EDUCATION & DEBATE

Registration of drugs for treating cancer and HIV infection: a plea to carry out phase 3 trials before admission to the market

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Drugs for cancer and HIV infection tend to be admitted to the market on the basis of results from phase 2 trials. Assessing the benefit-risk balance with phase 2 trials often is difficult—the effect of the drug is usually temporary; the correlation between response or improvement of clinical measurements and the patient's wellbeing is often poor; and the side effects of drugs for these fatal diseases are serious. Therefore, although sometimes difficult to conduct, comparative trials that use standard treatment, placebos, or best supportive care remain the cornerstone for reliably assessing the benefit-risk balance.

The common criterion of drug regulatory committees for registration of a drug is that efficacy and safety have been shown in extensive pharmaceutical, pharmacological, toxicological, and clinical studies. Usually the clinical aspects of a drug are studied in phase 1, 2, and 3 trials, but whether all three phases are necessary for the registration of drugs for cancer and HIV infection is a matter of debate in Europe and the United States.

The media, the pharmaceutical industry, and the patients involved all put pressure on the drug regulatory authorities to accelerate the procedures and to relax the criteria for admitting oncolytics and drugs against HIV infection to the market. They argue that the three phases of clinical trials are time consuming and may withhold a potentially valuable drug from the patient for too long, and that this requirement is therefore not ethical. They advocate early registration if it appears from phase 2 trials that a tumor is responding and the outcome of the patients is better than that of historical controls; for such drugs phase 3 trials, in which the drug is compared with standard treatment, placebo, or untreated controls, can be omitted or done after marketing. They also say that drugs for HIV infection should be available as soon as possible—for instance, if a positive influence on surrogate end points has been shown.

In the United States and some European countries the authorities tend to allow early registration of drugs to treat fatal diseases and consider a positive outcome in phase 2 trials or a favourable effect on surrogate end points sufficient to authorise marketing. An accelerated approval may, however, come into conflict with the main task of the drug regulatory authorities: to assess the benefit-risk ratio of a drug. In contrast with prescribers and consumers, the authorities have the opportunity to review all the data on a drug, and thus can give an impartial judgment about the balance of its benefits and risks. Since the community is aware of this impartial judgment and relies on it, early registration has the danger that false expectations are created about the efficacy of the drug.

Are randomised controlled trials always necessary for a reliable assessment of the risk or benefit of a drug? In some circumstances the answer could be no: if the results of phase trials indicate that the efficacy is unequivocal (a formerly fatal disease is cured) and the

safety acceptable, marketing of the drug could be approved early. Observations in a few patients or even a "n=1 trial" theoretically would suffice for registration if the action of the drug is impressive. This situation, however, is rare. Although several classes of drugs have high "cure rates" (fluoroquinolones in urinary tract infections, omeprazole and H2-receptor antagonists in peptic ulcer disease, for example), most drug regulating authorities have not registered them without comparative trials.

Should other criteria be applied in fatal diseases? My answer is no, because especially in cancers and HIV infection, the benefit:risk ratio is much more difficult to assess than in other diseases.

Is treatment efficacious or beneficial?

In cancer or HIV infection it is very difficult to conclude whether a drug is efficacious or whether the treatment offers benefit to the patient. Most advanced malignancies and HIV infection cannot yet be cured with drug treatment. Mostly, the effect of the drugs is temporary; and best, death is postponed.

Cure is an unrealistic requirement for registration of oncolytic agents or drugs used in HIV infection, and the criteria for efficacy of these drugs have already been loosened. In the treatment of cancer the efficacy of a drug is determined by the number of patients responding (complete or partial disappearance of the tumour), duration of response, disease free interval, and the increase in survival. The effect of any cytostatic drug depends on the nature and extent of the particular malignancy, and in most advanced malignant diseases only 25-30% of patients may respond to the drug. Survival, although better than in untreated patients, seldom exceeds one or two years. Whether these figures are clinically relevant depends on the definitions of response, the proportion of patients achieving a complete response, and the implications of a complete response in the course of the disease. Such figures should not be underestimated, but such percentages would be unacceptably low for registration of drug treatments in many other diseases.

Examples are numerous: at present relatively low response percentages and a limited increase in survival can be achieved with registered treatments for malignancies of the gastrointestinal tract (5-fluorouracil for metastasised colon cancer),[1] in head and neck cancer (cisplatin),[2] and non-small cell lung cancer,[3] renal cancer (recombinant interleukin 2),[4] AIDS related kaposi's sarcoma (interferon alfa),[5] and, more recently, paclitaxel for cisplatin resistant ovarian cancer.[6] The new purine analogue cladribine for hairy cell leukaemia seems to be one of the exceptions,[7] as in phase 2 trials this drug looks far better than interferon alfa; administration is also more convenient for the patient and the safety profile is acceptable.

In HIV infection the most important measures of efficacy are the occurrence of AIDS related events,

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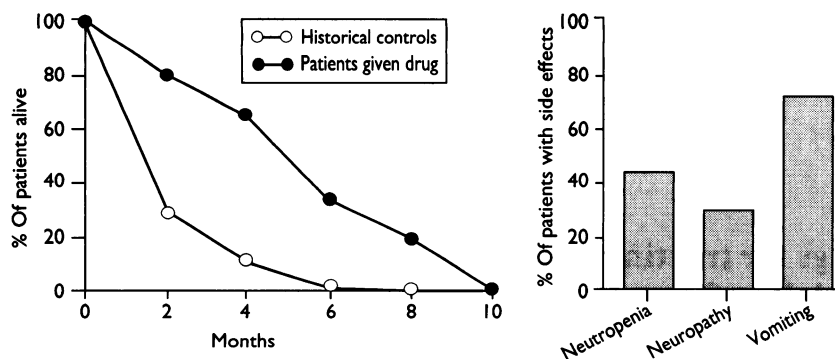
Hypothetical (a) change in survival curve of cancer patients and (b) side effects induced by a new oncolytic drug, illustrating the difficulty of assessing the benefit-risk balance of a new drug for cancer investigated without a control group

survival, and the course of surrogate measures (CD4 counts, virus RNA, p24 antigen). The therapeutic gain of the currently marketed antiretrovirus drugs is limited.[8] The increased survival of patients with AIDS taking zidovudine, a drug that was compared with placebo, is temporary and relatively short lasting. Didanosine and zalcitabine are registered in several countries for treating patients with AIDS who cannot tolerate zidovudine or no longer respond to it, but it is doubtful whether morbidity and survival are greatly improved. These drugs were admitted to the market mainly because of their favourable effect on surrogate measures, but it has become clear that such an effect is poorly correlated with clinical outcome.[9][10]

Toxic effects

The second reason why benefit is more difficult to assess for oncolytic treatment and in HIV infection is that the drugs are often toxic; neutropenia, gastrointestinal side effects, alopecia, mucositis, neuropathy, or (in case of didanosine) the risk of pancreatitis, as well as frequent hospital admissions for complications of treatment (such as infectious episodes and the need for blood transfusions), may affect the quality of life of the patient and should be set against the temporary effect. Furthermore, the action of a particular drug is harder to interpret when more than one cytotoxic drug is given or when antimicrobial agents are also used.

Of course, one also cannot conclude automatically that a drug with a limited effect, which prolongs life only slightly and possesses many side effects, is *not* valuable for a patient. For instance, the detrimental impact of the side effects of chemotherapy for advanced breast or colon cancer on the quality of life of cancer patients seems to be less than expected.[11][12] These data cannot, however, be generalised to all cytostatic treatments.

Whether the treatment is beneficial depends on the definitions of response. When response is correlated with benefit or obvious palliation, improvement of the patient's general condition, or improvement in symptoms, this should be taken into account. Particularly in phase 2 trials, however, either this is not the case or the correlation between response and clinical symptoms is vague.

Wellbeing of the patient

Before a marketing authorisation is delivered, studies of the impact of the treatment on the patient's wellbeing should be required. One approach is to investigate the influence of the drug on simple clinical symptoms or laboratory markers associated with the malignant disease or HIV infection (fatigue, body weight, pain, dyspnoea, anaemia, anorexia, etc); another is to formally assess quality of life with validated questionnaires.[13]

Comparative trials seem most appropriate, as the absence of a control group makes a reliable assessment of the results nearly impossible (figure). The nature of

the reference treatment depends on whether there is a standard treatment for the disease. If not—in patients with an advanced malignancy who have already received extensive treatment, or when the drug is used as second line treatment—the reference treatment should consist of placebo and best supportive care. Many supportive measures,[14] such as transfusions, haematopoietic growth factors, analgesics, antimicrobials, antiemetics, and even corticosteroids,[15] may influence the quality of life favourably; best supportive care is therefore justified as reference treatment.

Such trials may be difficult to perform. The ethics of using a placebo arm in a fatal disease is disputed in some countries,[16][17] and many physicians and patients will be reluctant to participate because of high (often unrealistic) expectations of new drugs. One solution would be to incorporate patients' preferences in the randomisation.[18] A comparison with historical controls may seem easier to perform, but problems arise in interpreting results—in particular, there may be differences in patient characteristics, criteria for response, accuracy in the disease staging, and the use of supportive measures and drugs.[19]

Placebo controlled trials might be avoided by performing carefully designed dose finding studies, looking for the dosage that has the lowest toxicity but is still effective. These trials are not easy to perform with cytotoxic drugs or antimicrobial drugs. Dosage of a cytotoxic drug is often based on the maximum tolerable dosage (found in phase 1 studies) and that of antimicrobial drugs comes from in vitro susceptibility studies.

Conclusions

In cancer, HIV infection, and possibly other fatal diseases, comparative trials either with placebo or with best supportive care seem to be inevitable for a reliable assessment of the benefit-risk ratio. The drug regulating authorities could themselves be helpful in making clear to the public that, especially in these diseases, such trials, although time consuming, offer the best guarantee against drugs being registered too early and possibly being a disappointment afterwards.

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