ELSEVIER

European Journal of Cancer 41 (2005) 2210–2212

European Journal of Cancer

www.ejconline.com

Review

The difficulties industry is facing with investigators

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Received 29 November 2004; accepted 30 November 2004
Available online 7 January 2005

Abstract

The number of new agents being developed for the treatment of cancer has, over the past 10 years, increased dramatically which has resulted in increased interactions between the pharmaceutical industry that discover and develop most new agents and investigators in academic institutions, hospitals and office practices. This close interaction has inevitably led to a number of issues being identified on both sides and this paper will attempt to identify some of these and propose solutions.

Keywords: Industry; Drug development; Investigators; Institutes

There is an interesting climate at the present time around anti-cancer drug development. The beginning of the new century should be one of the best times to be developing anti-cancer medicines. There is good evidence in many countries that better cancer treatment is resulting in an improvement in outcome. For example, in the United Kingdom, despite an increased incidence of cancer, cancer death rates have fallen by 12% between 1972 and 2002 [1]. There is now a better understanding of the biology of cancer, and through this, we can identify new approaches to cancer therapy. There are more people than ever before committed to cancer research and cancer treatment.

These are positive influences. Nonetheless, this is actually one of the most difficult times ever to be involved in developing anti-cancer medicines. There are dramatic increases in cost and there is also continuous and corrosive criticism. A market research exercise recently showed that pharmaceutical companies are held in the same respect as tobacco companies and Dr. Richard Horton, Editor of the *Lancet*, was reported as saying in the Times on 21st September, 2004, ''For research we have to have the industry on our side. It's a bargain with the devil''. In addition to this, the regulation of medicines is changing worldwide and this has created new challenges for pharmaceutical companies and investigators alike. In addition, we can be considered to be spoilt for choice. There is a surfeit of new targets and new molecules directed at those targets. Most of the purported targets will be irrelevant and most of these molecules will either be sub-effective or ineffective and therefore there is a very high level of redundancy built into what is already a risky process of new drug development.

There have been many changes over the past 10–15 years. Fifteen years ago, cancer treatment was not big business. The amount of anti-cancer medicines sold totalled in the region of 2–4 billion Euros worldwide. Now the available cancer treatments will have a value of approximately 20 billion Euros worldwide in 2005. That level of expenditure will attract the interest of pharmaceutical companies and will require for effective drug development, the expertise and the development capabilities that only pharmaceutical companies have available. Cancer is also now perceived to be a more common disease. As we become more successful at treating infection and cardiovascular disease, the two big disease areas of older age are cancer and central nervous

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doi:10.1016/j.ejca.2004.11.020

system disease. Therefore, there is an increased awareness of the likelihood and indeed risk of cancer for an individual. In addition, the amount of evidence required by physicians, patients, regulators and reimbursers has increased, and because of the number of drugs in development and the number and size of trials required by regulators, this is beginning to exceed the investigators' ability to deliver, particularly in the United States. A system therefore exists which is under significant pressure.

The industry and investigators have much in common. People come to work in the morning with the same aim – they want to "beat" cancer, and we are all constrained by time, money and the people available. However, patients are happy to be in clinical trials. In a review, a quantitative survey of public attitudes towards cancer clinical trials [2], 97% of patients in trials felt that they received quality care; 97% felt they were treated with dignity; 93% had a positive experience and more than 75% of those patients would recommend the trial and felt that they were not treated as 'guinea pigs'. This reflects a very positive patient attitude and good motivation to be included in such trials.

Nonetheless, differences exist and these reflect the different agendas that a pharmaceutical company and a university, for example, must inevitably have. A curriculum vitae for an academic physician will look very different from a curriculum vitae for an employee of the pharmaceutical industry. Academic investigators will often want to make an area of interest into something that lasts for the duration of a career. In the pharmaceutical industry, each new drug development is treated as a project with a finite length of time to demonstrate its benefit. Different procedures for research exist between academic research and research in drug development which have to rely on good clinical practice (GCP), good laboratory practice and good manufacturing practice.

When investigators are looked at they can be divided into three groups. The good investigators, the majority, deliver the objectives of the trial. Great investigators develop the objectives of the trial. However, there are bad investigators who cause harm to themselves and potentially damage to others.

The number of bad investigators is small, but there is a consistency about the way in which they carry out their work. There is often a relaxed attitude to inclusion and exclusion criteria in clinical trials. Since trials have been designed to study specific populations, this results in the potentially unnecessary treatment of patients and also affects the statistical basis for the trial.

There can also be a selective attitude to data collection, particularly safety data. Oncologists are trained to expect a number of side-effects of anti-cancer drugs and, therefore, in spite of a legal requirement for the collection of adverse events, common side-effects tend to be under-reported. Since the development process is critical in establishing a drug safety profile, especially for events that occur in less than 10% of patients, many patients need to be studied and the kinds of analysis carried out to identify and categorise these events are different from those conventionally used in academic research. It has been shown that investigators do not assess adverse events well. Fromme *et al.* [3] carried out a study where adverse events were assessed both by the patient and the physician and the conclusion of the authors was that even in a tightly controlled clinical trial, physician reporting was neither sensitive nor specific in detecting common chemotherapy adverse events and with adverse events that could be detected by both patient and physician, physicians missed 38% of fatigue, 65% of pain, 77% of dyspnoea, 65% of insomnia, 70% of anorexia and 60% of constipation.

It is clear given the legal framework within which investigators and industry must now work, that this is inappropriate for future studies. Some Phase I investigators claim that Phase I should only be conducted at one site to allow one expert to gain an understanding of the nature of the side-effects and also efficacy of a new agent. However, with many of the newer agents, particularly when pre-clinical toxicology suggests that there will not be conventional cytotoxic side-effects, there is no reason for carrying out Phase I and early clinical evaluations at a single site, and indeed some studies may be possible in normal volunteers and with a well networked group can be successfully and effectively carried out at a number of sites. However, it is of course important to ensure that there is good communication between all members of a team who are working together.

There is no doubt whatsoever that some investigators are under severe pressure and in great demand. This is particularly true in the United States of America and increasingly in Western Europe. Part of the reason for this is that many of the biotech companies are based in the United States and therefore only have sufficient resource to carry out studies within the remit of one regulatory authority. However, increasingly there are well-trained and experienced oncology investigators in Central and Eastern Europe, Latin America and China and South East Asia. If the rate of discovery of new molecules for cancer continues, the resources of the whole world will have to be used to carry out the necessary clinical and translational science investigations.

There will inevitably be tensions in a relationship which is needed but which involves people with different agendas and motives. One of the best ways of overcoming this is by working as a team. Teams work well when they consist of a group of people who have different roles, but who have an appreciation of the different roles of others. It is important that when someone has been assigned a role they are left to get on with the job. In

terms of who does what industry will usually be the sponsor. This is defined by law in some countries and by International Conference on Harmonization (ICH) GCP in others. The law primarily relates to patient protection, drug supply and product liability. The trial protocol design should be a shared responsibility with the principal investigators and industry. Trial conduct is primarily the responsibility of the investigators and trial reporting and interpretation should be shared role. Where there is a need for shared roles, it is important that there should be an agreed team who work to achieve those shared roles. It is important that there is an element of permanence about these teams so that they can observe and therefore adjust to changing factors, both internally and externally. This can be achieved by actually including investigators in the company's strategy team or having standing advisory boards which ensures that opinions are tested and validated over time.

In summary, industry, by and large, does not have difficulties with investigators. There are always some bad investigators and there probably always will be, who are prepared to ignore the protocol or even in some extreme cases break the law. However, working with the "great" investigators is the area where most thought needs to be invested. If the effort is made in these cases, then drug development should improve and be a more efficient and effective process bringing important new agents to cancer patients and their physicians.

Conflict of interest statement

None declared.

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