Prescrire International Editorial

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The imaging mirage

In placebo-controlled clinical trials of cytotoxic drugs, in which the primary endpoint is progression-free survival, progression is often determined on the basis of imaging or laboratory endpoints that sometimes worsen well before the patient's clinical condition. And some protocols stipulate that once patients in the placebo group are considered to have "progressed", they will then receive the same cytotoxic therapy as the active group.

This was the case in a placebo-controlled trial of *regorafenib* (reported on p. 234), in which nearly all patients in the placebo group received *regorafenib* a few weeks after their inclusion in the trial, due to progression (usually imaging-defined progression) of a gastrointestinal stromal tumour. Seventeen months later, half of the patients had died, with no difference detected between the two groups.

In effect, this type of protocol is comparing immediate initiation of the cytotoxic drug following diagnosis, versus delayed initiation of the same drug at a date determined by the results of clinical investigations. In these diseases, in which progression is inevitable without treatment, almost all patients receive the study treatment sooner or later. It is therefore difficult to detect a difference in efficacy in terms of overall survival or to evaluate the new drug's adverse effects, since nearly all patients were exposed to the drug.

In summary, the narrow design of these trials means that they add very little to our understanding of the treatments concerned. Marketing authorisation is granted on this basis, i.e. evidence of an effect on imaging findings… while patients and health professionals are left not knowing to what extent the drug affects the disease itself.

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