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Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

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While they account for one-fifth of new cancer cases, rare cancers are difficult to study. A higher than average degree of uncertainty should be accommodated for clinical as well as for population-based decision making. Rules of rational decision making in conditions of uncertainty should be rigorously followed and would need widely informative clinical trials. In principle, any piece of new evidence would need to be exploited in rare cancers. Methodologies to explicitly weigh and combine all the available evidence should be refined, and the Bayesian logic can be instrumental to this end. Likewise, Bayesian-design trials may help optimize the low number of patients liable to be enrolled in clinical studies on rare cancers, as well as adaptive trials in general, with their inherent potential of flexibility when properly applied. While clinical studies are the mainstay to test hypotheses, the potential of electronic patient records should be exploited to generate new hypotheses, to create external controls for future studies (when internal controls are unpractical), to study effectiveness of new treatments in real conditions. Framework study protocols in specific rare cancers to sequentially test sets of new agents, as from the early post-phase I development stage, should be encouraged. Also the compassionate and the off-label settings should be exploited to generate new evidence, and flexible regulatory innovations such as adaptive licensing could convey new agents early to rare cancer patients, while generating evidence. Though validation of surrogate end points is problematic in rare cancers, the use of an updated notion of tumor response may be of great value in the single patient to optimize the use of therapies, all the more the new ones. Disease-based communities, involving clinicians and patients, should be regularly consulted by regulatory bodies when setting their policies on drug approval and reimbursement in specific rare cancers.

Key words: rare cancers, clinical trials, research methodology

introduction

These recommendations were worked out through a multidisciplinary and multistakeholder consensus process, promoted by 'Rare Cancers Europe' (RCE). They are proposed to the health and research communities as a contribution to improve clinical studies about rare cancers, given the peculiar difficulties they pose. The ultimate goal is to make sure that rare cancer patients are not discriminated against because of the rarity of their diseases.

Having regard to the area of clinical research, they expand Political Recommendations on rare cancers (http://www.rarecancerseurope.org) selected in 2008 as the founding basis for RCE. RCE is a multistakeholder initiative dedicated to putting rare cancers firmly on the European policy agenda, advancing the way rare cancer patients are diagnosed and treated

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in Europe, and improving translational and clinical research on rare cancers.

basic considerations

- Rare cancers account for as many as 20% of new cancer cases [1]. According to conventional methodologies, clinical trials need considerable numbers of patients that are difficult to collect in rare cancers. By definition, therefore, clinical evidence is more difficult to build in rare than in frequent cancers.
- Efforts to set up large collaborative clinical trials merit special attention in rare cancers. Collaborative networking is crucial and needs to be funded properly. However, the limiting factor of large collaborations may be a lack of clinical expertise. In principle, inappropriate clinical performance might flaw the outcome of a clinical trial to the same extent as methodological biases.
- It follows that alternative ways to conceive study design, analysis of data and combination of results would be exceedingly important. It is possible that some innovative solutions may imply a price to pay in terms of a higher uncertainty. However, discriminations in rare cancer patients' access to effective care are inevitable, if a higher degree of uncertainty is not accepted when compared with more frequent conditions.

clinical decision making in rare cancers

1) The problem of rare cancers is one of a higher uncertainty. By no means does this imply that decision making in rare cancers should be conceptually different from that in more frequent conditions. As usual, it is crucial for the clinician to address decision making rationally. In the language of decision theory, this means to properly manage 'probabilities' and 'utilities' [2]. Also in rare tumors, therefore, an effort should be made to shape the results of clinical research in such a way that they provide the physician, and the patient, with informative probability distributions on major expected outcomes, with the central value corresponding to the 'risk' and the distribution representing the 'uncertainty' thereof, and, when probability curves as a function of time are available, with their full shape over time made understandable. Patient's 'attitude toward risk' should be taken into account for an individualized decision making.

2) Likewise, quality of life should be incorporated as much as possible as an end point also in clinical studies on rare cancers, with the aim to let the physician describe it as precisely as possible at the patient's bedside, in order to elicit individual patient's utilities factoring their individual values and preferences.

3) Third payers, regulatory agencies and local health systems should avoid discriminations against rare cancer patients. The cost/efficacy thresholds used by any third payer for decisions on resource allocation can well be the same as for frequent cancers, but the uncertainty on quantification should be accepted as possibly higher in rare cancers. This also applies to definition of state of the art through clinical practice guidelines, and the like.

4) Rare cancer patients often argue in favor of relaxing the usual risk-averse attitude of medical decisions [3]. In fact, under an individual perspective, the trade-off between risks of side-effects deriving from a new treatment and the certainty of progressive cancer is often solved, rationally, by choosing to try the new treatment. To a reasonable extent, this should be taken into consideration also by regulatory bodies when assessing the risk/benefit ratio of new treatments in bad prognosis scenarios.

5) Innovative approaches to summarize available evidence should be encouraged [4]. They should allow to make the most of all available knowledge, which is particularly critical when the direct experimental evidence is scanty, or of suboptimal methodological quality. The principles of systematic reviews should be followed. In addition to randomized clinical trials, also preclinical evidence, as well as uncontrolled trials, observational studies and analyses of retrospective case series, or anecdotal cases, should be considered when summarizing the available evidence. Medical journals should consider the rarity of diseases when shaping their editorial policies, to make sure that any additional evidence is made available. Especially in the case of very rare cancers, even evidence from similar diseases can be taken into consideration. A degree of subjectivity is inevitable under this approach. However, formal methodologies can be followed and consensus processes can be put in place, in an effort to reduce subjectivity. It has been proposed to score available studies for their validity and pertinence [5]. Validity of studies is based on their design (randomized or uncontrolled, prospective or retrospective etc.) and their quality (presence of flaws in a randomized trial, existence of prespecified external controls in an uncontrolled trial etc.). Pertinence is scored according to how much the study focused on the same disease, the same treatment, the same patient subgroup, and the like. Consensus processes should be put in place to generate such scores. Methodologies should be developed to this end. However, since scores would be made explicit, the assumptions of all conclusions could be publicly reviewed and discussed. Likewise, sensitivity analyses could be made to evaluate to which extent conclusions are sensitive to the assumptions and arbitrary values incorporated in the model (i.e. by assessing how the final probability distributions are affected by changes in these assumptions and values).

study designs in rare cancers

1) Clinical studies on drugs are classically divided into phases, according to their primary objective: definition of the optimal dose for phase I, drug activity for phase II and efficacy for phase III [6]. In rare cancers, where large trials may be unfeasible, the methodology of phase II uncontrolled studies has often been applied to trials whose aim was indeed to explore efficacy, not simply antitumor activity. On the contrary, an effort should be made: (i) to identify and clearly express the true aim(s) of each trial, in order to avoid ambiguities that may compromise its validity and hamper the unequivocal interpretation of its results; (ii) to adopt the methodologies that are appropriate for these aim(s) or, whenever this is not possible, to acknowledge the suboptimal

methodology of the trial while accounting for its limitations in its analysis and interpretation.

2) When the enrollment in a study of an adequate number of eligible patients is not feasible, an option is to carry out low-power randomized clinical trials [7]. In this way, the principle of internal controls is met, and the biases from uncontrolled studies are avoided. However, the risk of missing a moderate/small treatment effect is high, and the low power of the trial should be acknowledged in the study protocol. The minimum difference for which good power is met should be made explicit in the protocol, as well as the actual power for the expected minimum difference of clinical interest. This may allow reviewing committees to make informed decisions as to the added value of a new study.

3) Research on biomarkers should be an inherent part of research on new drugs, because it may help identify those patient populations in which the drug is able to provide remarkable benefits. Clinical studies into these selected patient populations are exposed to all problems of rare diseases, but the sample size can be lower if the expected difference is high, and a sufficient power to detect this difference can be attained even with a reasonably low number of patients. In principle, studies on small selected populations where large benefits are expected should always be preferred to large studies on unselected populations where moderate or small benefits are expected. Regulatory bodies should encourage clinical studies seeking large benefits, even if the target populations are small, possibly tolerating a higher degree of uncertainty as a result of the paucity of eligible patients [8]. Statistical significance *per se* should never be the only factor to be considered for regulatory/reimbursement as well as clinical purposes [9]. The most likely magnitude of benefit should be regarded as a key factor for any decision.

4) If the choice is made not to plan a trial with an internal control arm, external controls must be used. Controlled studies are usually felt to be unnecessary (or unethical) when: (i) dramatic beneficial effects (e.g. cure) are likely, although in a minority of patients, in the lack of effective alternatives; (ii) an important and frequent beneficial effect was seen in a series of patients, in the presence of a clear-cut mechanism of action of the treatment; (iii) there is universal consensus on the lack of equipoise. Stringent methodological requirements are needed, including: rigorous patient selection criteria; record of refusals (inasmuch as the intent-to-treat principle is even more important); identification of external controls in the protocol before any analysis; formalization of statistical considerations as in a conventional randomized trial; proper selection of end points (response, duration of response, survival). The problem of 'stage migration' with historical controls is particularly important, and the introduction of new biomarkers may amplify it.

5) Adaptive trials allow to change aspects of the study while this is ongoing, depending on analyses of data obtained from patients enrolled in the same or other studies [10]. Rare cancers take special benefit from adaptive trials, because of the difficulty to find patients for clinical studies and the consequently long recruitment timelines. The development of a new drug, all the more in rare cancers, can be easier and faster thanks to adaptive mechanisms, such as, for example,

the intensive use of stopping rules, the transformation of a phase II into a phase III study ('seamless phase II/III designs') in case the early stage of the study was positive, or the use of 'drop-the-loser' or 'play-the-winner' designs. Appropriate statistical techniques are available to handle the following adaptations: (i) adaptations of eligibility criteria based on results of the same or other studies, or difficulties in recruitment etc.; (ii) unexpected deviations from hypothesized base risks and event occurrences; (iii) stopping rules for futility or safety reasons; (iv) changes in data analysis based on accumulating external evidence [11]. Other mechanisms are considered to be more problematic, such as all those based on unblinded interim analyses of efficacy. Obstacles to adaptive designs may be the duration of treatment, as well as the time to treatment effects and use of surrogate end points. Thus, the use of adaptive mechanisms should be accurately planned by the clinical researcher and the statistician, and specified in the study protocol. Availability of an effective data monitoring committee is critical. However, it is recommended to make efforts to assess the feasibility of adaptive designs when planning clinical studies in rare cancers. Likewise, it is recommended that methodological research is promoted to address the problems still faced with adaptive studies.

6) The conventional frequentist approach to clinical studies is focused on the control of the probability of false-positive results under the null hypothesis of no treatment effect (type I error) and on the probability of a false-negative result under an alternative, prespecified hypothesis of treatment efficacy (type II error). The '*P* value' represents the probability of observed (or more extreme) results in the case the null hypothesis were true. On the contrary, Bayesian-design trials are marked by the use of a prior probability distribution and the generation of a posterior probability distribution of the treatment effect [5, 12, 13]. Bayesian analyses produce probability distributions of the treatment effect, that is, estimates of the probability that the true treatment effect lies between any two values (e.g. that the risk reduction is between 10% and 20% etc.) or is below or above any specified threshold (e. g. a risk reduction <5%, >30% etc.). To use Bayesian methodologies, evidence available outside the trial needs to be considered, not only in planning the trial, but also in its analysis and interpretation. In Bayesian trials, there is not a pre-fixed number of patients to enroll, the target number of patient being dictated by the desired precision of the summary estimate of treatment effect, i.e. the width of the range of its plausible values. Furthermore, probability distributions provided by a Bayesian analysis can be directly used by the clinician in the clinical decision-making process, e.g. within a formal decision analysis. The main weakness of the Bayesian approach is the dependence of its conclusions on the prior probability distribution, whose definition entails an arbitrary, though not necessarily subjective, component. In general, consensus mechanisms should be arranged before setting up a Bayesian study in a transparent way to elicit prior probability distributions, and sensitivity analyses should be foreseen.

7) Efficacy is generally intended as an average effect observed under ideal conditions, i.e. in a clinical trial, which may well be different from what happens in real conditions, i.e. in the

actual clinical practice. This is often called 'effectiveness'. In this sense, there may be an issue about the generalizability of a trial on a new treatment, i.e. as to which extent efficacy demonstrated in the trial can be converted into effectiveness in real life. However, clinical research is done to improve clinical practice, which then has to change according to the new results of research. Therefore, the lack of generalizability of a new treatment when a trial has shown its superiority should be properly addressed by finding ways to transfer it into clinical practice and should not be viewed as an obstacle in principle to the introduction of the new treatment. This is all the more true of rare cancers, where the expertise is less accessible and the driving force of the market is lower to attract for-profit players.

8) It has been claimed that the availability of electronic patient records, which can be connected through wide data networks, gives rise to the opportunity to measure effectiveness in real conditions. Particularly in rare and very rare cancers, the substantial amount of data generated thereby is felt as a great opportunity to evaluate the effectiveness of available treatments in real conditions. In principle, there is no qualitative difference between the efficacy and the effectiveness of a new treatment, and the latter simply represents the actual translation in real conditions of the former, which in a sense is an 'unobservable' property of the treatment. Therefore, the same biases which hamper the estimation of efficacy outside a formal trial (and also within trials) prevent the use of routine clinical data to provide unbiased estimates of effectiveness. In other words, estimates of treatment effectiveness obtained from observational studies are exposed to major biases, and the statistical methods used to adjust imbalances in baseline factors cannot take into account unknown or unmeasured confounders, and therefore cannot assure that patients who received different treatments are actually comparable. As a consequence, clinical data extracted from current clinical practice can be used: (i) to provide information of the appropriateness of patient management in the real world, through the use of indicators consisting of surrogate end points (e.g. response rate etc.) and of markers of quality of care (e.g. early mortality etc.); (ii) to generate specific hypotheses to be tested in future trials (e.g. on treatment efficacy in specific subgroups); (iii) to create historical series of consecutive, unselected patients that provide information on time trends in prognosis and occurrence of specific outcomes in the general population. These series can be used as controls in subsequent uncontrolled studies, or to compare periods where different treatment approaches were used, whenever radical prognostic changes due to the introduction of a new treatment are assumed to be plausible.

surrogate end points in rare cancers

1) Surrogate end points are those which can replace the natural clinical end points by having the property of being measured sooner and/or easier (e.g. relapse-free survival, in the adjuvant setting, or progression-free survival, in the advanced). In addition, their effect may be amplified in comparison to natural end points (e.g. differences in tumor response are likely to be of a higher magnitude than corresponding differences in survival). However, they require to be validated in order to be used appropriately [14]. Validation needs high numbers, which are the problem of rare cancers. On the other hand, sometimes surrogate end points can be the only way to show improvements timely. In addition, some of them may recapitulate properties which might be perceived by patients as a value in se, as, for example freedom from progression or freedom from relapse inasmuch as quality of life is concerned, so that they may not require any formal validation in specific presentations. A new treatment could also be used temporarily, under the assumption that the surrogate end point is valid, while waiting for final results.

2) While validation of surrogate end points is problematic in rare cancers, their use is of great value in the clinic, as a tool to better describe and evaluate treatment benefits at the patient's bedside, and also to modulate therapies. Conceptually, any benefit in terms of antitumor activity actually observed in the individual patient increases the likelihood of an efficacy advantage in that patient (e.g. a patient who responds to a medical therapy is more likely to take some benefit on a longer time span, in comparison to a non-responding patient). Therefore, a given treatment could be administered for a short time span and continued only provided a short-term effect on a surrogate end point, such as any kind of 'tumor response', is observed. This may be relevant to overcome regulatory and reimbursement limitations to patient access to new treatments in rare cancers. For example 'pay-by-result' approaches, and the like, may well help optimize cost/efficacy on a population basis.

3) Tumor response is the most typical indicator of antitumor activity. Unfortunately, it was originally conceived as a dichotomous tool to screen drugs worth testing in a phase III setting, essentially aiming at its reproducibility [15, 16]. This may explain its limitations as a surrogate end point for clinical efficacy. Currently, an additional difficulty is given by the possibly nondimensional nature of tumor response to many molecularly targeted agents, while standard response criteria are mainly based on tumor shrinkage. Sometimes, they may slow down tumor progression, though progression is not avoided, so that tumor response and progression-free intervals may not be fit to render the whole potential benefit of the drug. It is recommended that methodological research addresses the problem of tumor response in medical oncology, trying to redefine it as an indicator which may have clinical meaning, in addition to being reproducible. Modern medical imaging, including functional imaging, should be fully exploited. Given the mechanism of action of new molecularly targeted drugs, nondichotomous definitions of tumor response may be useful, as well as those catching the impact on the growth rate of the tumor [17].

critical organizational aspects of clinical research in rare cancers

1) Collaborative health care 'reference networks' involving centers of expertise along with other centers able to provide good quality of care are a crucial instrument to improve quality of care in the field of rare cancers [18]. Quality

control programs should be in place in order to make sure that quality of care is evenly distributed across the network. Reference networks on rare cancers improve health care and improve accrual in trials, as well as clinical quality within clinical trials.

2) Patient information about trials should be made widely available. Patients should be aware that there is always an added value in entering a trial. On the other side, patient communities should be involved as much as possible in the conception of new clinical trials, particularly in regard to study design and the selection of study end points.

3) Rare cancer trials need to be rich in information in order to maximize their efficiency. For example a long follow-up for each patient would be crucial to generate information on the natural history of the disease etc. This applies also to biological information. Limitations to the duration of follow-up of patients enrolled in clinical trials should be overcome. Likewise, limitations to the opportunity to share the results across trials should be overcome. Efforts should be made toward clinical trial database sharing [19]. Regulations, including those on data protection, should remove obstacles. New models regarding 'precompetitive collaborations' and in general collaboration across pharma companies, should be explored.

4) The review of pathologic diagnosis, if not made at reference centers, is crucial in rare cancers, to make sure that the quality of care is high [20, 21, 22]. This obviously applies to clinical trials and to clinical databases suitable to be used for retrospective research. Telepathology, expert panels, dedicated training facilities are useful tools in this direction.

5) There have been patient-driven efforts to feed databases of studies and of cancer registries, which may become a formidable tool to gain new knowledge in rare conditions. This implies methodological challenges, which should be addressed.

6) Incentives for orphan drugs encourage pharmaceutical companies to launch clinical studies on new agents in rare cancers. However, given the inherently low number of patients, the risk of failing approval due to lack of evidence may all the same discourage from developing drugs in most rare cancers. In addition, screening of new drugs in rare cancers is by definition less likely to happen, since phase I studies will privilege frequent cancers (more likely to be enrolled in comparison to any single rare cancer in any phase I study), and hints of activity from the phase I setting will be therefore lacking in rare cancers. It is recommended that mechanisms are put in place to regularly screen new drugs also in rare cancers. This could be achieved through formal collaborations among reference centers by using framework study protocols on specific rare cancers liable to be exploited to test sequentially new drugs in their phase II stage of development. Bayesian approaches could be used, in order to efficiently formalize probabilities of activity for new agents in specific rare cancers. Mechanisms of conditional approval and 'adaptive licensing' should be actively exploited, because they may allow rare cancer patients earlier access to drugs with potentials of efficacy and at the same time generate new evidence [23]. For this use of new drugs, patients should be referred to centers and networks of

expertise, scientific and ethical scrutiny should be arranged and publication of all results should be foreseen.

7) The compassionate and off-label use of new drugs is more widespread in rare cancers [24]. Regulations thereof should be harmonized as much as possible, by acknowledging the likelihood that orphan indications may not be properly and timely covered by approval and reimbursement. In return for some relaxation in rules on compassionate and off-label use of drugs in rare cancers, this could be exploited to generate data in ways close to what is done in formal clinical studies. Also for this use of new drugs, patients should be referred to centers and networks of expertise, scientific and ethical scrutiny should be arranged and publication of all results should be foreseen.

8) In rare cancers, national, international, even global collaborations should be pursued to make investigator-driven studies possible. These are vital, for example to provide hints of activity of new agents in very rare cancers, which could be tested within industry-sponsored trials in case of a positive result from early low-cost studies. They are vital also to assess the value of new treatment strategies, with special regard to multidisciplinary approaches. Currently, the main obstacles to investigator-driven wide collaborations are regulatory and need to be overcome as much as possible.

9) Biobanks for medical research are crucial to advance the development of new treatments in rare cancers. They should be maintained by dedicated personnel in a centralized way, to realize good quality control, proper access, regulatory and ethical competence and harmonization and standardization. Currently, major obstacles have to do with data protection. While data confidentiality needs to be protected by putting in place all reasonable available means, the right of patients to donate their tissues for research, if they will, should be protected as well. The patient should be able to give a 'broad consent' for his/her data and tissues to be used for research purposes by the treating institutions, avoiding the need to re-consent whenever a new retrospective research is decided [25, 26]. Of course, proper ethics and scientific reviewing mechanisms for new researches should be in place.

10) In rare cancers, all cases may be useful to advance science. Thus, prospective clinical databases, registries and connection of electronic patient records on a network basis should be encouraged. Collaborative reference networks focusing on health care should be implemented and properly funded for quality of care reasons, but their added value in terms of generating new evidence should always be factored.

11) Cancer registries are essential because they provide vital data on incidence, prevalence and survival. Population cancer registries may allow to conduct high-resolution studies on selected topics. Proper derogations from the requirement of patient's informed consent are needed for population-based cancer registries to survive as crucial public health facilities [27].

12) Observational clinical studies on selected patient subgroups should be encouraged, because they can allow to gain vital information on the natural history and clinical characteristics of entities which sometimes are described only pathologically, and can generate external controls for uncontrolled

clinical studies. Data generated by health care databases should be exploited, overcoming unneeded regulatory constraints.

13) Given the key role played by regulatory bodies through their scientific advices to pharmaceutical companies embarking into development of new drugs in cancers, regular consultations between these bodies and the rare cancer-based communities (both patient- and physician-driven) would be vital to tailor the way new drugs are developed in rare cancers. Confidentiality issues and conflicts of interest should be managed. In principle, the value of the disease-based communities should be acknowledged and regulatory/reimbursement bodies should view them as active partners in establishing criteria for approval of new treatments in rare cancers.

disclosure

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appendix

Rare Cancers Europe (RCE) Consensus Panel

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