drug companies or agencies specialising in continuing education (15).

In summary

Reputation and expertise are not sufficient to guarantee that a source will provide thorough and reliable information. Healthcare professionals know there are ways to avoid undue influence: the lack of financial ties with companies is a first determinant of independence and impartiality. But nothing can replace a critical mind, even when it comes to information provided by a renowned professor.

No doubt many academics see no harm in accepting fees from drug companies in return for their services, and may even think they are "doing the right thing" by accepting funds to boost their research. But how many of them would continue to accept such funding if they knew they were being "managed"; that their "performance" was being evaluated; or that they represent a simple marketing tool, on a par with medical sales reps?

Finally, national authorities seeking to ensure access to quality healthcare must protect patients and healthcare professionals from the influence of key opinion leaders. Independent clinical research is more than ever necessary.

a- The experiment is reminiscent of Stanley Milgram's work in 1961, in which he showed that individuals were willing to give life-threatening electric shocks when ordered to do so by a person in a white coat (ref 16).

b- In 2006 a US marketing agency estimated that drug companies spent 15% to 25% of their marketing budgets on conferences, mostly involving key opinion leaders (ref 8).

c- Management of key opinion leaders is a highly profitable sector: one agency specialising in marketing and key opinion leaders has a page on its website entitled "Earn enough money to play more golf" (ref 17).

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Lessons from the other side of the Atlantic

Abstract

● **In the United States, *bevacizumab* was approved for use in combination with *paclitaxel* for the treatment of metastatic breast cancer on the basis of a single trial showing a beneficial impact on progression-free survival, a surrogate endpoint. The indication in breast cancer was withdrawn in 2011 when a new review of the data showed no increase in overall survival.**

● **In the European Union, *bevacizumab* was approved for use in combination with *paclitaxel* or *docetaxel*, again based on an improvement in progression-free survival. Following a review of clinical trials using this same endpoint, the indication for combination with *paclitaxel* was maintained while the indication for combination with *docetaxel* was withdrawn in 2011. Furthermore, *bevacizumab* was approved for use in combination with *capecitabine* on the basis of progression-free survival data.**

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The differences in the regulatory histories of *bevacizumab* in breast cancer between the United States and Europe clearly illustrate the issues associated with the evaluation of cancer drugs.

United States: reluctance from the beginning, leading to eventual withdrawal

The US Food and Drug Administration (FDA) usually requires two trials with similar results showing a gain in overall survival before authorising a cytotoxic drug. In exceptional cases, a single, well-designed trial showing a significant survival benefit may suffice (1).

The initial clinical evaluation of *bevacizumab* in metastatic breast cancer submitted to the FDA and considered by the ad hoc committee on 5 December 2007 only contained data from the E2100 trial, for use in combination with *paclitaxel* (2). The committee voted 5 to 4 on the recommendation for marketing authorisation. Despite the lack of a documented improvement in overall survival, some experts considered that a difference of 5.5 months in progression-free survival was clinically relevant. This decision triggered a heated debate on the use of progression-free survival as a valid endpoint in clinical trials (3,4). On 20 July 2010, the same committee reviewed the results of the Avado and Ribbon-1 trials and voted 12 to 1 against authorising first-line use of *bevacizumab* in metastatic breast cancer, given the lack of an overall survival benefit in these trials. Moreover, these trials did not show the same magnitude of benefit in progression-free survival as in the E2100 trial. This indication was finally withdrawn in 2011.

Progression-free survival is a poor choice of primary endpoint

Progression-free survival is a surrogate endpoint (2,5). The main criticisms against the use of this endpoint that were raised during the debate in the United States support those previously published in this journal (3-5). ▶▶

▶ Progression-free survival simply reflects changes in tumour burden. It does not address the patient's quality of life, which may be undermined by the adverse effects of treatment: in the E2100 trial, for example, 21% of patients experienced serious adverse effects due to the addition of *bevacizumab*.

Nor is progression-free survival a very sensitive endpoint. For example, a normal chest radiograph does not rule out metastases. The measurement must be made by blinded, independent assessors. It is difficult to assess cases in which no measurable tumour is visible on imaging studies. The results also depend on the times when progression is assessed, and they may be biased by missed evaluations, incomplete baseline assessment, and unscheduled evaluations performed in different patients.

In Europe, drug companies, not patients, get the benefit of the doubt

In early 2012, the European Medicines Agency still considers that progression-free survival, determined by imaging methods, is an acceptable measure of efficacy directly attributable to a treatment. This agency does not require an improvement in progression-free survival to be accompanied by a gain in overall survival, but simply that overall survival is not inferior in the treatment group, which would indicate a detrimental effect in the long term (6).

As in the United States, the European Union granted initial marketing authorisation for *bevacizumab* in combination with *paclitaxel* on the basis of single trial (E2100) versus *paclitaxel*. The indications were extended to include *bevacizumab* combination with *docetaxel* in 2009, based on the results of the Avado trial (7,8).

In February 2011, the European Medicines Agency reviewed the entire dataset from the E2100, Avado and Ribbon-1 trials. For *bevacizumab* combination with *paclitaxel*, subgroup analysis of the Ribbon-1 trial showed a non-statistically significant difference of 3.1 months in progression-free survival in favour of *bevacizumab* adjunction. The EMA experts considered that the lack of statistical significance was due to the small size of the subgroups, and that the results of the Ribbon-1 trial confirmed those of the E2100 trial. They recommended maintaining the indication for combination with *paclitaxel*, as the analysis of overall survival in these trials showed no adverse impact of *bevacizumab* adjunction. Regarding *bevacizumab* combination with *docetaxel*, the experts considered that, in the initial Avado trial, the gain in progression-free survival due to bevacizumab adjunction was smaller (1.9 months) and that it was only 0.8 months in the Ribbon-1 trial. Moreover, they considered that there was a trend towards an adverse impact on overall survival with the addition of *bevacizumab*, although it was not statistically significant. Consequently, they recommended withdrawing the indication for use in combination with *docetaxel*.

In Europe, another compromise

On 14 April 2011, the European Medicines Agency recommended extending the indications of *bevacizumab*, for combination with *capecitabine*, based on the Ribbon-1 trial in first-line treatment and the Ribbon-2 and AVF 2119g trials in second-line treatment. These trials showed that adding *bevacizumab* to *capecitabine* prolonged progression-free survival by respectively 2.9 months (statistically significant), 2.8 months (not statistically significant) and 0.7 months (not statistically significant), without prolonging overall survival (9).

However, because of less favourable results, use of the *bevacizumab* + *capecitabine* combination was restricted to patients who could not receive taxane or anthracycline therapy or who had received such drugs as adjuvants for more than one year.

Marketing authorisation for cytotoxic drugs must be based on robust data

The history of marketing approval for *bevacizumab* in the treatment of breast cancer on the two sides of the Atlantic shows that it is unwise to grant hasty marketing authorisation on the basis of a single trial using a surrogate endpoint. Two trials yielding similar results should be the minimum requirement. Based on three trials and a robust endpoint, overall survival, FDA experts firmly rejected the use of *bevacizumab* in breast cancer. In contrast, EMA experts accepted an imprecise surrogate endpoint, while quibbling over what magnitude of improvement in progression-free survival was needed to be considered "clinically relevant". They further complicated the situation by taking into account "trends" towards statistical significance. This resulted in convoluted indications, leaving patients unable to estimate the possible benefits while faced with well-documented adverse effects.

Thus, at least two robust trials with an unambiguous endpoint are needed to make decisions that are clearly in patients' best interests.

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