Title: COVID-19 in patients with cancer: Case series of the first 10 inpatient cases in a Cancer Health Board

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Abstract

Introduction

The clinical features, disease course and severity of COVID-19 may differ in individuals with cancer or undergoing cancer treatment. Cancer patients have been identified as a vulnerable group, but empirical evidence supporting this, or characterising disease course with cancer as a comorbidity, has not yet been reported.

Methods

A rapid clinical case review was conducted of the first 10 patients under the care of the Edinburgh Cancer Centre (NHS Lothian Health Board) with confirmed COVID-19 infection.

Results

Ten patients were admitted with confirmed COVID-19 prior to 8th April 2020. Of these, two have died and eight have been discharged. Median age was 56 (Range - 39-84). Of the two deaths, one was on treatment with a tyrosine kinase inhibitor, the other best supportive care, both of whom had metastatic disease. Three patients were neutropenic on admission, all three of whom survived. All 10 patients presented within 1 week of developing symptoms.

Conclusions

Rapid assessment and clear decision making on escalation status is necessary in cancer patients with suspected COVID-19. Serum markers such as CRP and Neutrophil-lymphocyte ratio (NLR) may aid risk stratification, as does extent of disease burden. Chemotherapy induced neutropenia does not necessarily lead to a worse outcome.

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Introduction

The emergence in Hubei Province, China, during December 2019, of the SARS-CoV-2 virus, known as COVID-19, has now grown to a global pandemic. COVID-19 has been confirmed in over one million cases worldwide (1). While most confirmed cases result in an asymptomatic or mild viral-like illness, and many more occur without virological confirmation, healthcare systems are buckling under the burden of managing those that require hospital care. In severe cases, this leads to an acute respiratory disease syndrome (ARDS) requiring ventilator-assisted breathing, with fatal outcomes in perhaps 1 in 4 of those admitted to hospital (2).

Infection frequently presents in an atypical manner in cancer patients, who may be undergoing immune-suppressing or immune-activating therapies. It is likely that standard diagnostic criteria and triage will need to be modified in the cancer context. There is currently little data to help us characterise COVID19 in patients with cancer but there remains concern that it may have a higher incidence, severity and mortality compared with the general population. Early evidence out-with the cancer context suggests older patients with existing health conditions such as cardiorespiratory comorbidities have worse outcomes (2). Studies of COVID19 in cancer patients are limited by their small number (3,4). Some have hypothesised that patients with cancer, who have a flattened immune status, may be less susceptible to the overwhelming inflammatory response associated with severe COVID-19 infection (5), whilst it is also well understood that those on potentially immunosuppressive chemotherapy may be at higher risk of developing the infection. The largest analysis of hospitalised COVID19 patients with cancer identified any form of cancer treatment within the last 14 days as a specific risk factor for a composite end point of either ICU, ventilation or death (Hazard ratio - 4.079 (1.086-15.322) (6). This has prompted the cancer field to evaluate priority areas for cancer care during the pandemic (7). However, evidence remains unclear due to small study number as to the specific relationship between COVID19 and cancer, particularly in relation to prognostic markers and ways of identifying patients at risk of rapid deterioration.

Since the first case of COVID19 emerged in Scotland in early March 2020 (8), our cancer services have evolved in preparation for the pandemic. Edinburgh Cancer Centre serves a population of 1.5 million people. We evaluated the clinical journey of the first ten patients with cancer diagnosed with COVID19 in NHS Lothian, which represents 60% of the whole region our Cancer Centre serves. Our aim was to identify early trends in their presentation and management which might aid cancer care decision making.

Methods:

We collated the clinical data from the first ten patients with a confirmed diagnosis of COVID-19, by polymerase chain reaction (PCR) test of a respiratory viral swab, admitted to the Edinburgh Cancer Centre and within the catchment of the NHS Lothian Health Board. In addition to basic demographic data, we recorded baseline blood tests in keeping with potential prognostic tests, including blood tests (neutrophils, lymphocytes, CRP) and imaging (Chest Xray, CT chest) where available.

Data were summarised to an extent necessary to protect against disclosure of personal data. The case series underwent rapid review and approval by the Chair of the Edinburgh Cancer Information Programme Board. Caldicott approval was obtained, noting that this is a public health emergency, and anonymisation principles had been followed. In the interest of patient

involvement, all patients were contacted to confirm agreement regarding inclusion prior to publication.

Any statistical analysis was performed with Graphpad Prism 8.4.1 and was non-parametric in all cases unless otherwise stated.

Results:

The first 10 patients were admitted to our regional cancer centre before 8th April 2020 and a summary of patient characteristics in shown in Table 1.

Of the ten patients, two died and eight were discharged. Apart from two patients, all presented with one or more of shortness of breath, cough and/or fevers. The two patients without these features presented with predominantly gastrointestinal symptoms. Of the ten patients, all presented after a week or less of acute symptoms. When comparing the last available lymphocyte count pre-COVID admission with that on admission, the lymphocyte count was lower (Median lymphocyte count: 0.72, IQR 0.49-1.105), in keeping with other studies of non-selected patients. The median lymphocyte count pre-COVID admission was below the lower limit of a normal lymphocyte count 1.23 (IQR 0.80-2.44) (Figure 1a).

The neutrophil count was not different between those who died and those who survived (Figure 1b). Neutrophil to lymphocyte ratio (NLR) was higher in those with severe infection (Died vs Discharged, Median 7.26 vs 2.42), suggesting this may be more useful that lymphocyte count (Figure 1c).

The two patients who died had a clinical course that was characterised by deteriorating hypoxia having required oxygen from the point of admission. Only one was on active treatment - a daily tyrosine kinase inhibitor taken up to the point of admission. Both were on a palliative pathway with a high burden of metastatic cancer. They had the highest CRP level on admission amongst the ten patients, and both had a normal neutrophil count (Table 2)

Eight out of the ten patients had a documented discussion regarding escalation including ventilation. No patients were admitted to ICU, and the two patients who died had documented discussions regarding escalation and resuscitation on admission such that ICU was felt not to be appropriate. None of the other patients were unwell enough to warrant discussion with ICU due to an acute deterioration.

Only one patient who survived required oxygen on admission. The three patients who were neutropenic (<1.0) on admission were all discharged, and two of these cases had a normal chest X-rays.

Discussion

Most available evidence originates from centres dealing with high infection rates in early 2020. A focused evaluation of 18 patients with cancer affected by COVID-19 in China suggested the incidence was higher in patients with cancer than in the overall Chinese population (1% versus 0.29%) with a higher mortality rate (4). A study of 1099 cases included only 10 patients with a concurrent or past diagnosis of cancer. The primary composite endpoint was admission to ICU, mechanical ventilation or death (= severe event) – this occurred in 6.1% of all patients, and 10% (one case) in a patient with cancer (9). The largest study to date with 28 patients showed that 53.6% patients had a severe event and suggest worse outcomes may be seen in patients who

had undergone treatment in the last 2 weeks or had stage IV disease (6). Another report of 12 cases suggested patients were older (median age = 66 years), a notable proportion had non-small cell lung cancer (7 patients), but only five patients were on active treatment (10).

The NLR was higher in patients with more severe disease, but this was not universally true. Notably, we noted our patients generally had a baseline lymphocyte count lower than the lower limit of normal. This suggests lymphocyte count may not be as useful in cancer patients in identifying those with severe disease. We also note that the neutrophil count was low in three patients with a good outcome, and two of these had no chest Xray changes. It may be that these patients cannot mount an immune response and therefore do not suffer an acute inflammatory response to the virus.

None of our patients underwent care in ICU, and the two patients who died had discussions on admission that ICU would not be in their best interests. We note this is different to other studies where more patients were escalated to ICU. Our Centre has a policy to discuss escalation and resuscitation at the point of admission, with the aim to do so with involvement of the patient and their family. In their study of 28 cancer patients with COVID19, Zhang and colleagues (6) reported over 21.6% were admitted to ICU, over a third had mechanical ventilation and nearly a third died. Given that 18/28 patients in their study had a cancer at stage I-III (not further subdivided), in comparison with three patients in this study, theirs may have been a more appropriate cohort for aggressive management. This is particularly pertinent given a subsequent study comparing outcomes between cancer and non-cancer patients with COVID19 suggests patients with stage I-III cancer have the same outcomes as non-cancer patients diagnosed with COVID19 (11). Our study is too small to make meaningful comparisons regarding survival, but note that in our patients, disease burden rather than recent treatment was a more notable difference between those who died and survived.

Our series supports prior publications suggesting that CRP and NLR (12) are also early indicators of disease severity in cancer populations. This builds on interest in NLR as a prognostic marker in cancer patients that was emerging prior to the pandemic (13,14).

Interestingly, the patients in our case series with neutropenia did not have worse outcomes. Of the three patients with neutropenia, all survived and two had normal chest X-rays. A paediatric oncology data series also suggested immunosuppressed patients with cancer also had a mild or asymptomatic COVID19 infection, and suggested that oncology treatments should not necessarily be delayed (15), although it should be noted that children are generally considered to have a less symptomatic COVID19 course (16).

Across the whole of NHS Lothian, in the same time period as these 10 cases occurred, there were 617 confirmed cases of COVID19 and 397 patients admitted as a result of COVID19 (17). The Edinburgh Cancer Centre covers the care of patients in multiple Health Boards of which NHS Lothian represents 60% of the whole area served. This suggests cancer patients are not an overwhelming proportion of COVID19 inpatients in our region. We are developing robust methods to accurately capture all cases of COVID19 in patients with cancer to understand more fully the relationship between COVID19 and cancer which will become increasingly relevant as the pandemic continues and the prevalence of COVID19 increases.

We are aware there are limitations to this case series. Due to the current UK testing guidelines, which are to test for necessary diagnostic purposes, we acknowledge that there may well be

other cancer patients infected, but not diagnosed. Clearly, we present a small cohort of patients and as such cannot infer broad conclusions until a larger cohort can be evaluated.

Conclusion

Our experience suggests patients with cancer diagnosed with COVID-19 require rapid assessment and decision making around escalation. Serum markers such as CRP and NLR may aid risk stratification for a worse outcome. It is not clear that a chemotherapy induced neutropenia necessarily leads to a worse outcome as previously suggested by the literature. Larger studies will allow further lessons to be learned in order to optimise use of cancer therapeutics as well as COVID19 management during the COVID19 pandemic.

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17. Lothian Safety Huddle, courtesy of Chris Stirling, Site Director, Western General Hospital, 8th April 2020

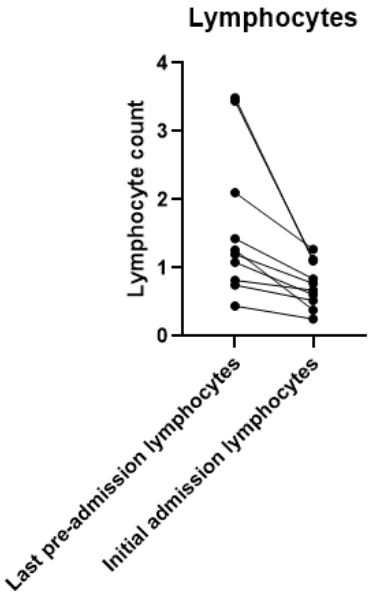
Table 1: Summary of patient characteristics

Age	Median (Range)	56 (39-84)
Gender	Female:Male	4:6
Cancer	Sarcoma	3
	Breast	2
	Other	5
Treatment with 8 weeks	Chemotherapy alone	3
	Targeted therapy	3
	Immunotherapy	0
	Chemo/Radiotherapy	1
	None	3
Treatment intent	Curative	3
	Palliative	7
Days since last systemic anticancer therapy	30-50	1
	10-30	2
	0-10	4
Outcome	Discharged	8
	Death	2

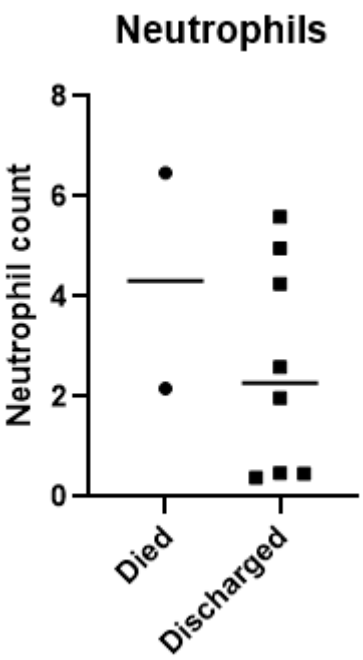
Table 2: Features of 9 patients. Remaining inpatient has been omitted to avoid breach of anonymity, and will be added to the relevant outcome table when outcome is known.

		All	Death	Discharged
Temperature	>37.5	5	1	4
	<37.5	5	1	4
Lymphocytes	>1.5	0	0	0
	1-1.5	3	1	2
	<1	7	1	6
Neutrophil count	>4	4	1	3
	1-4	3	1	2
	<1	3	0	3
CRP	>100	3	2	1
	10-100	4	0	4
	<10	3	0	3
CXR	Features inkeeping with infection e.g. consolidation, opacification	5	2	3
	Non-infective changes, or normal	5	0	5
Days to outcome	>5	4	0	4
	2-4	3	2	1
	<1	3	0	3
Age	71-90	2	1	1
	51-70	5	1	4
	31-50	3	0	3
Active Treatment in last 8 weeks?	Yes	7	1	6
	No	3	1	2

Figure 1:



a)



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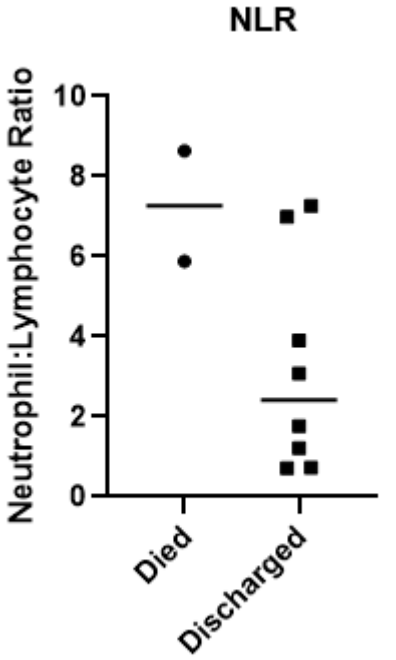

c)

1a) Last pre-admission lymphocytes and initial admission lymphocytes of ten patients with cancer, Lymphocyte count: units – cells x10^9/L. 1b) Admission neutrophil count by outcome - Neutrophil count: unit – cells x10^9/L. 1c) Neutrophil:Lymphocyte Ratio (NLR) by outcome.

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