Authors' reply

We thank Benjamin Kessler and Robert Hoffman for their interest in our work,[1] and agree with them that there are insufficient data to recommend this regimen without further trials. A large cluster randomised controlled trial is required to compare effectiveness against the current regimen.

We recognise differences in the approach to management of this common problem in the UK compared with most other countries, notably in the initial paracetamol concentration deemed to place patients at potential risk.

We would stress that the reason for our search for better acetylcysteine protocols relates to concerns about the high incidence of adverse reactions with the current intravenous regimens, not just economic considerations. However, even extending the initial infusion from 15 min to 1 h does not reduce these adverse effects,[2] and they occurred with sufficient intensity in our study[1] to require treatment interruption in 30% of cases in the control group. Importantly anaphylactoid reactions are more frequent in patients with low paracetamol concentrations, who are generally at least risk of hepatic injury.[3,4]

We would never foresee treating paracetamol poisoning with this shorter 12 h regimen without a measurement of blood paracetamol concentration, international normalised ratio, and liver function tests following antidote therapy. It has been shown that the speed of increase in alanine aminotransferase (ALT) in patients correlates with hepatic injury,[5] and in our series all patients who had no ALT rise had no detectable paracetamol concentrations by routine laboratory assay at 12 h after antidote administration, suggesting that it should be relatively easy to select patients for early discharge. We also believe that increasing availability of novel biomarkers should assist in improved patient selection for treatment and early discharge.[6]

SHLT is a member of the UK Commission on Human Medicines. All other authors declare that they have no competing interests.

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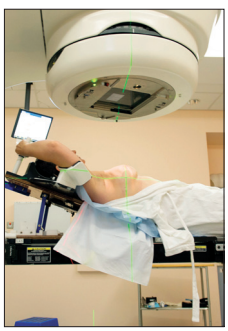
Late effects of breast radiotherapy

We thank Heather Goodare and colleagues for their Correspondence (Feb 15, p 602)[1] regarding the publication of the START (Standardisation of Breast Radiotherapy) trial 10-year results,[2] but wish to correct some misunderstandings and respond to their comments.

The START 10-year paper reports 5-year and 10-year clinical assessments of late adverse effects,[2] whereas the results published in 2008 and 2010 related to photographic and patient self assessments.[3–5] Although absolute rates of late adverse effects reported using these three forms of assessment (scoring of change in photographic breast appearance blind to treatment allocation, clinical assessments, and patient self-assessments) vary, they are fully consistent with each other in discriminating between the randomised schedules. Vocabulary is matched to the user; for example, patients score breast "hardness", whereas clinicians score "induration". The occurrence of bone necrosis was not collected in the trials although rib fractures were reassuringly rare. We acknowledged in our paper[2] that the timescale for some adverse effects such as cardiac events is long, and that we are continuing to receive follow-up data on the START patients. However, recent analysis suggests that hypofractionation might be gentler on the heart than is standard fractionation, but the real priority is to protect the heart whatever dose schedule is used, and heart-sparing protocols are now widely practised.[6,7]


Dr P Marazzi/Science Photo Library

Stratification by multiple prognostic factors can be problematic and is usually unnecessary in large-scale phase 3 randomised trials. In the START trials patients were stratified by treatment centre, type of primary surgery, and tumour bed boost, with the randomisation generating balanced groups with respect to multiple patient, tumour, and treatment factors, including tumour grade. We presented subgroup analyses in our paper,[2] which showed that there was no differential effect of the hypofractionated schedules on either tumour control or late adverse effects according to tumour grade.

Finally, Goodare and colleagues[1] are correct to highlight that a tailored approach according to each patient's particular cancer might be more appropriate. Current radiation research is looking at exactly that, with advances in translational research enabling more detailed examination of the link between tumour and patient characteristics and radiation

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sensitivity. The START trials have provided important information about the sensitivity of breast cancer and normal tissues to radiotherapy dose, but they are just part of the whole spectrum of research aiming to optimise radiotherapy treatment for breast cancer.

We declare that we have no competing interests.

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Standardised packaging and tobacco-industry-funded research

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Standardised tobacco packaging is intended to reduce the appeal of tobacco products by removing advertising and increasing the prominence of health warnings. This measure has strong support from health professionals, particularly as rates of child uptake of smoking are still unacceptably high.[1]

The first country to introduce standardised packaging was Australia in December, 2012. It is not expected to have an immediate effect on youth smoking rates, but rather, as with other tobacco control interventions, to have a long-term effect on youth uptake.[2]

Tobacco industry misrepresentation of the evidence in order to try to block public health interventions by manipulating policy making and public opinion is well documented.[3]

Recently, Philip Morris International funded an analysis of smoking among Australian adolescents aged 14–17 years showing "an absence of any plain packaging effect".[4] We have reviewed the data presented in Ashok Kaul and Michael Wolf's paper[4] and conclude that in view of the short time span since the measure was introduced, the variability in the measure, and the small sample size, this is neither an unexpected nor a meaningful conclusion. Kaul and Wolf[4] used data collected by a market research firm using door-to-door surveys, including about 200–250 different children each month. Reported smoking prevalence varied widely from month to month (eg, between 3% and 13% in 2011–14). Between 2001 and 2013 smoking prevalence was falling by 0·44% per year, during a period when a range of interventions had been implemented.[2] At the time standardised packaging was introduced, smoking prevalence was 6%. In the previous year, mean deviation from this trend was –0·6%, whereas in the year after it was –0·4%. We estimated standard deviations of 1·67 in the year before and 1·45 in the year after implementation. Conversion to standard errors reveals that a reduction of 1·25% in the year after plain packaging compared with the year before would be required to be statistically significant using this analysis. Against the background decline of 0·44% per year, this would equate to a fall of 1·69%; nearly a four-fold increase in the rate and far exceeding the likely effect. We are surprised that Kaul and Wolf do not mention this rather obvious limitation in their discussion of the results.[4]

The publication of Sir Cyril Chantler's review on standardised packaging of tobacco on April 3, 2014,[5] which concludes that the available evidence does support standardised packaging of tobacco products, is welcome—as is the UK Government's announcement that it will be bringing forward draft regulations on standardised packaging by the end of April, 2014. However, the lesson from Australia is that the tobacco industry's struggle against standardised packaging will not cease and it is essential to guard against continued misrepresentation of the evidence.

We declare that we have no competing interests. DA is chief executive of Action on Smoking and Health which receives core funding from the British Heart Foundation and Cancer Research UK and project funding from the Department of Health to help support implementation of the Tobacco Control plan for England.

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