzumab serum concentration to intravenous pertuzumab serum trough concentration was 1·22 (90% CI 1·14–1·31), with the lower limits of the two-sided 90% CIs above the prespecified non-inferiority margin of 0·8; results regarding pathological complete response were also similar between groups. Concerning safety, the only notable difference was a higher frequency of low-grade injection site reactions. The authors therefore conclude that the combined subcutaneous administration of trastuzumab plus pertuzumab is more convenient and less invasive, and equally effective compared with the conventional intravenous route. In addition, the fixed-dose combination offers the chance for administration at home, which holds further promise for improving treatment convenience.

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