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ABSTRACT (354 words)

Background

Early reports on cancer patients with COVID-19 have suggested a high mortality rate compared to the general population. Patients with thoracic malignancies are thought to be particularly vulnerable given their older age, smoking habits, preexisting cardio-pulmonary comorbidities, in addition to cancer treatments. Aim of the study is understanding the impact of SARS-COV2 infection on patients with thoracic malignancies.

Methods

This registry is a multi-center observational study composed of a cross-sectional component and a longitudinal cohort component. Eligibility criteria were the presence of any thoracic cancer and a COVID-19 diagnosis, laboratory confirmed with RT-PCR, suspected with symptoms and contacts or radiologically suggestive. The goals of this consortium are to provide data for guidance to oncology professionals on managing patients with thoracic malignancies while understanding the risk factors for morbidity and mortality from this novel virus. Clinical outcomes including hospitalization, ICU admission and mortality were collected using questionnaire in REDCap. The association between demographic/clinical characteristics and outcomes were measured with odds ratio with 95% confidence intervals using logistic regression model. This is a preliminary analysis of the first 200 patients.

Results

As of April 12, 2020, a total of 200 patients with COVID-19 and thoracic cancers from 8 countries have been identified; median age was 68 (62-75) years, ECOG PS 0-1 (72%), majority were current and former smokers, 76% had NSCLC, 74% were on therapy at the time of diagnosis and 57% were on a first line. One hundred and fifty-two (76%) patients were hospitalized and 66 (33%) died, with the majority (91%) not being offered intensive care therapy. Univariate analyses revealed that age, smoking status, chemotherapy alone and the presence of comorbidities were associated with increased risk of death. However, in multivariate analysis only smoking was associated with increased risk of death.

Conclusions

With an ongoing global pandemic of COVID-19 our data suggests a high mortality and low admission to intensive care in thoracic patients. It has still to be determined whether this mortality could be reduced with intensive care. With improved cancer therapeutic options access to intensive care must be discussed in a multidisciplinary setting based on cancer specific mortality and patients' preference.

Introduction

Coronavirus disease 2019 (COVID-19), a respiratory tract infection caused by the severe acute respiratory syndrome (SARS) coronavirus (CoV), also named SARS-CoV-2, emerged in Wuhan, China in late 2019 [1]. The rapid global spread led the World Health Organization to declare a pandemic in early March 2020 [2] with more than 2,113,226 confirmed cases and 140,371 deaths as of April 16, 2020 [3]. Due to limited testing capacity the true global infection and mortality rates likely far exceed the confirmed cases [4].

One of the first publications describing patients infected with SARS-CoV-2 came from The National Health Commission of China and reported on 1,099 patients from 552 hospitals [5]. They noted that 24% of patients had comorbidities associated with a more severe SARS-CoV-2 infection. In patients admitted, the median duration of hospitalization was 12 days, 5 % required an admission to the intensive care unit (ICU), 2.3% required mechanical ventilation and 1.4% died. The most common presenting symptoms at time of hospitalization included cough and fever. In the largest Italian report on 1591 COVID-19 patients admitted to the ICU, 88% required mechanical ventilation, 68% had at least one comorbidity with hypertension in 49% of patients [6]. At the time of publication 16% of patients were discharged and 26% had died, with age being the most significant risk factor for mortality. Many other reports describe similar clinical features of patients presenting with COVID-19 [7-11]. The differences in patients' demographics and mortality between the reports from China and those from Italy and other countries have not yet been fully explained. Data on how the virus impacts patients living with cancer has also emerged. A report of 1,524 cancer patients who were screened at Zhongnan Hospital of Wuhan identified COVID-19 in 12 (0.79%) patients, 7 of whom had Non-Small Cell Lung Cancer (NSCLC) and over half of whom were on active therapy. One patient required an ICU admission and three patients died leading the authors to conclude that patients with cancer had a higher risk of mortality compared with the community [12]. A second report from Wuhan on 1,590 hospitalized patients with COVID-19 noted a higher incidence and risk for ICU admissions and/or mortality in patients with cancer [13]. These publications are limited by

their small sample size and the inherent bias that cancer patients were more likely to be tested for the virus by nature of their symptoms and frequency of contacts with the medical system [14-15].

In a recent editorial Lipsitch and colleagues posed several important questions that need to be answered in order to characterize the impact of this new virus on patients, including elucidating the full spectrum of the disease, ranging from asymptomatic to fatal. They also emphasized the need to identify subgroups most likely to have poor outcomes thereby deserving specific prevention and therapy efforts [16]. Many scientific societies have provided clinical recommendations for the management of cancer patients, revisiting standards of care, allowing for a better risk/benefit ratio in this period of rapid viral circulation, including minimizing hospital visits, identified as a contamination risk [17, 18]. Regarding systemic treatments, a particular emphasis has been placed on immune checkpoint inhibitors (IO), assumed to result in higher complications in patients who are infected with SARS-CoV-2 infection, without any reliable scientific evidences [19].

Unfortunately, epidemiological data suggests that the pandemic will continue for months if not for years [20]. The improvement in lung cancer mortality reported in 2020 is thought to be due to major advances in NSCLC patients with advanced stage disease treated with TKIs and IO [21]. The fear and anxiety created by the outbreak of COVID-19 has resulted in a major shift in cancer care delivery with hospitals reducing patient visits, implementing telemedicine while delaying surgery, systemic therapy and routine follow up. Screening rates allowing for earlier detection have also undoubtedly dropped as may health care system with postponed elective imaging procedures, as similarly and dramatically observed for breast, colon and cervical cancer screenings [22]. While such draconian measures are necessary in the short term to protect patients from SARS-CoV-2 infection, prolonged treatment delays may lead to an increase in cancer related mortality. Therefore, it is crucial to understand the impact of COVID-19 on cancer patients in order to deliver optimal care. Thoracic cancERs international coVid 19 cOLlaboraTion (TERAVOLT) is the first global

registry aimed at understanding the impact of SARS-CoV-2 infection on patients with thoracic malignancies.

METHODS

Study design and paticipants

Institutions from around the world were invited via email to collaborate on this database. Main eligibility criteria were thoracic cancer patients (NSCLC, Small Cell Lung Cancer (SCLC), mesothelioma (MPM), thymic epithelial tumors (TET), and other pulmonary neuroendocrine neoplasms) with a COVID-19 diagnosis defined as: 1. Laboratory confirmed (RT-PCR techniques); 2. Suspected with symptoms including fever >37.5°C, decrease of oxygen saturation of at least 5%, cough, diarrhea, otitis, dysgeusia, myalgia, arthralgia, conjunctivitis and rhinorrhea and when available known exposure to person with confirmed COVID-19; or 3. Radiologically suspected cases with lung imaging features consistent with SARS-COV-2 pneumonia and symptoms. Patients of any age, sex, histology, stage, in active treatment as well as in clinical follow-up were considered eligible. Participating centers were asked to enroll consecutive patients with these characteristics. Data collected are divided in four main categories, demographics, oncologic history and comorbidities, COVID-19 diagnosis, course of illness and clinical outcomes (Supplementary Table 1). Oncological outcomes will be collected until the end of the study for all patients included to evaluate the impact of this pandemic on treatment delays. Full eligibility criteria are listed in the trial protocol, available with the full text in the Appendix. Initial CRF variables were designed based on available data from literature and are updated based on emerging evidence [23].

Data Collection

Local Institutional Review Board (IRB) approval is required prior to data entry. Data is entered into a de-identified database with each institution assigned a unique number. Data for this study is collected in a

REDCap® (Research Electronic Data Capture) database. REDCap is a secure web platform for building and managing online databases and surveys. REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). More information about the software platform and system security can be found at http://www.projectredcap.org/.

All study procedures were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. According to the regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, the following requirements regarding personal data were guaranteed (pseudonymization and encryption, confidentiality, integrity, availability, resilience of treatment systems and services, the ability to restore the availability and access of data in the event of a physical or technical accident).

The study has no funding

Statistical analysis

This registry is a multi-center observational study on thoracic cancer patients that experienced COVID-19. Clinical data was extracted from medical records of consecutive patients from January 1st, 2020 and they will be collected until the end of pandemic declared by WHO. The study, by design, is composed of a cross-sectional component and a longitudinal cohort component. The cross-sectional part describes the patients and disease characteristics both for cancer and for COVID-19 disease, including treatment received and complications due to therapy; the longitudinal component is related to the association between potential prognostic factors and outcome.

Descriptive statistics of patients demographical (e.g. age, sex) and clinical characteristics (e.g. comorbidities, severe events, therapy) were reported with 95% confidence intervals. Summary measures for association between factors and outcomes were assessed by univariate and multivariate logistic model (Odds Ratio (OR) with relative 95% confidence intervals (95%CI)). Basic demographic characteristics,

including age, sex, smoking status, race, stage of disease at COVID-19 diagnosis (American Joint Committee on Cancer [AJCC] clinical stages), type of thoracic malignancy, current oncological treatment, comorbidities, concomitant medications, method for COVID-19 diagnosis, and hospitalization were recorded. For hospitalized patients, the length of hospital stay and need for admission to ICU were also recorded. Criteria for ICU admission were defined as needing a higher level of care including more intense monitoring, ventilation and resuscitation. Patients were divided into two age groups (≤65, and >65 years). The association between these characteristics and patient outcomes including hospitalization, death and prolonged hospitalization (> 8 days) is assessed by univariable logistic model and measured with the OR and 95% CI for each factor. In multivariable analysis, gender, age (>65 years, ≤65 years), smoking status, hypertension and COPD, all factors known from literature to be associated with outcomes in general patients' population, were selected for assessing their association with death. Subjects with missing values were excluded from univariable and multivariable analysis. No power analysis was performed to calculate the sample size, and the aim was descriptive in nature, focusing on estimation rather than hypothesis testing. All analyses were conducted using R version 3.6.

However, with about 150 centers and about five patients from every center, a sample size of approximately 750 patients can produce a confidence interval for the categorical estimate of <8%. In this study, we present the preliminary data on first 200 consecutive patients, the cut-off number was not dependent by previous knowledge of results but was driven by the emergency and the lack of data provided in this setting so far. However, with a confidence interval <14% we think that the results can assure a reasonably precise preliminary estimate for the purpose of our study.

The corresponding author had full access to all of the data and the final responsibility to submit for publication

RESULTS

In this report, we present data from eight countries including 200 patients from 42 institutions entered between March 26th, 2020 to April 12th, 2020. This is a preliminary unplanned report made to give information at a critical time. One hundred eighty (91%) patients had a diagnosis on RT-PCR, 5 (2%) had a COVID-19 diagnosis based on clinical symptoms (fever >37.5, cough, dyspnea, oximeter decrease of 5%), and 13/198 (7%) with radiological findings that were highly suggestive of COVID-19. The median follow-up since COVID-19 diagnosis was 15 days (interquartile range [IQR]: 8-24). Median age is 68 years (IQR: 62-75), 30% are females and the majority are Caucasians, current or former smokers (Table 1). The most common histology was NSCLC (76%) followed next by SCLC (14%), 74% had stage IV disease, and 147 out of 200 (74%) patients were on systemic therapy. Treatments included tyrosine kinase inhibitors (TKI) alone (19%), chemotherapy alone (33%), chemotherapy in combination with IO (14%) and IO alone (23%); the majority of patients were on first line treatment (57%). Sixteen percent of patients had no comorbidities; in those with comorbidities, the most common were hypertension and COPD in 47% and 26% of patients, respectively, and 22% of patients were on steroids.

The most common presenting symptoms were fever, cough and dyspnea in 64%, 52% and 53% of patients, respectively (Table 2). The median number of days between onset of symptoms and diagnosis was 5 days (IQR: 2-7). The median number of days of hospitalization was 7 (IQR: 2-13). Out of 200 patients, 157 developed complications to date, with one third of patients still hospitalized at the time of data cut off. The most common complications included pneumonia/pneumonitis in 80% of patients and acute respiratory distress syndrome (ARDS) in 27% of patients. Twelve percent of patients were asymptomatic, where the majority (54%, 13/24) were tested in hospitals due to known exposure to a positive patient followed next by secondary findings on routine imaging for anticancer therapy or surveillance (25%, 6/25).

Of the 152 hospitalized patients, 134 (88%) met criteria for ICU admission, but only 13 patients were admitted to the ICU and 5 were mechanically ventilated. Predominantly, this was reported as not indicated which included institutional policy against ICU admission, underlying cancer diagnosis and decision not to escalate to ICU, or not indicated due to severity of COVID-19 illness and physician recommendation not to escalate to ICU for futility in advanced stage cancer patients, with only 6 patients who were offered ICU level care declining ICU admission (Table 2). Thirty-one patients had a prolonged hospitalization, defined as 8 days or longer. For patients who died (33%), the majority died in hospital due to complications from COVID-19 infection (52/66 patients), 8 died in the ICU and 3 patients died at home. Eleven deaths were due to disease progression and 3 are unknown.

Univariate analyses revealed that age>65 (OR 1.88; CI95% 1.003-3.623), smoking status (OR 4.243 CI95% 1.695-12.946), chemotherapy alone (OR 2.538; CI95% 1.089-6.113) and the presence of comorbidities (OR 2.653; CI95% 1.094-7.458) were associated with increased risk of death. Univariate analyses for the risk of hospitalization, prolonged hospitalization and death are illustrated in supplementary Table 2. In multivariate analysis only smoking history (OR 3.178; 95%CI 1.114-9.062) was associated with increased risk of death (Table 3).

DISCUSSION

TERAVOLT is a global consortium that was formed to characterize the impact of SARS-CoV-2 infection on patients with thoracic cancers. Our initial report from the first 200 patients indicates that the mortality in thoracic cancer patients is 33% and may be as ominous as previously reported for patients in China [12-13, 17]. In the multivariable analysis, only smoking habits maintained a statistically significant association with outcomes. Interestingly, some of the prior comorbidities such as hypertension, coronary artery disease, that are associated with increased risk of death in the general population, did not appear to be a

predictor for poor outcomes in our patient population. The question as to whether smoking vehiculated the effect of other clinically associated variables (like COPD and other comorbidities) or there is a net effect of smoking, merits further insights. However, these are preliminary data and we acknowledge that we need more events to see effects.

Of note, while the majority of patients died during hospitalization, only 13 (9%) patients in our cohort were admitted to the ICU and 5 received mechanical ventilation. This is in contrast with previous reports where 16% of hospitalized patients were cared for in the ICU and 88% received endotracheal intubation and mechanical ventilation [6], as well as with the recent report from New York showing that patients with all types of cancer were frequently intubated than over COVID-19 patients [24]. Part of this could be explained by the geographical locations, which were mainly Europe (Italy, France and Spain) included in this initial cohort. All of these regions were particularly hard hit and they have universal health systems that differ from other countries. In addition, the database includes heterogeneity among types of hospitals (comprehensive cancer centers and general hospitals).

We tried to capture the reasons for the lack of ICU admission. Difficult decisions were made limiting ICU admissions to cancer patients and others with terminal illness due to equipment and personnel shortages. However, we are aware that behind these choices there may also be patients' decisions, cultural and institutional choices that our work is unable to properly capture. Given that our database is longitudinal, TERAVOLT will evaluate the impact of SARS-CoV-2 infection outcomes on patients in hospital systems that are not as stressed with time in future reports. Nonetheless, as targeted therapy and immunotherapy have dramatically shifted the paradigm of care and life expectancy for patients with metastatic NSCLC, the decision to escalate care must be decided in a multidisciplinary setting and not based on old preconceptions limiting access to aggressive care for these patients.

Importantly, our data suggests that the type of systemic therapy, including TKI, chemotherapy and immunotherapy, did not impact survival in patients with COVID-19. Although the number of patients is small, in particular patients with TKI were less likely to be hospitalized (ORR 0.21; 95% CI 0.077-0.708) and despite rumors and fears of increased mortality, immunotherapy did not worsen outcomes for cancer patients with COVID-19 in our analysis. This would suggest that withholding or discontinuing such therapy for a patient out of fear of COVID-19 may not be warranted. We note, however, that more data with larger patient numbers are needed to make a final verdict on the role of treatments. Moreover, it is important to acknowledge that prior studies have indicated that frequent contact with the healthcare environment increases risk of SARS-CoV-2 infection and thus a goal of minimizing such contact, especially during cancer therapy, is important [7, 17].

The most common presenting symptoms for thoracic patients with COVID-19 are also those symptoms frequently noted by this patient population, including dyspnea, cough and fatigue. However, very few patients died due to progressive disease, with most dying of complications of COVID-19 itself. Furthermore, the majority of our patients had a stage IV disease (74%) and a large proportion were on active oncological treatment (74%) at the time of SARS-CoV-2 infection; in particular, 57% on first line with a median of seven days from the last treatment. This could represent a selected population since this initial cohort did not capture enough patients after surgery or radiotherapy; effort will be made to expand TERAVOLT participation beyond medical oncologists to include other thoracic cancer disciplines (e.g., thoracic surgeons and radiation oncologists). Furthermore, we recognize that this is a preliminary report, made to give more information to clinicians at a critical time, but that it does not have the statistical power yet to give final answers on subgroups.

While the data presented hereby are representative of mainly symptomatic patients with NSCLC stage IV disease on systemic therapy and importantly only includes a small fraction of patients who were managed

at home for their COVID-19 illness, data are urgently needed to plan the optimal diagnostic and therapeutic pathways for cancer patients in an environment where SARS-CoV-2 is still in circulation, often accompanied with only mild or no symptoms. Although consecutive inclusion of patients controls the risk of selection bias, thus assuring a correct description of patients' characteristics and outcomes, major limitations in the estimate and in the correct interpretation of associations were related to control of confounding factors. More data on the prevalence and outcomes of COVID-19 on asymptomatic thoracic cancer patients may emerge as hospital systems implement broader testing on all patients seeking care.

TERAVOLT is a unique effort aimed at providing real time data to support the optimal diagnostic and therapeutic pathways for all thoracic cancer patients. Given our data suggesting an unexpected high risk of severe infection and/or death for patients with thoracic malignancies, a tailored approach is needed. Calabró and colleagues have proposed routine testing for cancer patients on active therapy [25], the continued shortage of testing kits and variances across countries makes such an approach difficult to oblige, although may indeed be the optimal therapeutic approach once an effective therapy for COVID-19 can be administered. For now, emphasizing social distancing and encouraging measures such as wearing masks within a community may help minimize a surge of cases allowing the medical system to keep up with testing and decrease the need for physicians to triage care based on age and comorbidities. Protecting all vulnerable members of our societies, based on our current knowledge on SARS-CoV-2 infection, using additional protective measures must remain our priority, while respecting the needs of each individual including optimal care management.

Our data would suggest that a multidisciplinary approach to the treatment of thoracic patients with SARS-CoV-2 infection should consider both the individual cancer specific mortality and risk of a morbidity or mortality from COVID-19. At this time, it is not clear if intubation and more aggressive care could improve COVID-19 specific survival, or if such processes would simply prolong the dying process. However, in the

absence of clear data, the integration of patients' preference could provide a benefit especially in decisions in which uncertainty is high [26]. In this perspective a shared decision-making paradigm will allow both patients and clinicians to recognize and pursue the option that best fits the individual.

Author contributions section

FA, RB, GB, AB, EB, JB, MB, CC, EF, GF, CG, RG, FeG, FrG, VG, SI, SL, NLV, YLW, DMS, EM, GM, GP, AP, ES, VS, PS, LV and SZ collected data. FB collected data, participated in study design and data interpretation, reviewed the manuscript. JC collected data and reviewed the manuscript. AC participated in study design, data analysis and interpretation, manuscript drafting. PG, AMD, JM, ADT and GV participated in study design, data collection and interpretation, manuscript writing. GF enrolled patients. LCH participated in data analysis and data interpretation. VP participated in study design, data analysis and interpretation, and wrote the manuscript. SP participated in literature searching, study design, data collection, analysis and interpretation, wrote and reviewed the manuscript. MT collected data, participated in data interpretation and manuscript writing. MCG, AT and LH participated in study design, data analysis and interpretation, wrote the manuscript. OM took part in the development of electronic CRF and reviewed the manuscript. JPVM participated in data collection, analysis and interpretation, reviewed the manuscript. HW participated in conception and design of the database, literature searching, data analysis and interpretation and wrote the manuscript.

Declaration of interest

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