

Lung Cancer, Covid-19 Infections and Chemotherapy

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Abstract. *Background/Aim:* The Covid-19 epidemic has severely strained health care systems across the globe. The impacts are multiple especially for patients cared for cancer. The Covid-19 epidemic has several impacts on the management of lung cancer patients. The aim of this work was to summarize the available epidemiological data on patients diagnosed with lung cancer infected with Covid-19 and describe the different strategies to improve the management of these patients by summarizing the recommendations in this area. *Patients and Methods:* The Teravolt cohort is an observational multicenter registry, including patients with non-small cell cancer, small cell cancer or mesothelioma but also epithelial tumors and a diagnosis of Covid-19. The Theravolt registry indicates an unexpectedly high mortality rate in patients with thoracic malignancies with COVID-19. *Results:* Between March 26 and April 12, 2020, 200 patients treated in 8 countries were included. They had a performance status (PS) of 0-1 in 72% of cases, were smokers or ex-smokers in 81% of cases, had non-small cell cancer (76% of cases), were under treatment in 74% of cases, and the majority were first-line cases (57%). The hospitalization rate was 76% and the mortality rate 33%; only 10% of patients with criteria for intensive care hospitalization were admitted

to the intensive care. *Conclusion:* Data presented in this registry suggest a high mortality in patients with thoracic cancer and Covid-19. Therefore, the importance to create a safe healthcare system during Covid-19 pandemic is underlined along with the need for essential effective clinical service delivery to patients with lung cancer.

Lung cancer is the second most common cause of malignancy worldwide among both females and males. The main risk factor for lung cancer remains smoking. Lung cancer is divided in two cell types: small cell lung cancer and non-small cell lung cancer, representing 15 and 85% of all lung cancer cases. The histology and genetic profile of lung cancer are important factors for treatment choices and preventive strategies (1, 2).

The Covid-19 epidemic has had several impacts on the management of lung cancer patients. Tensions over care systems have led to diagnostic delays, the need to arrange for the management of systemic treatments, but also oral treatments, and finally delays in the management of surgery and radiation therapy.

It does not appear that lung cancer is an extremely important risk factor for susceptibility to Covid-19 or worsening of infection, at least not in the same way as other comorbidities such as cardiovascular disease, diabetes and chronic obstructive pulmonary disease. In contrast, it appears that when infected, patients with lung cancer have a higher risk of worsening.

Patients and Methods

Soon after the pandemic outbreak, prospective cohorts were set up to identify the characteristics of Covid-19-infected lung cancer patients. One of the first international studies was European, from Italy. The Teravolt a multicentre observational study composed of a

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cross-sectional component and a longitudinal cohort component. This is an observational multicenter registry, including patients with non-small cell cancer, small cell cancer or mesothelioma but also epithelial tumors and a diagnosis of Covid-19, either confirmed by polymerase chain reaction (PCR) or with an evocative clinical picture and radiology consistent with Covid-19 pneumonia.

Results

The cohort began on January 1, 2020 and first results were published recently. Between March 26 and April 12, 2020, 200 patients treated in 8 countries were included. They had a performance score (PS) of 0-1 in 72% of cases and were smokers or ex-smokers in 81% of cases. Cancer was mainly non-small cell cancer (76% of cases), while 74% of cases were under treatment in, and in their majority, they were first-line cases (57%). The hospitalization rate is 76% and the mortality rate is 33%; only 10% of patients with criteria for admission to intensive care were admitted to intensive care.

The variable studied was age, being older than 65 years (HR=1.88, 95%CI=1.00-3.72), smoking status, being a current or former smoker (HR=4.24, 95%CI=1.70-2.95), treatment modality, receiving chemotherapy (HR=2.54, 1.09-6.11) and the presence of comorbidity (HR=2.65, 1.09-7.46) were associated with an increased risk of death. Mortality was 32%, only 33% continued their systemic treatment after Covid-19 infection. Interestingly, treatment with immunotherapy seems to decrease the risk of mortality (OR=0.6, 95%CI=0.5-0.97), perhaps due to the fact that immunotherapy has the role of stimulating the immune system. Immunotherapy has been a new standard of care for advance/metastatic lung cancer. The prominent characteristics of cancer immunotherapy is the induction of immune memory followed by endured treatment response. Immunotherapy simultaneously boosted cytotoxic T lymphocyte (CTL) immune responses against virus-infected and neoplastic cells (3).

Discussion

Covid-19 infection tends to be more severe in patients diagnosed with lung cancer. Abundant literature has been developed very rapidly on the various aspects of lung cancer management at the time of the Covid-19 related pandemic (4-10).

A team from Milan (11) developed, according to clinical data and therapeutic modalities, an extremely interesting support algorithm. This algorithm established from sex, PS, age, sex BMI, comorbidities, treatment or not corticosteroids, and tumor characteristics and treatments, classifies patients into 3 risk categories:

- A low-risk category that allows maintained cancer management as planned before the epidemic, delay or reduced the number of visits to the hospital, using teleconsultation tools, or using systemic oral treatments;

- An intermediate-risk category where management of the disease is systematically considered to be delayed;
- A high-risk category that requires not only acute treatment, but also closer monitoring of clinical and biological signs.

In that series, the therapeutic modalities (history of surgery, history of irradiation, systemic treatment) do not appear to have an impact on severity of Covid-19 infection. The authors found no biological factor particularly significantly associated with severity (11).

The impact of the Covid-19 pandemic on lung cancer treatment. Lung cancer is associated with increased mortality and Covid-19 infection overshadows patient prognosis. Current treatment options involve surgery chemotherapy, radiotherapy, targeted therapy and immunotherapy.

All virtual meetings in the field of oncology focused on patient management during the Covid-19 pandemic. An English team (12) retrospectively analyzed 40 patients treated with durvalumab in maintenance for a locally advanced disease. They showed that a telephone consultation and a switch from administration of the treatment every 2 weeks to administration every 4 weeks is feasible and does not appear to have deleterious effects on patient safety. A study by the Institute Gustave Roussy (13) evaluated a Covid-19 infection screening strategy combining a computed tomography (CT) scan without injection and PCR samples in asymptomatic patients undergoing radiotherapy. From March 18 to May 1, 2020, among the 507 patients included in the study, 257 had CT-scan abnormalities, so 34 (8%) were Covid-19 compatible (CO-RADS 3); 102 had PCR after the scan; 24/449 (5.3%) were considered Covid-19 positive: 19 with a positive PCR and 5 on the appearance of the scanner. Almost half of the patients were asymptomatic or not very symptomatic.

The challenge of Covid-19 in patients treated by chemoradiotherapy for a locally advanced cancer is also existence of differential diagnosis with other causes of radiological abnormalities like radiation-induced pulmonary fibrosis which is a common complication of thoracic radiotherapy for lung cancer (14, 15). Radiation-induced pulmonary fibrosis leads to irreversible destruction of lung architecture and disruption of gas exchange. Immunotherapy might simultaneously boost cytotoxic T lymphocyte immune response against virus-infected and neoplastic cells. This immune stimulation might cause the exacerbate the disease, but a recent study has shown the opposite that it is safe to continue continued use of PD-1 blockade during the Covid-19 pandemic (16). It is very important to distinguish Covid-19 pneumonia from other lung pathologies for a correct treatment and early as possible.

In Romania we have been trying to continue cancer treatments wherever possible; in cases where it was possible, we increased the period between treatment cycles, we

reduced the time with patients in consultations and where possible we performed telephone consultations.

The effects of Covid-19 pandemic on the healthcare system affected both hospitals and patients. Due to the large number of Covid-19 patients who needed hospitalization, the reallocation of human resources reduced the number of newly diagnosed patients and access to treatment for lung cancer complications.

The Covid-19 pandemic led to postponement and cancellation of surgery. The impact of delayed cancer surgery due to the Covid-19 pandemic was analyzed in a study that reported that a three-month and six-month delay of surgery decreased the anticipated global survival obtained after surgical treatment by 19 and 43%, respectively (17).

The recommendations we took into account during this period were:

- To prioritize in multidisciplinary meetings remote organizations, telemedicine or video conferencing;
- To provide for screening processes for the symptoms of Covid-19 infection before receiving patients in hospitals during the day, in conventional hospitalization and/or for the diagnostic procedures;
- To limit the exposure of the environment and family during consultations or upon arrival to hospital centers for technical examinations, radiological and endoscopic;
- To maintain a diagnostic strategy that takes into account for differential diagnosis for suspected cases of Covid-19 disease;
- To adapt the modalities of follow-up to the reality of the epidemic, in particular a reasoned economy of examination *e.g.* imaging, discussion of the most appropriate moment for surgical procedures, the possibility, in some cases, to perform radiotherapy on localized tumors rather than surgery if the surgical health system is energized;
- Febrile neutropenia and infection, remain major toxicities associated with myelosuppressive systemic cancer chemotherapy. According to the recommendations in patients who have an approximately 10% or higher risk for febrile, primary prophylaxis with a hematopoietic colony-stimulating factors will have to be started at the first cycle and continue through subsequent cycles of chemotherapy;
- For immunotherapy, most companies have adopted longer rates for administrations, every 3, 4 or 6 weeks depending on the agent used;
- For small-cell lung cancer, especially in the first line, the recommendations are to follow the deadlines for the care of these rapidly evolving patients, and for radiotherapy, to discuss modalities in order to have fewer sessions, therefore get the patient to the hospital less often.

Conclusion

The amount of knowledge on the interactions of lung cancer and Covid-19 infection has become richer, especially due to

studies that included a large number of patients in multicenter. It is, therefore, important to create a safe healthcare system during the Covid-19 pandemic and it is essential to sustain effective clinical service delivery to patients with lung cancer.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

BH was responsible writing of the manuscript. AZ and BH were responsible for reviewing and editing of the manuscript. AZ, BH, XB and CB made substantial contributions to the conception or design of the work. RA were responsible for the critically review of the manuscript. All Authors read and approved the final manuscript.

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