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A microsimulation model to assess the impact of SARS-CoV-2 on cancer outcomes, healthcare organization and economic burden

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Background: SARS-CoV-2 pandemic has deeply modified healthcare seeking and services in Europe since February 2020 with delays in treatment delivery and changes in the hospital data, show a 2.25% increase of the 5-year risk of death and that the burden of cancer care is key. Simulations of individual projections from treatment delays and modifications will result in 49 additional 5-year cancer-specific deaths (+2.25% of 5-year deaths), mainly in liver, sarcomas and head and neck cancer pts.

Conclusions: In a resource-constrained context, optimization of the benefit-risk ratio between COVID-19 and cancer care is key. Simulations of individual projections from treatment delays and modifications will result in 49 additional 5-year cancer-specific deaths (+2.25% of 5-year deaths), mainly in liver, sarcomas and head and neck cancer pts.

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Dutch oncology COVID-19 Consortium (DOCC): Outcome of COVID-19 in patients with cancer in a nationwide cohort study

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Background: The coronavirus disease 2019 (COVID-19) pandemic is having significant impact on oncological care (Jodee et al, Eur J Cancer 2020;136:132-139) and patients with cancer might have an increased risk for severe outcome of COVID-19. In order to identify risk factors associated with a worse outcome of COVID-19, a nationwide registry was developed for patients with cancer and COVID-19.

Methods: This ongoing multicentre nationwide observational cohort study was designed as a quality of care registry and is executed by the Dutch Oncology COVID-19 Consortium (DOCC), a collaboration of oncology physicians in the Netherlands. A questionnaire was developed to collect pseudonymised patient data on patients’ characteristics, cancer diagnosis, cancer treatment, and outcome of COVID-19. All patients with COVID-19 and a cancer diagnosis or cancer treatment in the past 5 years were eligible for inclusion.

Results: To date, >600 cancer patients diagnosed with COVID-19 have been registered by 45 Dutch hospitals. Data of 442 registered patients with at least 4 weeks follow-up were cleaned and 351 patients could be included for the first analyses. The main cancer diagnoses were non-small cell lung cancer (13.4%), breast cancer (13.4%), and chronic lymphocytic leukaemia (8.8%). Overall, 114 (32.3%) out of 351 patients with cancer died from COVID-19. In multivariate analyses, age ≥65 years (p < 0.001), male gender (p = 0.035), prior or other malignancy (p = 0.045), and active diagnosis of haematological malignancy (p = 0.040) or lung cancer (p = 0.003) were independent risk factors for a fatal outcome of COVID-19. In a subgroup analysis of patients with active malignancy, the risk for a fatal outcome was mainly determined by tumour type (haematological malignancy or lung cancer) and age (≥65 years).

Conclusions: The findings in this registry indicate that patients with a haematological malignancy or lung cancer have an increased risk of a worse outcome of COVID-19. Further research is ongoing; COVID-19 pandemic these vulnerabilities should avoid exposure to SARS-CoV-2, whereas treatment adjustments and prioritization vaccination, when should be also considered.

Legal entity responsible for the study: Erasmus Medical Center.

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Background: There is ongoing controversy regarding the outcome of COVID-19 in cancer patients. This is one of few registries on the impact of COVID-19 in cancer patients in a country severely affected by the pandemic.

Methods: This cohort study is collecting data on symptomatic SARS-CoV-2 infected patients with a cancer diagnosis from 23 Swiss sites, starting March 1, 2020. The main objective of the study is to assess the outcome of COVID-19 infection in patients with solid and hematological malignancies, while the main secondary objective is to define prognostic factors of COVID-19 outcome.

Results: With a cutoff date of July 16, 2020, 357 patients with a diagnosis of cancer and symptomatic COVID-19 were included in this first analysis. The most frequent malignancies were breast in 63 cases (18%), lung in 40 cases (11%), prostate cancer in 24 cases (7%) and melanoma in 16 cases (5%), with 104 (38%) patients having non-curable disease. Anticancer treatment within 3 months prior to the diagnosis of COVID-19 included chemotherapy in 65 patients (18%), targeted therapy in 54 patients (15%), steroids in 39 (11%), checkpoint inhibitors in 22 (6%) or no anticancer treatment in 155 patients (43%). 230 patients (65%) were hospitalized for COVID-19 or were already in hospital; 167 of the hospitalized patients (73%) required oxygen therapy (Singshot, Monocle II) and stratified per condition. Pathogen- or tumor-directed T-cells were defined based on clonal selection (Zhang, Nature, 2018). To identify ICI responsive cells, we calculated a score derived from a validated gene set denoting ICI reactivity (Okamura, J. Autoimmun, 2019).

Results: We identified 3 CD8+ T-cell lineages, with ‘Naive’ T-cells transitioning into ‘Effector Memory’ cells and then branching into either ‘Recently Activated Effector Memory’ (TEMRA) or ‘Resident Memory’ (TRM) cells. In COVID-19, clonal expansion indicating a SARS-CoV-2 antigen-specific T-cell response, was mainly observed in the highly cytolytic TEMRA lineage. In contrast, tumor-specific T-cells were found in the TRM lineage. Of importance, the ICI responsiveness rate was significantly higher in the non-pathogen-directed TEMRA and TRM cells in COVID-19. In cancer, TEMRA cells were shown to be ICI responsive as expected.

Table: LBA81 Demographics and characteristics of study cohort

| Description                                      | COVID-19 pneumonia (n = 19) | Non-COVID pneumonia (n = 10) |
|--------------------------------------------------|----------------------------|------------------------------|
| Age (y)                                           | 60 (55.5-69)               | 69.5 (62.75-75.25)           |
| Men                                              | 14 (74)                    | 5 (50)                       |
| Women                                             | 5 (26)                     | 5 (50)                       |
| Time from illness onset to sampling (d)           | 19 (16-25)                 | 15 [9-19]                    |
| SARS-CoV-2 PCR positive                          | 6 (32)*                    | 0 (0)                        |
| Other viral PCR positive                         | 4 (21)b                    | 1 (10)c                      |
| Bacterial culture positive                       | 3 (16)                     | 2 (20)                       |
| PIP PCR positive                                  | 0 (0)                      | 4 (40)                       |
| Respiratory support                              | 10 (100)                   | 7 (70)                       |
| Non-invasive ventilation                         | 0 (0)                      | 1 (10)                       |
| Invasive ventilation                             | 15 (79)                    | 2 (20)                       |
| Extracorporeal membrane oxygenisation            | 4 (21)                     | 0 (0)                        |
| Antiviral therapy (<7d)                          | 13 (68)d                   | 0 (0)                        |
| Antibiotics (<7d)                                | 19 (100)                   | 8 (80)                       |
| Immunomodulatory therapy (<7d)                   | 5 (26)*                    | 0 (0)                        |

Conclusions: We are the first to provide a mechanistic rationale for an aggravated COVID-19 disease course in ICI-treated patients. Whereas ICI reactivates tumor-directed ‘exhausted’ T-cells in cancer, it preferentially potentiates non-pathogen-directed T-cells in COVID-19, thereby contributing to lung damage without boosting the antiviral immune response.

Clinical trial identification: In-depth Immunological Investigation of COVID-19 (ConTAgiouS). - Clinical Trial identifier: NCT04327570. - Ethical approval obtained by the Ethics Committee of University Hospitals - KU Leuven. File number S63881.

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LBA81 Keeping exhausted T-cells in check in COVID-19

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Background: Clinical data suggest an aggravated COVID-19 disease course in cancer patients treated with immune checkpoint inhibitors (ICI). European guidelines advise to defer ICI therapy until complete resolution of COVID-19. However, mechanistic insight into how ICI impacts COVID-19 immunopathology is absent.

Methods: We performed single-cell RNA- and T-Cell Receptor-sequencing (TCR-seq) on bronchoalveolar lavage fluid of COVID-19 pneumonia (n=19) and non-COVID pneumonia (n=10), and co-analyzed CD8+ T-cells with publicly available tumor-infiltrating T-cell data of treatment-naive and ICI-treated patients (Sade-Feldman, Cell, 2018; Lambrechts, Nat Med, 2018). Cell lineages were determined by trajectory inference (Singshot, Monocle II) and stratified per condition. Pathogen- or tumor-directed T-cells were defined based on clonal selection (Zhang, Nature, 2018). To identify ICI responsive cells, we calculated a score derived from a validated gene set denoting ICI reactivity (Okamura, J. Autoimmun, 2019).

Results: We identified 3 CD8+ T-cell lineages, with ‘Naive’ T-cells transitioning into ‘Effector Memory’ cells and then branching into either ‘Recently Activated Effector Memory’ (TEMRA), ‘Exhausted’ (TEx) or ‘Resident Memory’ (TRM) T-cells. In COVID-19, clonal expansion indicating a SARS-CoV-2 antigen-specific T-cell response, was mainly observed in the highly cytolytic TEMRA lineage. In contrast, tumor-specific T-cells were found in the TRM lineage. Of importance, the ICI responsiveness rate was significantly higher in the non-pathogen-directed TEMRA and TRM cells in COVID-19. In cancer, TEx cells were shown to be ICI responsive as expected.

Conclusions: We are the first to provide a mechanistic rationale for an aggravated COVID-19 disease course in ICI-treated patients. Whereas ICI reactivates tumor-directed ‘exhausted’ T-cells in cancer, it preferentially potentiates non-pathogen-directed T-cells in COVID-19, thereby contributing to lung damage without boosting the antiviral immune response.

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Funding: Kom op tegen Kanker (Stand up to Cancer).

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