Journal of Cancer Policy 8 (2016) 38–41

Contents lists available at ScienceDirect

Journal of Cancer Policy

journal homepage: www.elsevier.com/locate/jcpo

Could information improve patient access to new emerging drugs in rare cancer trials?

Ornella Gonzato

SPAEN (SarcomaPatientsEuroNet), Italy

ARTICLE INFO

Article history:
Received 18 March 2016
Accepted 24 April 2016
Available online 6 May 2016

1. Introduction

In these last few years, many efforts have been made by both the scientific and patient communities in the field of rare cancers in order to allow patients access to promising new experimental drugs and to limit discrimination against them. There is a greater sense of urgency about developing and bringing treatments to patients as soon as possible [1]. Rare cancers pose additional, particular challenges if compared with the more common tumours, due essentially to the small numbers of patients involved. Meanwhile, the current regulatory constraints require that the benefit of new drugs be proven in a large number of patients, which is unfortunately impossible, considering the scarcity of numbers [2].

The consequence is therefore an elevated risk of failing to gather enough evidence to obtain the approval for a new drug and, to compound the problem, the development of the drugs themselves is discouraged by the exorbitant costs to the industry of running small trials.

How can this scarcity of numbers be overcome in order to allow patients earlier access to the new therapies? There are, essentially, two ways: one involves working on the methodology with which clinical trials are conducted, reducing the stringent limitations connected with numbers. The second way is to organize large-sized clinical trials. In both of these methodologies, patient information is crucial.

2. Working on the methodologies

Working on the methodologies means looking for alternative ways to conceive study design, analysis of data and evaluation of results. The adoption of Bayesian logic, the identification of new surrogate endpoints and adaptive trials are all instrumental in obtaining evidence, refining the current approach by taking into account a higher than average degree of uncertainty in these cancers. In addition, innovative ways of summarising available evidence should be considered, ranging from observational studies to the analysis of retrospective case series or anecdotal cases, up to preclinical studies, with a strong rationale for evidence coming from the treatment of biological equivalence in similar diseases.

Methodology is a problem that is also present in the switch in current oncology from chemotherapy to target therapies, with the relative cost of these expensive new drugs. More precisely, the problem here is the untargeted use of target therapies. The limited benefits of these expensive drugs are often due to the small size of the target subgroups in the clinical trials. In other words, more closely targeted trials are needed. But the more the patient population of subgroups is targeted, the more statistical significance, according to the rules of conventional statistics, is lost. So methodology is once again crucial.

Moreover, the possibility of incorporating a preclinical rationale in the generation of data, if and only if it is strong, is once more a matter of methodology. Even a sole patient may be highly significant if the preclinical rationale is very strong. A new kind of statistic, conceived to evaluate the importance of even a small piece of evidence, could be significant, if the preclinical rationale is strong, and would provide a valuable tool.

All of this requires an innovative regulatory approach, one that would relax the existing rules and take into account patients' attitudes towards risk in rare cancers. These patients live in the hope

E-mail addresses: ornellagonzato@yahoo.it, ornella.gonzato@sarcoma-patients.eu

http://dx.doi.org/10.1016/j.jcpo.2016.04.001

that effective therapies will be discovered, and are willing to accept risks correlated to a higher uncertainty, and this attitude should be factored in by regulatory authorities.

The good news is that last October the EMA (European Medicines Agency) hosted a meeting with representatives of Rare Cancers Europe [3], a multi-stakeholder initiative representing patient associations, medical societies and industry, to discuss RCE's recent publication of a consensus paper on the new methodology of clinical trials in rare cancers [4].

Following this event, another important workshop on chordoma, a very rare cancer occurring in the skull base or in the spine and affecting only one person in a million per year, was held at the EMA to discuss the challenges in developing drugs and to identify possible new methodological solutions that could work for this and other very rare cancers [5].

Correct, appropriate information from clinicians is always crucial, both in creating patient awareness during the decision-making process that should be rational and shared – all the more so in rare cancers- and in giving patients and their representatives the support they need to speak up with regulatory authorities.

Delivering information on the methology of trials in rare cancers to patients (but to their clinicians as well) is a major challenge, but one that could allow patients to reach a "shared" decision, to the extent to which this is possible. Educating and training Patient Advocacy Groups (PAGs) in this methodology represents one of the main tools by means of which these goals may be achieved.

3. Current methodologies and clinical trials

The other way to overcome the problem of scarcity of numbers is the organization of large clinical trials, for which extensive collaborative networks are needed [6]. However, there are several limiting factors in these large collaborations, ranging from the funds needed to support them to national regulatory constraints, which can cause delays and further additional difficulties in trial management. Collaboration is, instead, vital in assessing the value of new treatment strategies; regulatory obstacles to global investigator-driven collaborations and shared databases are certainly among the principal impediments that must be removed.

Another important limitation is often, however, the management of information, at various levels.

To lend statistical significance and value to trial results, at least in accordance with the current methodologies and rules, as many patients as possible must be recruited. Therefore information is essential.

Following a stressful, disorienting diagnosis, as that of a sarcoma always is, patients and families begin to seek information on the disease that has been diagnosed and its relative treatments. This is the beginning of a patient's journey into the uncertainty of the pathology and its treatment, and it is of the essence that this stage be managed accurately, so that the patient does not miss out on the opportunity to take part in clinical research.

What are the main sources patients usually consult?

Fundamentally the following three:

1 First of all, the clinicians to whom they refer, although these clinicians are not always experts at sarcoma centres. Unfortunately, the criteria for identifying specialist sarcoma centres have not yet been adopted by all of the countries in Europe.

The National Cancer Patient Experience Survey (England, 2014) established that only 35% of sarcoma patients were asked by their clinician to participate inthese studies. 64% of these went on to participate, showing patient interest and willingness to take part when given the opportunity [7].

- Through the web, both websites and social media, especially if there are blogs/forums with experts who respond and patients sharing similar experiences;
- Patient Advocacy Groups, if they are already familiar names or operate at the unit, or if they can be contacted after a web search.

What problems do patients usually encounter?

In order, respectively:

1. The clinicians the patients turn to may not, themselves, be informed about ongoing trials.
2. The websites do not always supply reliable or updated information and clear entry criteria about open trials, making it difficult for patients to find the information in the first place; and when they do, it is often not easy for them to understand by themselves.
3. The PAGs may provide patients with local support in a particular structure but be unacquainted with ongoing CTs, the development of innovative drugs or new therapeutic options.

What's more, there may be a widespread basic problem regarding the nature of the clinical trials, in particular if they are randomized, and the benefits of participating in one. This often derives from a lack of correct information at the level of the general public. A basic, general awareness campaign targeting this level should be taken into consideration.

What, then, are the possible solutions?

Because any solution must necessarily be of an organisational and managerial nature if information is to be publicized effectively, a combination of synergetic actions is required, such as, in order:

1 By promoting and spreading information in the oncological community by means of all available channels (meetings, publications, conferences etc.). In addition, attention should be directed towards raising awareness of the importance of recommending trials to patients via a European campaign targeting clinicians, supported by charities, patient groups and research networks.

2 By operating on the Web, considering two different strategies: either by setting up a new dedicated website, ideally a European one-stop sarcoma portal for clinical trials, in order to concentrate patient search, avoiding information overload or, on the contrary, by establishing a fruitful collaboration with the EMA website register-the EU Clinical Trials Register- that provides public access to information from the European Union (EU) clinical trial database (EudraCT). The EMA register gives users the possibility to search for information on any Phase II–IV adult clinical trial recorded in EudraCT, any paediatric clinical trial and any trial listed in a paediatric investigation plan [8]. A strict collaboration between EMA and PAGs could achieve more effective results: information could be integrated and/or translated into "patient-friendly" language for a better understanding. In other words, instead of setting up a new dedicated website, EMA and PAGs could define an integration between their sites and their information, both allowing PAGs to be constantly updated on trials and maximizing the effects of the register information.

In addition, setting up social media such as FaceBook and Twitter, and uploading videos on youtube could be an effective way to amplify all this information, which must be supplied with clear and comprehensible content, translated into the different European languages.

For those patients who do not use the Web, the same data, in the form of both printed and audiovisual material, should be distributed to the infopoints at all treatment centres in order to be accessible to every patient.

A further activity is represented by the activation of blogs/forums for patient-specialist contact, as well as patient–patient contact, so that similar experiences may be shared.

- Involving PAGs in clinical studies from the very start, both to bring the patient perspective, in terms of needs and expectations, into study design early on and to promote a "ripple" effect in PAGs that may simply be operating at local level and have no access to this information. In other words, those PAGS who do take part in developing a trial would, in turn, transmit their experience to other, more peripheral PAGS.

4. The information management process

The quantity and quality of information required vary during the patient's journey. From the "beginning" to the "point of arrival", the patient requires information, to which emotional and psychological support must be added.

How could information be managed throughout this entire journey? The answer might be by developing a systematic methodological approach in order to define, for each phase, WHAT, HOW, WHERE, WHICH PLAYERS and WHICH RESOURSES should be involved.

WHAT calls for a definition of the specific need. For example, the need for information, depending on the phase, can mean information in general on what a trial is (as mentioned before) and why taking part in one is beneficial, where and to whom to turn to participate, but it can also mean detailed information on a specific trial, its side effects and risks and how to manage them. At the same time, information could mean a clear explanation in the content of the informed consent so that it is comprehensible and not only compliant with the regulatory requirements, or feedback on the results. In addition, information could mean receiving updates on the findings throughout the trial, as well as a summary of the study findings once it has come to an end, enabling patients to know the overall results of their trials, both positive and negative.

Moreover, information would be more effective if it concerned not only the ongoing clinical studies but the disease phases. This completely different approach would facilitate patient comprehension: listing and briefly describing clinical studies assessing new drugs may be useful but is not enough. It should be accompanied by an explanation of the phases of the disease, including proper information regarding both the standard treatment and the clinical studies running at that time, all of which would be more valuable both for patients and clinicians.This is another area in which PAGs could provide support.

HOW regards the INSTRUMENTS by means of which the need may be satisfied; and WHICH identifies the most appropriate CHANNELS or SETTINGS used to transmit the message, knowing that the "behavioural and utilisation models" of these instruments will vary with the different patient "targets", especially with regard to their age and sex.

In any case, it is necessary that the language used in every phase, including that of feedback on trial results, be clear and patient-friendly, not clinico-scientific or bureaucratic. The need for information connected to the informed consent, for example, requires informative material that is comprehensible, over and above the official document, as well as time on the part of clinicians or staff to answer any questions and facilitate comprehension.

Many patients, in fact, report difficulty in understanding the informed consent; they often feel they are not given sufficient information to make a fully informed decision. The instruments and settings used could be crucial in achieving this goal.

It is well known that informed consent documents are legal documents, designed to protect both the patient and the organization conducting the trial. However, these documents often not only fail to satisfy patients' information needs, but create alarm and anxiety in them. An example of this is that when they hear that the insurance will cover any "damage," that there may be problems regarding future fertility, that sexual activity during the trials is subject to some stringent constraints, or that their biological samples could be used for research without any temporal limits, their reaction is one of anger, repulsion, and even rejection, all the more so in the case of randomised trials. Instead of feeling that they are part of the decision-making in a modern system of treatment, they feel that they are being used and refuse to take part in the trials.

However, changes in the "informed consent", in order to make it more comprehensible, are not allowed because of the current regulatory constraints and this is particularly relevant for studies whose sponsor is the pharmaceutical industry. However. information on the "informed consent" could be improved by integrating additional media support. Providing information on the ongoing process is quite different from providing the consent form itself. User-friendly, informed consent sheets, such as information leaflets, as well as videos, pictures or diagrams should instead be added in order to provide adequate support. This is an area in which PAGs could play a very useful role.

More time should probably be devoted by clinicians or staff to providing their patients with detailed information. After the first meeting, which patients necessarily find stressful and during which they are generally unable to completely understand what is happening and interact effectively, there should be a second one in the space of a few days, when they have had time to reflect on the initial information and formulate any questions and/or express any doubts or objections.

Leaflets, audio-visual material, material integrating the informed consent, meetings, forums, blogs, social media, websites and infopoints at treatment centres are some of the instruments and channels that could be used.

The more carefully the patient target and the specific need of a particular phase of the process are defined, the more efficacious the instruments and channels will be.

Furthermore, the need for information can be bidirectional, such as in the case of the forms with which patients are provided to monitor and report data during the administration of a drug. This information is essential to clinicians, but the report form must be patient-friendly if the data is to be collected properly.

As for the PLAYERS involved, their roles must be identified in each of the different phases in terms of their main activities and support for patient needs. With particular regard to the PAGs, this ranges from representation of the patient perspective early on in the design study to identify the outcomes that are relevant for quality of life and minimization of the burden on the patient, to patient education regarding participation in the trials, information at different levels and direct support. All of this requires that PAGs, clinicians, and researchers act in increasingly close collaboration.

5. Public patient involvement: the EuroEwing experience

A very interesting experience evidencing both PAG involvement and a systematic approach to the management of information in large collaborative clinical trials on rare cancers is to be seen in the ongoing Euro Ewing Consortium clinical trials, where patient and public involvement represents one of the core activities within the project [9]. The aim is to involve patients and caregivers in the activities of the clinical trials on Ewing sarcoma and to ensure that relevant information is communicated and disseminated in a clear and efficient way within the Patient Bone Community.

The first step towards embedding PPI (Patient Public Involvement) in the EEC consisted in identifying patients, carers and organisations with an interest in working with the Partners. The lead Partner for this area, Sarcoma Patients Euronet (www.sarcoma-patients.eu) conducted a survey across Europe on groups/organizations with an interest in bone tumours. Patient groups (PAG) were mapped by sending them a questionnaire to find out if they focused exclusively on bone tumours. As expected, very few of these specialist groups were found, confirming that the patient bone community is very small, due to the rarity of these diseases. Most of the associations identified are small charities founded to commemorate a relative, which are not professionally organised. On the other hand, the larger organisations operating at national level were founded to deal not only with bone sarcoma but with all types of sarcoma, particularly gastrointestinal stromal tumours (GIST).

The list provided a starting point for establishing a core group of potential participants, from which a small group of active PPI representatives was set up. They provided useful input into the Euro Ewing Consortium (EEC) over the first period and assisted in expanding the group further, by making use of their own networks and finding opportunities to promote the EEC at external meetings (the above-mentioned "ripple" effect).

Many activities were carried out within the EEC project, bringing the patient point of view into the scientific community, ranging from the feedback on patient information sheets to the impetus for modifying protocol design for the rEECur trial to sessions held by patient representatives during the EEC meeting so that clinicians were given patient perspective on the research that was being carried out by the EEC.

In addition, patients and/or families, identified through the register of PPI partners, were offered introductory training and information.

By a virtual (web) process consultation, priorities of actions were also established among a list of activities relating to how patients and clinicians could support each other to achieve the best trial results.

Patient representatives' participation in the wider community of international collaborative projects, such as ENCCA (ENCCA-WP7 – EuroSarc – EEC – PROVABES – EURAMOS), was also activated to maximise patient information dissemination and communication [10].

Therefore the main information/communication channels used include the activation of a dedicated EEC website for partner information exchange, news updates and disseminating information to patients, social media, emails, publications, patient/experts face-to-face meetings, group teleconferences, patient participation in conferences and scientific meetings. Moreover, patients will be given an information card when they will start on the trial together with the link to the page on the website where they can find the information when it is convenient for them.

All of these are valuable means of disseminating information, to educate patient and public, to expand access to patients in all countries, to improve communication and collaboration between the patient and the scientific bone community.

6. Conclusions

In conclusion, information is a very critical issue both for recruitment and participation in clinical trials, and it must be accurately managed in all phases of the patient's journey.

Moreover, information constitutes both the premise (basis) and the core of several other activities, ranging from empowerment to awareness, education, communication, participation, and involvement, all the way to lobbying to propose innovative approaches to the regulatory authorities. All of these activities interact and support each other, and all of them aim at improving patient access both to new emerging therapies and to clinical trials and their results.

References

[1] G. Gatta, R. Capocaccia, A. Trama, C. Martínez-García, RARECARE Working Group, The burden of rare cancers in Europe, Adv. Exp. Med. Biol. 686 (2010) 285–303, http://dx.doi.org/10.1007/978-90-481-9485-8_17.
[2] G. Gatta, Rare Care Working Group, Rare cancers are not so rare: the rare cancer burden in Europe, Eur. J. Cancer 47 (November (17)) (2011) 2493–2511, http://dx.doi.org/10.1016/j.ejca.2011.08.008, Epub 2011.
[3] www.rarecancers.eu.
[4] P.G. Casali, P. Bruzzi, J. Bogaerts, J.Y. Blay, Rare Cancers Europe methodological recommendations for clinical studies in rare cancers: a European consensus position paper, Ann. Oncol. 26 (2) (2015) 300–306.
[5] Workshop on chordoma discusses challenges of drug development for rare cancers Press Release: Workshop on chordoma discusses challenges of drug development for rare cancers, 04 June, 2015.
[6] J.W. Gerss, W. Köpcke, Clinical trials and rare diseases, Adv. Exp. Med. Biol. 686 (2010) 173–190.
[7] www.quality-health.co.uk.
[8] www.clinicaltrialsregister.eu.
[9] www.euroewing.eu.
[10] Leo Kager, et al., The ENCCA-WP7/EuroSarc/EEC/PROVABES/EURAMOS 3rd European Bone Sarcoma Networking Meeting/Joint Workshop of EU Bone Sarcoma Translational Research Networks; Vienna, Austria, September 24–25, 2015. Workshop Report, Clin. Sarcoma Res. 6 (2016) http://dx.doi.org/10.1186/s13569-016-0043-5.