Medical writing for cancer trials and submissions

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Abstract

Cancer is currently a high-priority area for drug development. Most cancers are immediately life-threatening diseases demanding urgent treatment and therapies are usually highly toxic. This poses a range of specific challenges for the ethical conduct of clinical trials in cancer, including difficulties with performing placebo-controlled studies, blinding, and restricting off-protocol treatments that may impact on trial results. Overall survival is the gold-standard efficacy endpoint for cancer trials, but reliable results can require a long duration of follow-up. Other endpoints such as time to progression and tumour response rates are therefore also used. Where treatments are targeted at specific disease mechanisms, biological endpoints may also be assessed. Safety evaluations require an understanding of the effects of the disease and its treatment on the likely observed events and abnormalities. A thorough understanding of the specifics of the disease under investigation and established as well as experimental approaches to its treatment can help medical writers to produce consistent and accurate documentation throughout clinical development.

Keywords: Cancer, Clinical trials, Medical writing

Introduction

Cancer has been a top priority in drug development for over 50 years. Cancer drugs, whether already marketed or in development, represent a critical part of the portfolio of most major drug companies, and may be the sole focus for smaller pharmaceutical and biotechnology companies. Annual healthcare spending on cancer exceeds $125 billion in the USA alone and is projected to exceed $200 billion within 10 years.[1]

Late-stage malignant cancers are invariably fatal without adequate treatment, and there is a large unmet clinical need for several common cancers (e.g. lung, colon, and breast). Although the advent of chemotherapy, as well as radiotherapy and improved surgical options has turned many cancers from a short-order death sentence into a chronic condition that is manageable over at least a period of months or years, many cancers, when not identified early enough, remain incurable, and others are difficult to treat adequately at any stage.

The law of diminishing returns is clearly applicable to cancer drug development, with fewer genuine breakthroughs, and ever-smaller incremental advances. Nevertheless, despite the high cost of developing new cancer medicines and the inevitability of political discussions about how extravagantly we as a society are prepared to fund treatments of increasingly marginal benefit, there is no sign as yet of reduced investment in cancer research, with annual research and development spending by the top 18 pharmaceutical companies exceeding €3 billion.[2] Companies are confronting the financial pressures imposed by the regulatory and patent protection environment by devoting resources more strategically, for example, by cancelling unpromising leads at an earlier stage and instead spending on increasing the range of indications for effective products.

Cancer is not a single disease. Even when cancer is exhaustively classified by variables such as primary tumour site and location and extent of metastasis, every individual patient's disease is unique. What all cancers have in common is that they are a consequence of genetic mutations that result in a loss of normal control over cell growth and division. Classical chemotherapy for cancer tends to use a broad cytotoxic approach, aimed at killing the tumour or stopping its growth before the treatment kills the patient. Combination chemotherapy regimes have been developed, often specific to cancer types, and treatment is often delivered in cycles, allowing breaks in treatment so that the patient can recover. In contrast, modern approaches are often based on our ever-increasing

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understanding of disease mechanisms. They attempt to target specific aspects of tumour biology in the hope that this is both more effective and less harmful. Tumour markers may consist of specific mutations or over-expression of specific genes such as growth factor receptors or signalling pathway components. Some markers are now being used prognostically to identify patients who are expected to respond to a particular treatment. As cancer classification becomes ever more sophisticated, treatment is destined to become increasingly personalized in the future. As the target populations for novel therapies become smaller, this will create further challenges for the design and conduct of studies, and for the financial viability of effective products.

Ethical issues

Cancer, being a life-threatening disease demanding urgent treatment, poses several ethical and technical problems for study design that would not usually apply to other indications.

Thus, it is unusual to find placebo-controlled trials of cancer drugs. On the one hand, the test drug is typically applied in combination with an established chemotherapy or radiotherapy regime so that in controlled studies, all groups receive at least an established standard of treatment. Similarly, 'best supportive care' may be offered to all patients in a (effectively) placebo-controlled trial. On the other hand, when new products are tested in isolation, this is generally done in patients who have failed to respond to several established treatments and who are not eligible for other standard treatment regimes.

For first-in-man and other phase I trials, cancer drugs are rarely if ever piloted in the usual healthy male subjects, as most cancer drugs are so toxic that the risk to individuals who will not benefit personally is unacceptably high. Early development is typically performed in patients with advanced, usually incurable disease. Toxicity, which may result in characteristic side-effects, also presents challenges for blinding of trials, and usually investigators (and sometimes subjects) are not blinded to trial treatment. Where 'softer' efficacy endpoints such as progression-free survival are used, it is common to have a blinded independent committee assess patient data such as X-rays and computed tomography (CT) scans to determine progression. It is important to present both investigator and independent assessments when both are available, and you should not be surprised that investigator assessments, regardless of treatment, tend to be more optimistic than independent assessments.

Trial treatment may be for a defined duration or number of cycles, and typically patients who are still alive or show response may continue receiving treatment beyond the planned trial duration. An overly strict definition of concomitant treatments that cancer patients may receive during a clinical trial is also ethically questionable. Compared with other indications, cancer trials demand greater tolerance of reduced compliance due to missed treatments, and you can expect a wider range of permissible concomitant therapies. Cancer specialists have considerable freedom to determine the best treatment for each individual patient, and when a new product is administered alongside a particular established chemotherapy regimen, recruitment should be restricted to patients who would otherwise qualify for that regimen. Once patients leave a trial, they may receive a wide range of further lines of therapy for their underlying disease. Ideally, data on second- and further-line treatments are collected during follow-up in order to evaluate whether such treatments have influenced efficacy results.

Early development

Dose-finding studies will typically evaluate dose-limiting toxicities, i.e. adverse events serious and frequent enough to prevent further administration of treatment, or to prevent dose escalation. Dose-limiting toxicities will vary between indications and treatments.[3] They should be carefully defined in the trial protocol in conjunction with the number of such events, or the number of patients experiencing such events. As a single excess patient with a dose-limiting toxicity can prevent dose escalation, the study population should closely reflect the intended treatment population.[4]

Efficacy evaluations

As most products in development aim to cure or at least extend life, rather than providing purely palliative care, cancer trials lend themselves to the most solid endpoint available – survival. The gold standard endpoint is overall survival, which is typically expressed as the proportion of patients alive at one or more time points, survival over time (e.g. Kaplan–Meier analysis), and mean or median duration of survival. If overall survival endpoints are defined in advance, data are often not mature by the time the report has to be written. For example, if most patients in both treatment groups remain alive it may be difficult to establish any treatment effect on long-term survival. Conversely, a treatment effect resulting in increased (or even

decreased) short-term survival may not have the same effect on long-term survival. Comparison of survival between treatment groups may also be confounded by protocols allowing cross-over from the control to the experimental arm after treatment failure. Mature survival data as well as updates of survival and efficacy analyses may have to be provided in the form of report addenda or revisions after the first report.

Rather than survival itself, a commonly used endpoint is time to progression, or progression-free survival time. In this case, patients undergo regular clinical or radiological investigations (or both) to determine indicators of disease progression, such as further growth of the primary tumour, or new metastases. Data are often assessed by a blinded, independent committee to overcome investigator bias and any lack of investigator blinding.

Response to treatment may be assessed according to common criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST)[5] or WHO response criteria, alternatively disease-specific response criteria may be defined. The frequency of different response categories will be compared between groups and across studies, so response definitions should be standardized within a development programme. Surrogate or biological endpoints (such as tumour markers) may also be assessed, but are not adequate for licensing purposes.[6] Both the European Medicines Agency and Food and Drug Administration have published guidelines on acceptable endpoints in cancer clinical trials.

Follow-up can last almost indefinitely, and may range from simple survival follow-up at regular intervals until the patient has died to full data collection for patients continuing with trial treatment after having completed the defined treatment period.

New cancer drugs are increasingly targeted at specific molecular abnormalities of tumours. Specific pharmacodynamic endpoints may be evaluated alongside genetic characteristics of the patient population or detailed analysis of tumour characteristics, such as expression of specific genes, or presence of specific mutations. These may be compared among treatment groups, or be used to define subgroups, or (particularly at later stages of drug development) used as inclusion criteria.

Safety evaluations

Consequences of the severity of cancer and its treatment are a high rate of adverse events (AEs), serious AEs, and a high fatality rate. Differences between treatment groups may become exaggerated if the test drug is effective and results in increased treatment duration, whereas obvious differences in AE frequency may be apparent for established safety issues. Keep in-text AE presentations manageable by not presenting less common events that occur at similar frequencies across treatment groups in-text (these data should of course be available in the end-of-text tables). It is common to focus on related AEs or AEs of grade 3 or 4 by the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCICTCAE)[7] criteria rather than overall frequencies. Depending on the study design, relatedness may be attributed to individual components of treatment or to treatment in general: the approach used will determine the best way to present related AEs.

As patient narratives (required for clinical study reports) are often not adequately planned in advance, you should seek agreement with the study team as early as possible on criteria for narrative writing, and if necessary explain this policy in the report. There is no regulatory requirement to write narratives for Serious Adverse Events (SAEs) or deaths that were clearly unrelated to the product but unless criteria are set in advance, there is the risk that you will be asked to write large numbers of narratives for patients dying, entirely expectedly, of their underlying disease. A consistent policy should be applied to all reports for any given product and indication.

Laboratory evaluations can be difficult to interpret: the underlying disease and co-morbidities in the study populations can cause wide variations in several laboratory parameters. Individual frequencies of abnormalities and shifts by severity are more informative than mean or median values. You should also consider the possible effects on laboratory evaluations of any differences in time on study between treatment groups, or established toxicities of the trial drug.

Concluding remarks

This is not a comprehensive overview of all of the specific challenges you may face as a medical writer working in the cancer field. All the skills you apply when writing about other indications apply to writing about cancer. Medical writers working in this field are, however, expected to have some understanding of the molecular basis of cancer, the principles underlying cancer therapies, and to have an awareness of some of the specific issues that affect the conduct and evaluation of cancer studies. Although a medical writer has little direct influence on the business decisions made for individual products, this understanding can help

you to prepare high-quality documentation to ensure that the decisions on a product's future, whether made by regulators or the board of directors, are based on well-presented and accurately interpreted evidence.

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Author information

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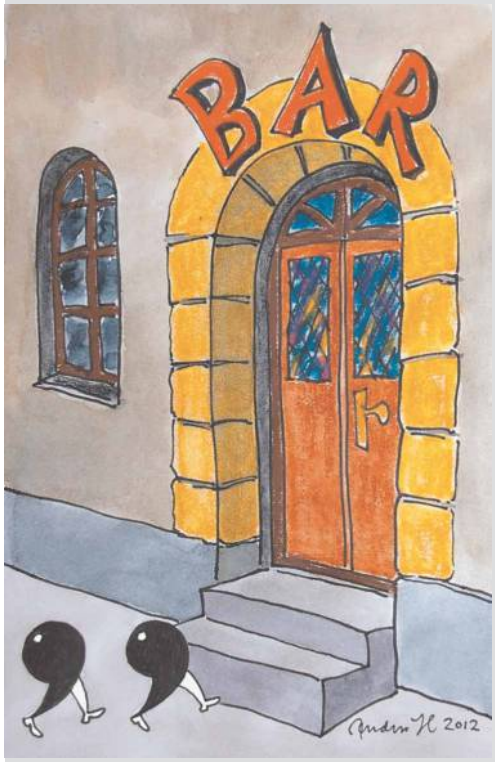
Bar Jokes from Graham Guest



A split infinitive decides to slowly walk into a bar.
It's a bar that a terminal preposition walks into.
Two misplaced apostrophe's walk into a bar.
And a conjunction walks into a bar first.
A reflexive pronoun walks itself into a bar.
An ellipsis […] a bar.
A diaeresis walks into a bär.
A Swedish accent walks into a bår.
A tag question walks into a bar, doesn't it?
An anagram walks into a bra.
A spoonerism baulks into a wahr.
A malapropism stalks into a car.

Graham Guest (graham@guest.org.uk) offers coaching for simplicity, grammar coaching, and consulting on the English language, continuing professional development and lifelong learning. He has a background in the management and administration of international professional associations, and experience as a career coach and a psychological counsellor.