Estimating the Risks from COVID-19 Infection in Adult Chemotherapy Patients

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KEYWORDS

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Abstract

The SARS-CoV-2 (COVID-19) novel corona virus represents a significant health risk, particularly in older patients. Cancer is one of the leading causes of death in most rich countries, and delivering chemotherapy may be associated with increased risk in the presence of a pandemic infection. Estimating this risk is crucial in making decisions about balancing risks and benefits from administering chemotherapy. However, there are no specific data about chemotherapy risks per se. Here we develop a simple model to estimate the potential harms in patients undergoing chemotherapy during a COVID outbreak. We use age-related case fatality rates as a basis for estimating risk, and use previous data from risk of death during influenza outbreaks to estimate the additional risk associated with chemotherapy. We use data from randomised trials to estimate benefit across a range of curative and palliative settings, and address the balance of benefit against the risk of harm. We then use those data to estimate the impact on national chemotherapy delivery patterns.

INTRODUCTION

The world is experiencing an outbreak of a novel coronavirus known as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2; COVID-19) and WHO has recently declared the disease a pandemic. Although the overall case fatality rate is lower than some other recent respiratory infections, the widespread pattern of infection puts many more people at risk[1]. Patients with cancer are more susceptible to infection than individuals without cancer because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments[2].

There are not yet any clear models to guide risk predictions in patients infected with COVID-19. One report by the Centres for Disease Control in China provided numbers of patients and fatalities divided by age, and by comorbidities. However, there was no cross-tabulation of factors, and so it is not clear how many patients in each age group had each comorbdity, nor how the risks associated with those co-morbidities interact with each other[3] . There is one small series of 18 patients with cancer, which suggests higher risks of intubation or death, but it is so small it difficult to draw robust conclusions, and the authors' conclusions have been criticised[4]. One other study suggests patients with a history of cancer have a higher risk of becoming infected with COVID. The data from CDC China have been used to simulate a population and then develop a risk model based on that simulated population[5]; Although a useful step, it almost certainly leads to "double counting" of risk (i.e. the increased risk of death in older patients and in those with hypertension is related, as hypertension is commoner in the elderly). Data from patients admitted to hospital show an increased risk of death in older patients[6].

Previous work in seasonal and pandemic influenza has highlighted that a history of cancer receiving chemotherapy within the last 6 months (ref) or immunosupression (including chemotherapy)[7–10] were all risks for death in patients infected with pandemic influenza. The risk estimates vary considerably, with odds ratios ranging from 3 to 12.

The available data indicates a strong age effect in the risk of death from COVID-19. There is probably an increased risk of death in patients with comorbidities, of which cancer is one. There are several studies indicating an increased risk of death in patients with cancer who are infected during influenza pandemics. There is limited data to suggest that patients who have recently received chemotherapy may be at increased risk of death from influenza infection. There are no good models to estimate the risk of death in patients who have chemotherapy and acquire COVID infection, but there are parameters from previous viral pandemics, all of which point to a higher risk of death in patients with cancer or those who are immunosupressed.

Medical practice does not always require precise estimates of risk. If a decision is binary (i.e. treat/ don't treat) then what we require is an estimate of risk that is good enough to make a decision, rather than being precise.The majority of adult chemotherapy offers modest benefit, particularly in patients with solid tumours. Although there are some diseases where chemotherapy offers very large benefits (e.g. germ cell tumours), the majority of patients derive modest benefit, and in the context of a COVID pandemic, the risks may outweigh the benefits. The immunosuppressive effect of chemotherapy may last for a considerable period of time, exposing patients to risk as infection rates rise. There has been little guidance so far: to date, we are aware only of individual centres publishing general information[11], and one charity-led initiative in the UK[12].

In this paper we estimate risks of death in patients who undergo chemotherapy and become infected with COVID. We use that model to illustrate several common chemotherapy scenarios

in both adjuvant and palliative scenarios, and provide code online for others to use. We use national chemotherapy data to estimate the number of patients whose treatment might be affected by these decisions.

MODELLING

We used combined data from the China CDC[3] , Italian public health authorities[13] and a COVID outbreak on a cruiseship[14] to estimate case fatality rates (CFR) by age group. We identified studies that estimated risk of harms (including death) in patients with cancer or immunosupression during influenza outbreaks and extracted data on risks of harm. We explored sensitivity by constructing models using central estimates of risk of harm and most optimistic estimates. We constructed clinical scenarios by identifying key clinical trials in the curative and palliative setting in five sentinel tumours sites (breast, lung, colorectal, prostate and brain), and extracted data on absolute benefit from treatment in those trials. For trials in the curative setting, we extracted data on the absolute difference in OS at the timepoint specified by the trial (typically 3 or 5 years). For palliative chemotherapy trials, we extracted data on the difference in absolute survival at 3, 6 and 12 month timepoints. We then compared the improvement in absolute survival from treatment with the potential harm if COVID infected, and visualised these results.

RESULTS

There is a clear impact of age on risk of death (Table 1). Data on risk of death with cancer in the context of influenza infection suggests and increased risk in the range of 3 - 12 fold. We chose the lowest reported odds ratio (3.67) as our optimistic estimate of risk. Combined with our age-based CFRs, these lead to estimates of risk by age in patients receiving chemotherapy who become COVID infected (Table 2). We summarise these results in figure 1, highlighting some potential benefit thresholds (3%, 5%, 10%) that are typically seen in adult solid tumour chemotherapy. Of the 9 scenarios, risk of death if COVID infected was higher than expected benefit in six of the seven, balanced in one and favoured chemotherapy in two cases. Readers can explore these data in a small associated program, available at https://gitlab.com/computational.oncology/covidcancerrisk

Although the instantaneous risk of COVID infection is small, the risk over the entire duration is likely to be considerable. While we can assume that the risk of infection in patients is the same as the expected population-level infection rate, population level infection may take many months to occur. A more time limited horizon is given by estimating the number of cases of time, and integrating that number.

DISCUSSION

It is clear that age is a significant risk factor for death in patients infected with COVID-19. In both this and previous viral pandemics, other comorbdities have been additional risk factors. There is reasonable evidence to suggest that patients who have cancer are probably at higher risk of death, and it seems unlikely to administration of chemotherapy will reduce that risk fur-

Age (years)	China		Italy		Diamond Princess cruise ship		Combined				
	Cases	CFR(%)	Cases	CFR(%)	Cases	CFR(%)	Cases	Deaths	CFR(%)	CI95%	
0-9	416	-	63	0	1	0	480	0	-	-	-
10-19	549	0.2	118	0	5	0	672	1	0.15	-0.14	0.44
20-29	3619	0.2	511	0	28	0	4158	7	0.17	0.04	0.29
30-39	7600	0.2	819	0.2	34	0	8453	19	0.22	0.12	0.33
40-49	8571	0.4	1523	0.2	27	0	10121	39	0.39	0.26	0.51
50-59	10008	1.3	2480	0.8	59	0	12547	144	1.15	0.96	1.33
60-69	8583	3.6	2421	2.7	177	0	11181	374	3.34	3.01	3.68
70-79	3918	8.0	2849	9.6	234	2.56	7001	592	8.46	7.80	9.11
>80	1408	14.8	2533	17.0	54	1.85	3995	639	15.99	14.86	17.13
Not reported	-	-	565	3.2	-	-	565	18	-	-	-
Total	44672	2.3	13882	5.8	619	1.13	59173	1833	3.10	2.96	3.24

Table 1. Case fatality rates by age group for available international data

Age	Cases	Deaths	CFR(%)	CFR with Chemotherapy (%)
0-9	480	0	-	-
10-19	672	1	0.086	0.23
20-29	4158	7	0.017	0.45
30-39	8453	19	0.22	0.6
40-49	10121	39	0.39	1.0
50-59	12547	144	1.15	2.9
60-69	11181	374	3.34	7.9
70-79	7001	592	8.46	16.9
>80	3995	639	15.99	15
Not reported	565	18	-	-
Total	59173	1833	3.10	7.6

Table 2. Estimated case fatality rates by age group with chemotherapy

ther, although providing an exact estimate of risk is difficult, and not yet possible. Due to the epidemic nature of the disease, with exponential growth in cases, while the risks today may seem small, the predicted risks over the next few months are very much higher.

There is consistent evidence to suggest that patients with a history of cancer are at higher risk of adverse outcomes when infected with COVID-19. A study of 138 patients with a baseline risk of ITU admission of 26%, 40% of those with a history of cancer required ITU admission[24], but included only 10 patients with cancer. A review of 18 cancer patients who developed COVID-19 infection showed a higher risk of harm (defined as requiring ventilation in ITU or death) 7/18 (39%) than the general population 124/1572 (8%). 12 of these 18 were being followed up after surgery, while the 4 who had undergone chemotherapy or surgery within the last month had higher risk still[4]. There is some evidence that patients with cancer might be at higher risk of infection[25].

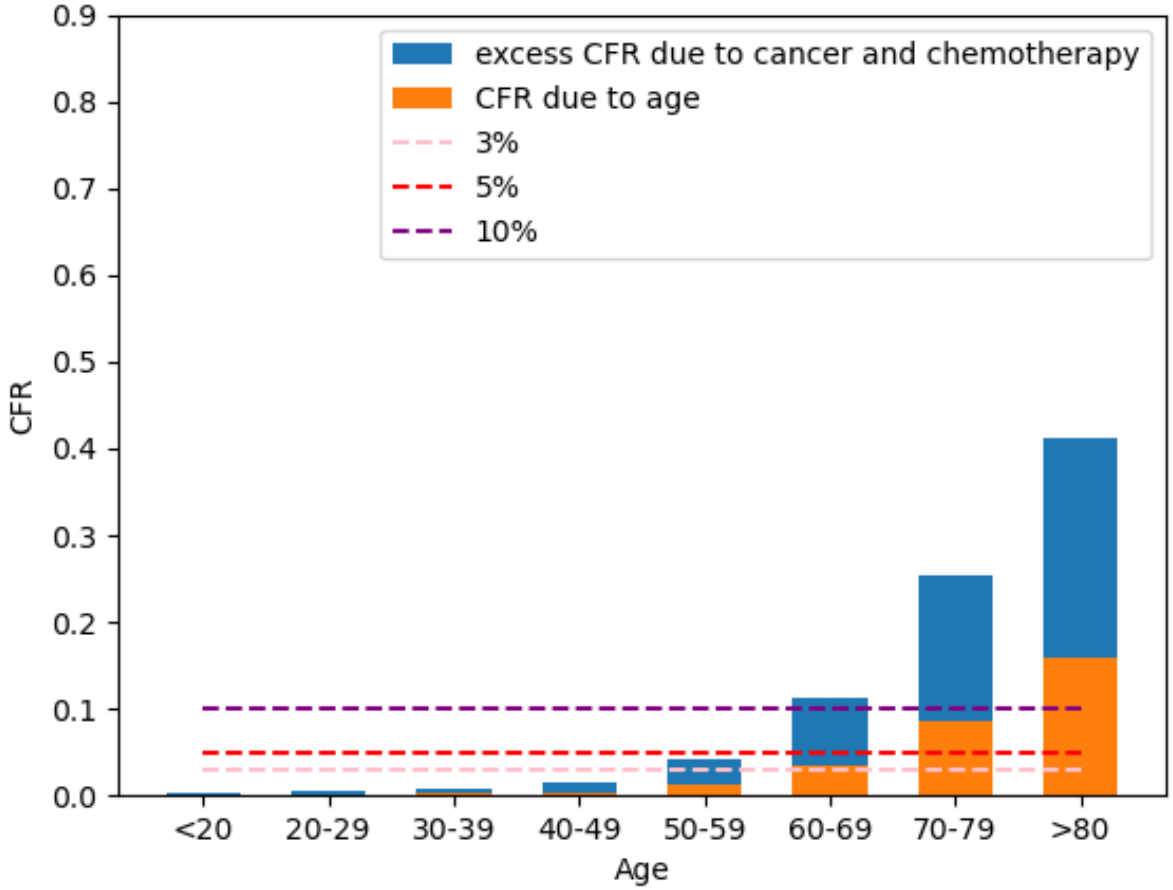

Figure 1. Optimistic model case fatality rates in patients with cancer infected with COVID-19, by age. Dashed lines represent common levels of benefit from chemotherapy in percent.

It is worth noting that the risks associated with cancer are based on small samples: aside from the two studies above (which included a total of 28 patients with cancer), the original dataset included only 107 patients with cancer. In contrast, the data on increased risk in older patients is much more robust, although the existing models do not adequately distinguish between risk due to age and that due to increased presence of co-morbidities in older patients.

Our model provides two estimates of risk in order to inform decisions. This model is based on the best available data, but is imperfect. We hope that better models will soon be available, but in the meantime oncologists need to make decisions about chemotherapy. Our model only requires oncologists to be able to specify the absolute improvement in overall survival, and then balance that against the predicted risk if the patient becomes COVID-19 infected. Most older adult patients with solid tumours have a level of elevated risk such that, even if we assume lower rates of infection and case fatality rates, the harms are likely to outweigh the benefits for most chemotherapy in most patients. The uncertainty about whether increased risk is due to having

Tumour Site	Case history	Chemotherapy Regime	Evidence	Outcome	CFR risk
ADJUVANT					
Colorectal	44yo male with resected stage III node positive AdenoCa of Colon.	5FU/Folinic Acid/Oxaliplatin	MOSAIC	10 year OS 59.0% vs. 67.1%; HR 0.80	CFR of 0.05. Benefit of chemotherapy outweighs risk
Breast	60yo female with resected Stage IIB adenocarcinoma of the breast.	EC-T Epirubicin/cyclophosphamide/Taxane	Early Breast Cancer Trialists' Collaborative Group (EBCTCG)	Reduced overall mortality from 40 to 35% (RR 0.84; 95% CI 0.78-0.91) OS at 6 months: 84.2 to 86.3%	CFR of 0.18. Risk outweighs potential benefit from chemotherapy.
Lung	66yo male with resected Stage IIIA NSCLC	Cisplatin-based doublet	LACE meta-analysis	Decreased risk of death of 5.4% at 5 years vs. no chemotherapy; HR 0.89, 95%CI 0.82-0.96	CFR of 0.18. Risk outweighs potential benefit from chemotherapy.
Brain	57yo male with WHO Grade IV resected GBM; MGMT Methylated	Temozolamide (150mg/m2)	Stupp et al 2009	14.6 vs. 12.1 months; HR 0.63, 95% CI 0.53-0.75. 2 year survival: 24% vs. 46% methylated group	CFR of 0.1. Benefit of chemotherapy outweighs risk
PALLIATIVE					
Colorectal	73yo male, metastatic colorectal AdenoCa Colon	5FU/Folinic Acid/Oxaliplatin	De Gramont et al	OS 16.2 vs. 14.7 months; Grade 3 or 4 neutropaenia 41.7% vs. 5.3%	CFR of 0.22. Risk outweighs potential benefit from chemotherapy.
Breast	68yo female, ER+ve, HER2-ve metastatic breast cancer	Capecitabine	ANZBCTG – capecitabine vs. CMF	OS 22 months vs. 18 months Probability OS at 18 months: 0.45 vs.0.52	CFR of 0.18. Risk outweighs potential benefit from chemotherapy.
Prostate	75yo male with metastatic prostate cancer	Docetaxel and prednisolone	Tannock 2004	HR for death 0.76 (95% CI, 0.62 to 0.94; P=0.009). Median survival 18.9 vs.16.5 months **OS @ 3 months:** 96% **OS @ 6 months:** 88% grade 3 or 4 neutropaenia = 9.6% febrile neutopaenia: <1%	CFR of 0.22. Risk outweighs potential benefit from chemotherapy.
Lung	73yo female; Metastatic non-small cell carcinoma;	Platinum-based doublet regime	NSCLC Collaborative Group. supportive care vs SC + CTx	HR, 0.77; 95% CI, 0.71 to 0.83; 9 month OS 20 to 29%. **3 month OS:** Probability of survival 0.65 to 0.75 **6 month OS:** 0.42 to 0.58	CFR of 0.22. Risk outweighs potential benefit from chemotherapy.
Lung	66yo female metastatic nonsquamous NSCLC, PDL1<50%, >1%	Platinum, pemetrexed and pembrolizumab	Keynote 189	OS @ 12 months: 69.2% vs 49.4% **OS@ 3 months:** 88% to 92% **OS@ 6 months:** 72% to 87% Grade 3,4,5 neutropaenia: 15.8% in pem group vs. 11.9% in plat+pem	CFR of 0.18. Risk and benefit of chemotherapy balanced.

Figure 2. Scenarios exploring absolute survival benefit and potential risks in a variety of common chemotherapy settings [15–23]

cancer, or receiving chemotherapy is of secondary importance. If it is due to having cancer, then we would suggest that receiving chemotherapy would simple increase in further. We would stress that any additional risk from administering chemotherapy is likely to be a multiplier on the risks seen here; thus small relative risks may translate to large changes in absolute risk for some patients. We have also assumed that both harm and benefits accrue over the same time period, whereas in reality, most improvements in cancer survival with chemotherapy are calculated at 2 and 5 years. For patients undergoing palliative chemotherapy, it is probably more reasonable to assume that the risks and harms accrue over a similar time period; for those having adjuvant treatment, where chemotherapy increases the chance of cure, the benefits may accrue over a much longer time period. In this sense, treatment is more valuable (in that it leads to more years of life) but harm from treatment also weighs more heavily.

Palliative chemotherapy may be given primarily for symptom relief, rather than to improve survival. Nonetheless, the risks of death are still elevated. Although radiotherapy incurs some of the same risks associated with hospital attendance, there are some situations where palliative radiotherapy might be substituted for chemotherapy with a reasonable expectation of it being safer. Decisions about continuing chemotherapy in those established on treatment are more diffi-

cult, as the relative benefits of (for example) longer vs. shorter courses of adjuvant chemotherapy have often not been explored in randomised trials. Where they have been, it may be worth exploring the incremental benefit in light of the increased risk. At the very least, because informed consent relies in part on understanding the balance between risk and benefit, given that the risk has changed, we would suggest confirming informed consent in patients who are continuing on chemotherapy. Non-cytotoxic agents (e.g. immunotherapy and bisphosphonates) almost certainly have different risk profiles. Nonetheless, there are some common concerns with patients receiving cytotoxic agents, in that they still attend hosptials, and may not be able to access care if services are overwhelmed.

The most striking finding is that under a range of conditions, most cancer patients are at $> 5\%$ risk of death if infected with COVID-19. It is notable that the 5% is greater than or equal to the benefit from most adjuvant chemotherapy for adult solid tumours. Although we accept that exact negative impact of COVID-19 in subgroups remains unclear, previous data during outbreaks of seasonal respiratory viral infections suggests that they are associated with an approximate doubling in risk. However, in contrast to outbreaks of seasonal infections, the majority of the population is expected to be infected with COVID-19 over a short-time period (3 - 6 months), there is no pre-existing immunity or vaccine, and the case-fatality rate is approximately 5 fold higher. For those reasons, decision-making in seasonal viral outbreaks does not directly transfer to the COVID-19 pandemic. Decisions about initiating or continuing cytotoxic chemotherapy in the context of a COVID pandemic need to be made carefully, and in light of the available data.

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