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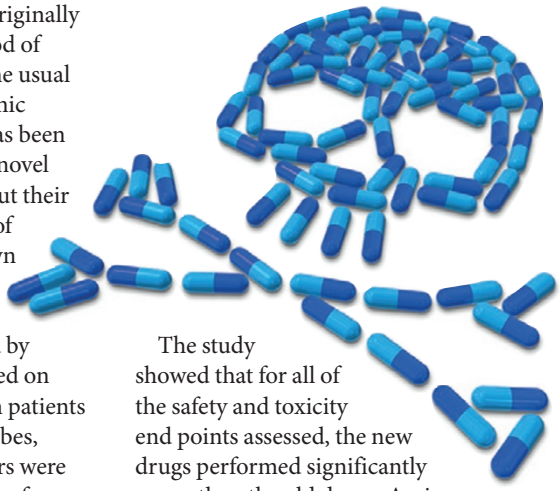
TARGETED THERAPIES

The toxic reality of new drugs

Targeted anticancer therapy was originally envisaged to be the optimal method of targeting cancer without having the usual toxic effects associated with systemic therapy. Part of the original aim has been realized, but unfortunately theses novel anticancer therapies are not without their drawbacks. Now, a meta-analysis of new anticancer therapies has shown that they are more toxic than their traditional counterparts.



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This meta-analysis was initiated by Eitan Amir and his colleagues based on previous work assessing toxicity in patients with breast cancer. As Amir describes, "we noted that aromatase inhibitors were associated with a higher frequency of certain serious toxicities than tamoxifen and, therefore, decided to extend the hypothesis that new drugs are more toxic than old drugs to a general cancer population." To test their hypothesis, the researchers identified 38 randomized clinical trials that each assessed a novel anticancer drug that was approved for the treatment of solid tumours by the FDA between 2000 and 2010. The meta-analysis of these clinical trials had three safety and tolerability end points: treatment-related death, treatment discontinuation related to toxicity, and grade 3 or 4 adverse events.

The assessment of these 38 trials was complicated by the fact that only 13 of the clinical trials reported the proportion of patients with at least one grade 3 or 4 adverse event. Six of the included studies did not report details of treatment discontinuation and, surprisingly, three of the trials did not report data on deaths related to toxicity. Taking these data alone, it seems that the systematic approach to the collection and reporting of toxicity that has been advocated by the FDA, had not been implemented at the time of these trials and is of crucial importance in the future.

The study showed that for all of the safety and toxicity end points assessed, the new drugs performed significantly worse than the old drugs. Amir summarized the more significant findings as: "despite improvements in cancer outcomes and occasionally overall survival, many new drugs are associated with increased toxicity across the board. It should be noted that as this study used data from clinical trials, it is anticipated that the use of drugs in clinical practice where patients are less selected for good performance status and few comorbidities may lead to an even less favourable balance between efficacy and toxicity."

In their article, the authors state that these toxicities are "the price we pay for progress." However, they also point out that many of the safety studies of new drugs are carried out at the phase I or II stage, with a small patient population. It seems that it is now time to ensure that phase III registration trials report on the risks as well as the benefits of a therapy, and that the follow up is sufficient after registration to protect patients.

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Original article Niraula, S. *et al.* The price we pay for progress: a meta-analysis of harms and newly approved anticancer drugs. *J. Clin. Oncol.* doi:10.1200/JCO.2011.40.3824