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Editorial Comment

Do we need randomised trials for rare cancers?

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Recently, representatives from the US Food and Drug Administration (FDA), patient advocacy organisations and the pharmaceutical industry argued that traditional (full) FDA drug approval may be warranted for rare cancers based on non-randomised trials assessing surrogate endpoints, such as response rate [1]. Their point of view raises an important question facing oncologists: what level of evidence should we demand in recommending treatment for patients with rare tumour types? While every cancer patient's situation is unique, and individual clinical decision-making will always be required, rare cancers highlight an ongoing tension in oncology. On the one hand, if we only accept randomised trials powered for hard endpoints (mortality and quality of life) to guide decision-making, we may struggle to enrol enough patients to answer even the most basic questions about drug benefits and risks. Alternatively, if we recommend therapies based solely on response rates, or other surrogate endpoints [2], reached in small, single centre, uncontrolled studies, we may adopt many therapies that, in reality, confer little or no benefit.

The recent statement on an alternative approach for approving drugs for rare cancers [1] did not fully acknowledge this dilemma. Instead, the authors fell squarely on one side. For rare diseases, the authors argue, we should embrace the use of historical controls and surrogate endpoints and that randomisation is not needed—and not just for accelerated, but even, traditional FDA approval. Unfortunately, the field of oncology performs a disservice to patients with rare tumours when we lower the bar for FDA approval, and accept medications based on weaker levels of evidence. Empirical evidence regarding bias in historically controlled studies, the un-reliability of surrogate endpoints, and importantly, the feasibility of randomised trials in rare tumour types, suggest that patients with rare disease deserve to have access to drugs that are held to the same standard as drugs for patients with more common tumours.

1. Historical controls

The fact that historically controlled studies exaggerate the efficacy of treatments has been repeatedly demonstrated. As early as 1982, Sacks and colleagues showed that historically controlled trials were more likely to reach favourable conclusions regarding the efficacy of treatment than randomised trials on the same topic [3]. Recently, Zia and colleagues compared the response rates for chemotherapeutic regimens in phase II studies and subsequent randomised trials. The

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authors examined identical regimens in identical patient populations. Among over 40 comparisons, the authors found that 81% of the time response rates were higher in the phase II trial than in the subsequent randomised study, highlighting the fact that uncontrolled trials assessing response rates are prone to exaggerate treatment efficacy [4]. As such, relying on these studies to guide decisions in rare tumours will surely lead to a substantial overestimate of the activity of new drugs, making individual risk–benefit assessments increasingly challenging.

2. Unreliability of surrogates

Response rates and progression free survival remain surrogates for the only true patient centred benefits that exist: improvement in survival or quality of life [2]. However, response rate is a notoriously poor surrogate for these more important benefits. Novel drugs and drug combinations have long been shown to improve tumour response rate, without corresponding improvements in survival [5]. An examination of 146 colorectal cancer trials and 191 lung cancer trials found that response rate was a poor predictor of survival, with R2 (r-squared) of 0.10 and 0.16, respectively. This result means that only 10–16% of the variability in survival gains was explained by improvements in response, a poor correlation [6]. Thus, if patients with rare disease have their care guided solely by improved response rates, without trials assessing survival, it is quite likely that much of their treatment would confer real toxicity without real benefit. We can never be sure which improvements in response are likely to translate to improvements in how patients feel, function or survive.

3. Impossibility of randomised trials

Finally, some maintain that randomised trials are difficult if not impossible to conduct in rare tumours, simply because of the problem in accruing enough participants for those studies [1]. Of course, there is some truth to this argument, as the number of randomised trials in more common cancers such as breast or lung far exceeds those for primary CNS lymphoma. Yet, at the same time, large randomised trials can and have been conducted by broad coalitions of collaborators for even ultra-rare tumours. The FIRM-ACT trial randomised over 300 patients with adrenocortical cancer (ACC) to two different cytotoxic regiments [7]. Although ACC has an annual incidence of 0.7–2 per million persons, FIRM-ACT was able to fully accrue in 6 years, and render a reliable verdict on an important clinical question [7]. Moreover, an analysis of US FDA cancer approvals for rare tumours shows no clear trend in the percent of trials that were randomised as the incidence rate for a cancer type fell from 6 to 1 case per 100,000. In other words, even though there was a sixfold difference in incidence between malignancies, there was no greater difficulty to conduct randomised trials, as would be expected if incidence rate were the prime barrier to randomisation [8]. In short, randomisation likely has more to do with our expectations in the research community, than the incidence of a tumour. When a broad desire to conduct randomised trials exists, as with ACC, they can be done.

4. Conclusion

Patients with rare tumours already face challenges in identifying providers with sufficient experience, interest and knowledge of their condition. Recent proposals by the pharmaceutical industry, patient advocates and the US FDA to lower the regulatory bar for drug approval for these lower frequency tumours are misguided in their attempt to help these patients. Patients are not truly benefitted when more drugs are approved based on weak evidence. Instead, as has been seen repeatedly in medicine, weak evidence likely overestimates the benefits of novel therapies, providing false inferences. The arguments that randomised trials are impossible in rare diseases, and historically controlled trials with surrogate endpoints are adequate for drug approval, are challenged by several decades of careful empirical work. All of us in oncology want nothing less than ensuring that all patients, including those with rare tumours, receive excellent and timely care. However, lowering the regulatory bar to achieve this is a dangerous and misguided approach. Instead, advocates for patients with rare cancers should demand that these patients not be excluded from the conduct of well-done, robust randomised trials, and that we work collaboratively to design and enrol patients in these trials. Having robust evidence—not just guesses—about treatment efficacy in rare cancers would benefit doctors and patients alike.

Conflict of interest statement

None declared.

References

[1] Simon R, Rothenberg ML, Sommer J, et al. The role of non-randomized trials in the evaluation of oncology drugs. Clin Pharmacol Ther 2015.
[2] Pazdur R. Response rates, survival, and chemotherapy trials. J Natl Cancer Inst 2000;92:1552–3.
[3] Sacks H, Chalmers TC, Smith Jr H. Randomized versus historical controls for clinical trials. Am J Med 1982;72:233–40.
[4] Zia MI, Siu LL, Pond GR, et al. Comparison of outcomes of phase II studies and subsequent randomized control studies using identical chemotherapeutic regimens. J Clin Oncol 2005;23:6982–91.

[5] George SL. Response rate as an endpoint in clinical trials. J Natl Cancer Inst 2007;99:98–9.
[6] Johnson KR, Ringland C, Stokes BJ, et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol 2006;7:741–6.
[7] Fassnacht M, Terzolo M, Allolio B, et al. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med 2012; 366:2189–97.
[8] Gaddipati H, Liu K, Pariser A, et al. Rare cancer trial design: lessons from FDA approvals. Clin Cancer Res 2012; 18:5172–8.