Di Bella's therapy: the last word?

The evidence would be stronger if the researchers had randomised their studies

Wonder cures for cancer appear regularly. The latest comes from Italian physiologist Luigi Di Bella, whose "multitherapy" comprises a mixture of melatonin, bromocriptine, somatostatin, a solution of retinoids, and, depending on the kind of cancer, either cyclophosphamide or hydroxyurea. Political and media support for Di Bella's treatment led to the courts ruling that Italian hospitals must provide it.[1] But research that we publish today (p 224),[2] which has already been reported in the media, suggests that the treatment is ineffective and toxic. The research could, however, have been better designed.

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The researchers, who were funded by the Italian government, conducted 11 independent uncontrolled multicentre trials in which 386 patients with different types of advanced cancer were given Di Bella's multitherapy. They found no evidence of a clinically important response, and treatment was discontinued

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in 86% of the patients because of disease progression, toxicity, or death. Most clinicians will, we suspect, find this convincing evidence, but it is not perfect. We don't know whether the patients enrolled into these studies (all people who had asked for Di Bella's treatment) were representative, and we don't know whether controls would have done better or worse. The researchers should have conducted randomised controlled trials.

Why were these trials not randomised? Even though some experts claim that phase II clinical trials are usually non-comparative,[3] and the authors argued that they were using these studies to assess whether randomised studies were warranted,[2] the best way of avoiding bias is through randomising patients to intervention and control groups.[4] The usual reasons for not randomising are difficulties with randomisation and recruitment, cost, ethical considerations, and time.[5]

Difficulties with randomisation or recruitment seem to be weak reasons. Most would agree that simultaneously performing 11 multicentre studies within 10 months is no mean feat. So why not take it a bit further? The authors claim that patients would probably not have agreed to be randomly allocated to different treatments (or, in this case, placebo). But is that really so? Given that "several thousand patients requested treatment with Di Bella's multitherapy," several hundred might well have agreed to participate in a randomised controlled trial. Costs may have played a part. Arguably it would have been better to assess Di Bella's therapy in fewer types of cancer, but there was obviously a need to test the treatment in a broad range of cancers. The authors also say that they could not have done randomised trials for ethical reasons—but these are not clear. Indeed, some would claim that the inferior design of these studies was unethical. Time was probably the most influential factor, as there was increasing public pressure on the Italian health minister to clarify this issue.[6]

The design of these studies is flawed; the results are already known; and Di Bella and his followers probably would not accept the findings, even if the studies had been randomised, double blind, and placebo controlled. So, why are we publishing this paper in the *BMJ*? Firstly, even though the results have appeared in the media, these studies and their design have not been formally published. Secondly, we should acknowledge this swift concerted action against a bogus therapy of nationwide importance. Thirdly, treating this topic seriously may prevent future cases—both of the implementation of treatments with unknown efficacy and side effects and of studies of weak design to answer important questions.

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5 Sibbald B, Roland M. Understanding controlled trials. Why are randomised controlled trials important? *BMJ* 1998;316:201.
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