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

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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

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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.