Patients with cancer and sepsis trials: an unfair representation?

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ABSTRACT

Approximately 20% of sepsis cases are thought to occur in patients with cancer. Thus, such patients are an important cohort to be represented and characterised among sepsis trials. However, patients with cancer are commonly excluded from sepsis trials, although the extent to which is unknown. In this opinion article, we discuss our findings that suggest that patients with cancer are being under-represented in sepsis trials, often with an unclear rationale. We question the validity of generalising results from sepsis trials to heterogenous cancer populations and call for wider inclusion of patients with cancer to bridge this knowledge gap in sepsis management.

KEYWORDS: sepsis, clinical trials, cancer

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Patients with cancer are an important cohort of patients at risk of sepsis

Sepsis remains a leading cause of death worldwide, accounting for up to 20% of all global deaths in 2017.[1] Patients with cancer represent an important cohort of patients admitted to hospital with sepsis, with up to 21% of sepsis cases related to cancer.[2] Such patients are at increased risk of sepsis secondary to immune suppression from cancer-related therapies and from the disease itself, tumour-related obstruction and major surgical procedures. Indeed, patients with cancer have been shown to be nearly 10 times more likely to acquire sepsis compared with patients without cancer,[3] with higher mortality from cancer-related sepsis compared with non-cancer related sepsis.[2–6] Significantly, sepsis is present in 30% of all deaths of patients hospitalised with cancer.[3] Research to improve outcomes in patients with sepsis has been recognised as a global health priority.[7] The importance of characterising the clinical and biological heterogeneity in sepsis has been emphasised in a move toward targeted medicine approaches.[8] Given that patients with cancer represent a substantial proportion of the patient population in sepsis, it is an important cohort to be represented and characterised among sepsis-related clinical trials. Furthermore, with increasing cancer survival, and a growing ageing population, the number of people living with cancer continues to increase. There were an estimated 3 million people living with cancer in 2020 in the UK, with this projected to increase to 4 million by 2030.[9] Thus, patients with cancer are and will continue to represent an important cohort to treat potentially reversible sepsis.

Exploring the exclusion of patients with cancer from highly cited randomised controlled trials in sepsis

Clinical trial development requires a balance of internal and external validity through use of specified exclusion criteria. Such criteria are important to trial development for efficiency, cross-trial comparability and safety, but can limit the generalisability of study results.[10,11] In a recent study looking at the exclusion criteria of randomised controlled trials (RCTs) published in high-impact journals, 37% of criteria were deemed 'poorly justified'.[11] The most common categories of poorly justified exclusions in this study included age, medical multiple health conditions and medication use. Malignancy was excluded in 16.3% of trials reviewed in this study, although patients with cancer were likely to be excluded in other categories, such as 'medication-related' and 'decreased life expectancy'. The extent to which patients with cancer are excluded in sepsis trials is unknown.

We performed a search of the most frequently cited RCTs in sepsis with the aim of analysing the frequency of exclusion of patients with cancer. Web of Science databases were searched and the top 500 cited trials in sepsis were reviewed for inclusion. Of these, 177 trials met our eligibility criteria of being in English, involving human participants aged 16 or older, and RCTs focused on sepsis with stated eligibility criteria. Exclusion of patients with cancer from these trials could be divided into four tiers: tier 1, exclusion of all patients with cancer (3/177 trials); tier 2, exclusion of subsets of patients with cancer (42/177 trials); tier 3, exclusion of features likely to relate to cancer, such as chemotherapy (42/177 trials); and tier 4, no cancer exclusion (90/177 trials). Overall, we found 87/177 (49%) RCTs excluded cancer in some form. Using the trials that included patients with cancer, we calculated that 17% of patients with sepsis also had cancer.

These findings suggest that patients with cancer are under-represented in sepsis trials. Although sepsis trials rarely directly

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exclude all patients with cancer, we found many exclude subsets of patients with cancer based on further specification, such as severity or cancer type. Exclusion of patients with cancer because of severity of disease was commonly ambiguous, with the terms 'uncured cancer' or 'advanced form of cancer' being frequently used. Ambiguity also arose in criteria pertaining to patients with cancer, with 'chemotherapy' or 'immunosuppression' frequently stated in eligibility criteria with no contextual detail. Not included in our tiers of cancer exclusion were the exclusion of patients related to prognosis and ceilings of care, important criteria that are likely to capture patients with cancer. Indeed, of all the trials included in this study, 54% excluded patients based on a limited prognosis, 27% excluded patients if not for full active treatment and 14% excluded patients with a 'do not resuscitate' order. Together, this highlights the varying complexity of the exclusion of patients with cancer from sepsis trials, with exclusion criteria often lacking clarity about exactly which patients should be excluded. Such uncertainty is a likely source of variation in terms of the recruitment of patients with cancer to sepsis trials among centres.

We estimated that patients with cancer represented 17% of patients with sepsis recruited to the trials that did not exclude such patients. Previous work estimated that 21% of patients with sepsis also have cancer,[2] suggesting that such patients are under-represented even in trials in which they are not directly excluded. Our findings suggest that there is a paradox, with an important cohort of patients who develop sepsis being under-represented in sepsis-related trials. This leaves an information gap regarding patients with cancer and sepsis and the question of whether we can apply results from sepsis trials to this population. Differences between patients with sepsis and without cancer exist, for example, because of immune dysfunction in patients with cancer, who are more likely to present with a neutropenia, a finding associated with higher rates of septic shock and mortality.[6,12] In addition, the microbiological aetiology of sepsis in patients with malignancy varies with higher rates of gastrointestinal infection, bacteraemia, fungaemia and infection of unknown origin,[2,4,13] which could result in the treatments tested in current trials not being applicable to these populations because they have not been part of the trial cohort. Whether such differences should be grounds for exclusion in sepsis trials is uncertain, but does question the validity of generalising results from sepsis trials to this population. In addition to the information gap about cancer-related sepsis versus non-cancer-related sepsis, there is also insufficient evidence available focussing upon the cancer population itself and the heterogeneity that exists within it. Differences in sepsis mortality exist depending on cancer type, with one study providing an estimate range of 28–46%[5] and another range of 42–82%[4] depending on cancer type. There has been a call for targeted medicine approaches in sepsis and a recognition that characterising clinical and biological heterogeneity within the syndrome is a priority.[14] We argue that such goals cannot be achieved with the current under-representation of patients with cancer in sepsis trials. There is a need to address the dichotomy of the population being represented by the sepsis trial literature and the sepsis population seen in practice.

Conclusion

We recognise that there are limitations in our approach, but our findings show that a significant proportion of sepsis trials (49%) exclude patients with cancer in some form. This suggests that an important cohort of patients most at risk of sepsis are under-represented in sepsis trials, often with an unclear rationale. As the number of people living with cancer increases, this lack of representation could also increase unless a shift for wider inclusion is made. This is important to ensure that trials in sepsis are most representative of the populations they intend to help. ■

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