

Management of lung cancer during the COVID-19 pandemic: Practical solutions for resource-constrained settings from adaptations of an international consensus

Health-care facilities vary widely across different geographical regions of the world. In particular, low- and middle-income group countries (LMICs) are emerging economies wherein resource availability, in general, is considerably lower than that in the developed countries (in particular the USA and Europe).^[1] Management of lung cancer in the context of the SARS-CoV-2 infection global outbreak and the COVID-19 pandemic is a highly complex issue wherein lack of available data leads to clinical judgment playing a pivotal role in making treatment decisions for the lung cancer community as a whole as well as for individual patients. Different countries have/are currently implementing varying degrees of lockdown leading to restrictions in travel as well as disruption in transportation (commercial and to a lesser extent cargo).

The article by Singh *et al.* and their multidisciplinary team from the University of Pennsylvania, Philadelphia, PA is an excellent attempt to address various scenarios that clinicians involved in the diagnosis and treatment of lung cancer patients are likely to encounter.^[2] It should serve as a very useful guide for multidisciplinary thoracic oncology teams in the US and even across the globe. However, there are some additional important factors that may influence decision-making, especially in resource-constrained settings:

Geographical/local factors:

1. Travel time between geographical areas of the patient's residence and the treating hospital. This may be of particular relevance if he/she cannot undertake the journey by his own car/vehicle and has to use public transport (air/rail/road). Furthermore, based on travel restrictions in force and subsequent curtailment of public transport schedules, longer journey times, and more frequent change of transport modes can be associated with a higher risk of infection with SARS-CoV-2
 2. Prevalence and transmission status of SARS-CoV-2 in both the local area of residence of the patient as well as the area wherein the health-care facility is located can help in decision-making regarding the safety of traveling. For example, patients living in areas wherein the infection/transmission rates are low and need to travel to their oncology center located in a high transmission zone would need to exercise extra caution
 3. Drug availability and supply chain disruptions: supply chains are known to have been disrupted globally and domestically in several countries due to issues related to raw material availability, closure of pharmaceutical industries, workforce shortage, and transportation of finished products. Patients on drugs (especially novel targeted agents and immunotherapy drugs) for which no generics are available would be critically dependent on the availability of that drug as opposed to drugs that are manufactured by a large number of pharmaceutical companies.
- Specific issues related to chemotherapy, targeted therapy, and immunotherapy:
4. Minimizing treatment-related adverse effects: a lower frequency as well as lesser severity of treatment-related adverse effects would be easier to manage (both from patient/caregiver's perspective as well as physician's perspective) if health-care facilities are overwhelmed or are busy tackling the pandemic. The development of severe (Grade 3 or higher) adverse events (AEs) may impose an additional burden on these facilities as well as impose greater risk of infection for the patient if he/she were required to visit the hospital for this purpose. In this context,
 - a. Sequential chemoradiation regimens, in general, are associated with lesser toxicity than concurrent regimens
 - b. Dose intense chemotherapy regimens: granulocyte colony stimulating factor (G-CSF) administration along with chemotherapy in the same (standard) dose is one suggested option in the article by Singh *et al.*^[2] However, this also entails an increased cost for the additional supportive care drug(s). An alternative to the above could be replacing cisplatin with carboplatin. Cisplatin-based chemotherapy regimens, in general, may be associated with a greater incidence of AEs, especially gastrointestinal and renal.^[3] Furthermore, a typical dose of cisplatin at 75 mg/m² for 3 weekly regimens may be modified to 65 or 70 mg/m² based on the anticipated risk of AEs.^[1]

The careful tradeoff between potential reduction in efficacy versus enhanced safety would be the key to decision-making.

5. Waiting for the results of molecular testing in metastatic nonsmall-cell lung cancer (NSCLC): As is done in routine clinical practice, for treatment naïve patients with metastatic lung adenocarcinoma (and other nonsquamous NSCLC histological types) in whom there is no compelling indication for starting chemotherapy (only mildly symptomatic/largely asymptomatic), waiting for results of molecular tests (especially the most common oncogenic drivers – epidermal growth factor receptor [EGFR] mutations and anaplastic lymphoma kinase [ALK] rearrangements) may be prudent before taking a decision on the need for chemotherapy.^[4] Again, one needs to also factor in the fact that molecular testing results may sometimes be delayed if these are outsourced and not available in the health-care facility itself. Reagents used in molecular testing are also dependent on intact supply chains. From a patient's perspective also, being treated with targeted therapy as opposed to conventional chemotherapy offers several advantages, including better efficacy, greater convenience, and favorable toxicity profile. Importantly, targeted therapies, in general, do not increase predisposition to infections
6. Adjuvant treatment for early-stage NSCLC: in most cases of surgically resected NSCLC, especially R0 resections and no adverse prognostic factors identified on surgically resected specimens, initiation, or continuation of ongoing adjuvant chemotherapy may be delayed/interrupted for a period of few weeks till the outbreak resolves. However, highly select cases with microscopic/macroscopic incomplete resections (R1/R2) and/or the presence of adverse prognostic factors on surgically resected specimens (e.g., perineural or visceral pleural or lymphovascular invasion or Spread Through Air Spaces (STAS)), may be offered the appropriate targeted therapy (tyrosine kinase inhibitors) in case they are harboring an EGFR mutation or ALK rearrangement and the perceived risk of contracting SARS-CoV-2 infection/complications related to COVID-19, if administered chemotherapy, are high (e.g., multiple comorbidities).^[5] It should be clarified both to patients and caregivers that this is not backed by robust evidence and would simply be an option to tide over the period of rapid ongoing community transmission. Such patients should be switched over to chemotherapy later once the outbreak settles
7. Drug interactions if lung cancer patients on targeted therapy develop COVID-19: Since there are no established protocols for treatment of SARS-CoV-2 infection (COVID-19), most patients currently are being treated with different drugs – an approach that largely remains experimental. If a lung cancer patient on targeted therapy develops COVID-19, there would be a need to assess the potential drug interactions between the targeted drug and drugs being used to treat COVID-19. One aspect is enhanced risk of hepatic and/or renal dysfunction and if so, this may mandate reducing either the dose or frequency of the targeted drug or even temporary discontinuation, if necessary.

Theoretically, if the patient is in clinical remission before acquiring COVID-19, a short duration of dose modification or discontinuation of the targeted drug is unlikely to adversely impact the disease status. However, the risk of tumor progression may increase if this interruption is sustained for several days. The second aspect is related to the use of targeted therapies known to have adverse cardiovascular toxicity profiles (especially vascular endothelial growth factor inhibitors). As there are emerging reports of myocardial dysfunction being an important contributing factor to COVID-19-related mortality, this class of drugs may need to be temporarily withheld till the patient has recovered fully from SARS-CoV-2 infection^[6]

8. Interaction between programmed cell death 1 (PD-1) and PD ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) and SARS-CoV-2 infection remains unknown. ICIs as a class of drugs, being novel in nature, and given that they have been developed and approved in a relatively short span of time, are very expensive. In LMICs wherein a substantial majority of the population have no or little access to insurance/reimbursement, affordability for ICI treatment remains a major concern. Furthermore, there are theoretical concerns about more severe pulmonary involvement (immunological flares) if such patients on PD-1/PD-L1 ICI contract COVID-19.^[7]
 - a. Extensive stage SCLC in whom the chemoimmunotherapy combination recently received regulatory approval may be substituted for chemotherapy alone, especially in individuals perceived to be at high risk for either COVID-19 or for ICI-related pneumonitis
 - b. Unresectable/metastatic NSCLC patients without oncogenic drivers (EGFR/ALK-negative) and PD-L1 score of 1%–49% may be offered chemotherapy or immunotherapy alone rather than the combination based on the perceived risk of treatment-related AEs and risk of SARS-CoV-2 infection.^[8]

In summary, available evidence related to treatment initiation and continuation of ongoing treatment in lung cancer patients during the SARS-CoV-2 infection (COVID-19) pandemic is currently sparse. This mandates that treating oncologists need to discuss individual scenarios with patients and their caregivers as well as the pros and cons of any given treatment approach. As compared to conventional evidence-based medicine, such an approach may imply using a lot of “common sense” or “gut instincts.” Ultimately, lung cancer patients, their caregivers, and the treating oncologist collectively need to decide the optimal treatment plan based on the perceived patient-specific infection risk and status of the disease.

Navneet Singh

*Department of Pulmonary Medicine, Nehru Hospital, Postgraduate Institute of Medical Education and Research, Chandigarh, India
E-mail: navneetchd@yahoo.com*

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