Rare cancers 2

The value of research collaborations and consortia in rare cancers

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Rare cancers are defined by an incidence of less than six per 100 000 people per year. They represent roughly 20% of all human cancers and are associated with worse survival than are so-called frequent tumours, because of delays to accurate diagnosis, inadequate treatments, and fewer opportunities to participate in clinical trials (because of a paucity of dedicated trials from both academic and industrial sponsors). In this Series paper, we discuss how these challenges can be addressed by research consortia and suggest the integration of these consortia with reference networks, which gather multidisciplinary expert centres, for management of rare tumours.

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Introduction

Rare diseases are often defined by their prevalence, with a cutoff that varies from 0·5 to 2 per 1000 in the general population. Although this definition could be applied to rare cancers, it is often deemed inaccurate because it does not take into account the often short life expectancies associated with some rare cancers.[1] A frequent disease associated with a short life expectancy, could inadvertently be classed as a rare disease, because of low prevalence. For this reason, the Surveillance of Rare Cancers in Europe (RARECARE) consortium has proposed a definition more in keeping with the natural progression of some diseases. Under this definition, rare cancers are those with an incidence of less than six per 100 000 people per year.[1]

In the past 10 years, more attention has been focused on rare cancers for several reasons. 20% of cancers are rare according to RARECARE data,[1] and collectively they represent a substantial burden of disease. Rare cancers have a higher proportion of deaths than do common cancers,[1] and improper therapeutic management is more common.[1–3] Patients with rare cancer and their primary physician have difficulties accessing information about diagnosis and treatment,[1] and access to clinical trials is a challenge. Innovative treatments are not readily available, even though some rare cancers have been paradigmatic models for targeted therapies of cancer (eg, gastrointestinal stromal tumour [GIST]).[4] Fragmentation of so-called common cancers into smaller molecular subsets as a result of routine molecular characterisation has substantially increased the number of rare cancers.

The aim of our Series paper is to discuss and analyse the achievements and experiences gained from networks of expert centres and research consortia for the treatment of rare cancers. We also describe remaining bottlenecks and limitations of consortium structures in terms of the goal of improved survival and outcomes for patients with rare cancers. We use examples from our own work with sarcomas, a heterogeneous group of rare tumours. Our analysis calls for the integration of research consortia (which are in charge of creating and implemeting research programmes) and reference networks (which organise the optimum management of patients in routine settings) for the management of rare cancers.

Reference networks and diagnostic accuracy

Management of rare cancers poses specific problems, including delays in diagnosis due to poor diagnostic precision, and therapeutic mismanagement.[1–3] The experience of the medical team and their awareness of rare tumours will determine the extent to which these issues arise. For example, only around 40% of patients with sarcoma are treated according to the recommended guidelines for localised disease; the other 60% of patients experience treatment mismanagement and have worse survival as a result.[2,3] Clinical research is also impeded because of low awareness or difficulties in patients accessing specialist centres running clinical trials for rare cancers. Additionally, because fewer clinical trials are done for rare cancers than for more common cancers, fewer new therapies are approved for these diseases.[1]

Several studies have investigated the frequency of diagnostic inaccuracies with rare tumours. One such study of sarcoma was done by the Conticanet Network (supported by the European Commission and national academic funding) in three European regions (Rhône-Alpes, Aquitaine, and Veneto) on exhaustive population-based tumour series.[5–7] Networks of pathologists in the three regions participated in the programme, in which all tumours suspected to be, or diagnosed as, sarcoma were centrally reviewed by a panel of pathology experts. Although this method results in a high burden for primary and expert pathologists, it is the only way to gather exhaustive data for tumours arising from all organs. The results showed that the incidence of sarcomas had been underestimated.[7,8] Whereas most comprehensive reviews suggested an incidence of two sarcomas per 100 000 patients per year, the incidence in the three regions was 5·8 per 100 000 per year—ie, three times higher than previously thought.[8] By allowing diagnostic inaccuracies to be corrected, the systematic histological review of the Concatinet Network study affected patients' treatment and outcome.[5–7]

Further investigation into discordances between local and expert pathologists in the Concatinet study showed that when central histological review was requested spontanesouly by the local pathologist (who was unsure of the diagnosis), their diagnosis was corrected in about 50% of cases (discordances included reclassification of benign tumours as malignant and carcinoma as sarcoma). When central review was done without solicitation by a primary pathologist (most patients in this study), 30% of the histology diagnoses were substantially modified,[5–7] suggesting that more than a third of diagnoses could be inaccurate. In a more recent study (unpublished), based on the Réseau de Référence en Pathologie des Sarcomes (an exhaustive nationwide network of reference centres in France), these numbers did not substantially change for major discordances—ie, the frequency of discordances between local and central diagnosis of sarcoma versus non-sarcoma was around 30% (figure 1). These data are in keeping with those from retrospective studies that did not include exhaustive samples.[9,10] Clearly, these results profoundly affect the proposed treatment.

For the **Réseau de Référence en Pathologie des Sarcomes** see https://rreps.sarcomabcb.org

Without centralised expert histological review, 20–30% of patients with sarcoma could be unduly included in clinical trials. Central review of pathology diagnoses is therefore mandatory for most clinical research groups—eg, the European Organisation for Research and Treatment of Cancer (EORTC). Practically, central pathology review before inclusion of patients can be complex, particularly for international trials. Central review is therefore done post hoc, which might result in a high proportion of non-eligibility, especially now that more and more clinical trials are done in histological and molecular subsets of cancers. Although not all cancers are as problematic to diagnose histologically as sarcoma, these difficulties point to the need for diagnostic support for cancers that are not frequently encountered by pathologists and for careful coordination between expert networks acting in routine settings and research groups.

Organisation of translational research

Research networks and consortia have key roles in the complexity of translational research in rare cancers, and the integration of molecular characterisation of the tumours. The increasing availability of genomic characterisation of cancer is strongly affecting the development of clinical research into rare tumours (figure 2A). Here again, the example of sarcomas is particularly useful. In addition to histological subtypes,[11,12] connective tissue tumours can be distinguished according to recurrent molecular alterations: translocations, mutations of receptor tyrosine kinases, tumour suppressor gene deletions, 12q13 amplification, gross genomic rearrangements, deletion of the *APC* gene or mutation of β-catenin for aggressive fibromatosis, or mutations of the H3F3 histones in giant cell tumours of the bone.[13–20]

These genetic alterations are now often inclusion criteria for clinical trials,[13–15] in recognition of the fact that the uncovering of an activating—or recurrent—molecular change in a histological subtype is more effective than histology alone for nosological definition of the disease entity and prediction of treatment efficacy. Molecular biology technologies that enable these complex molecular diagnoses are not available in all hospital facilities, and organisation of clinical trials via consortia enables crucial molecular testing to occur.

Since 2000, GIST has been an emblematic model for the development of targeted therapies for solid tumours in research networks because of the success of imatinib.[16–20] The effect of imatinib on the main molecular GIST subgroups was shown by a carefully preplanned meta-analysis of two phase 3 trials (by the EORTC and SWOG) in which two doses of imatinib (400 mg *vs* 800 mg)

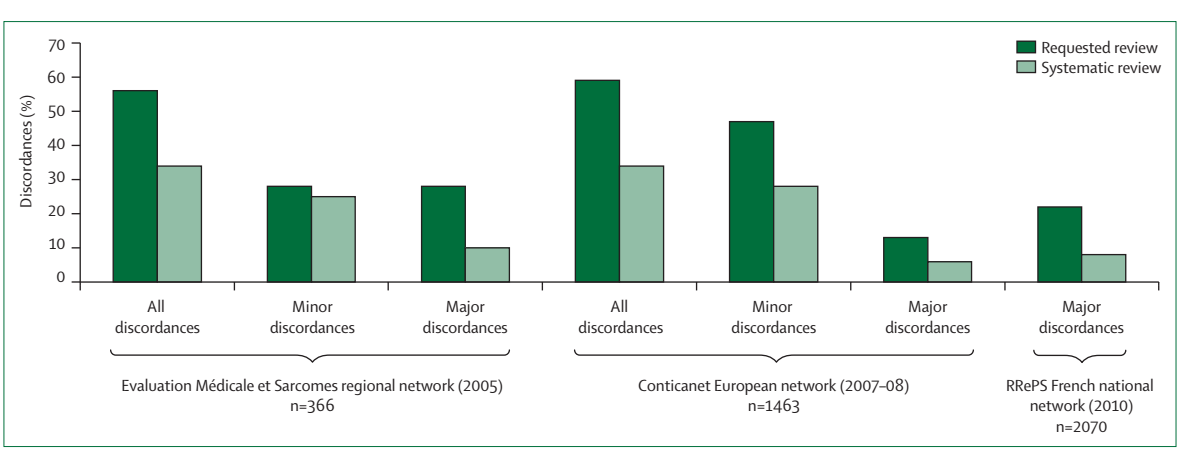

Figure 1: **Proportion of diagnostic discordances in three sarcoma networks**
In the Evaluation Médicale et Sarcomes study, major discordances were defined as changes between two different histological types, and minor discordances as changes between two different grades. In the Conticanet and RRePPS studies, major discordances were defined as changes between benign and malignant sarcoma or between sarcoma and non-mesenchymal diagnosis (ie, carcinoma). Minor discordances were defined as changes between two different histological types. RRePS=Réseau de Référence en Pathologie des Sarcomes.

were compared.[17–19] 12 molecular subtypes of GIST (eg, carriers of mutations in *KIT*, *PDGFRA*, *NF1*, *BRAF*, succinate dehydrogenase) have been identified, and they are now included in distinct clinical trials.[20] The integration of these genetic alterations into GIST diagnosis affects not only the treatment of metastatic disease, but also choice of adjuvant treatments.[16,20] This fragmentation into ultrarare entities of a disease, for which the ontological identification took place in 1998, foreshadows future oncology developments targeting specific molecular alterations, such as personalised medicine.

These rare tumours are likely to be treated within research consortia, which provide a framework enabling accurate molecular diagnosis and rapid accrual of patients in international clinical trials. As an example, to do a clinical trial of a new drug for D842V *PDGFRA*-mutated GIST, the yearly incidence of which is close to 0·2 per 100 000 in Europe and in which risk of relapse is close to 10%, would necessitate an established set of expert centres, each enrolling patients in their region, and accurate molecular diagnosis as early as possible.

Research into dermatofibrosarcoma protuberans also shows the complexity of clinical trials in very rare entities and the usefulness of coordinated clinical research in multinational consortia. Dermatofibrosarcoma protuberans is a slowly progressing cutaneous sarcoma that rarely metastasises, is chemoresistant, and is characterised by a translocation fusing *COL1A1* with *PDGFB*, producing an autocrine growth factor.[21–23] A retrospective study[22] showed significant antitumour activity with imatinib, leading to early registration of the drug for this orphan indication before a prospective clinical study. Two phase 2 trials (by the EORTC and the US Sarcoma Alliance for Research through Collaboration) were subsequently done and merged for publication.[23] Flexibility and adaptation within two academic research networks were key to the optimum use of the data accumulated by both trials.

Conversely, the development of the IGF1R antibody in Ewing's sarcoma was less efficient because a less coordinated approach was used. Ewing's sarcomas contain gene fusions that encode transcription factors that regulate gene expression, including the inhibition of IGFBP3 expression. Through its interaction with IGF1, IGFBP3 inhibits the proliferation of cells and promotes apoptosis in Ewing's sarcoma cell lines.[24] Phase 1 and 2 trials of an IGF1R antibody showed that only some patients have long-term responses to these treatments.[25] The research programmes overseeing independent, distinct phase 2 trials did not identify a reliable biomarker to predict long-term response in patients given IGF1R antibodies. Thus, no pharma-sponsored clinical trials are ongoing, even though a proportion of patents had prolonged tumour control. However, the EuroSARC FP7 consortium, together with the EORTC, has launched a proof-of-concept clinical trial exploring linsitinib, an IGF1R tyrosine-kinase inhibitor, in patients with Ewing's sarcomas, with translational research exploring biomarkers for response.

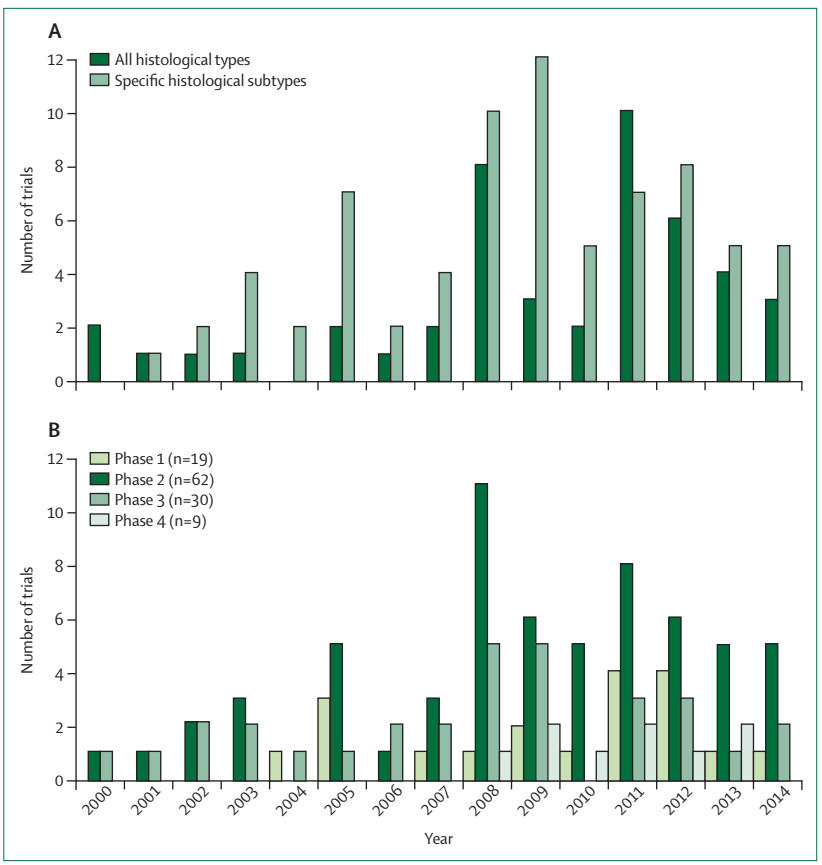

Figure 2: **New interventional trials in a rare cancer (sarcoma) by the French sarcoma network, 2000–14, by histology (A) and phase (B)**
Of the 120 trials overall, 63 were academic trials and 57 were pharmaceutical industrial trials.

This example shows the value of academic research networks in the investigation of important clinical questions for small subsets of patients whose illnesses are not explored by pharmaceutical companies.

Clinical trials for which inclusion criteria include histological and molecular characteristics of tumour cells are increasingly being proposed (figure 2A). Research networks, linked with reference networks (ie, consortia of research teams and networks in charge of routine central review and molecular diagnostic platforms), have a key role in the development of these trials. When these platforms are not available, original strategies are starting to be developed by cooperative groups. Within the EORTC, the Screening Patients for Efficient Clinical Trial Access (SPECTA) programme is focused on central collection and analysis of tumour samples of patients with rare tumours to enable subsequent inclusion in molecular clinical trials.[26] This strategy is highly relevant to the need for expert histological review and molecular characterisation of tumour samples in rare tumours. The molecular characterisation proposed by the 28 platforms of molecular testing of the French National Cancer Institute is a similar strategy:[27] at a national level, these platforms have enabled characterisation of mutations in key driver genes in more

For the **French National Cancer Institute** see http://www.e-cancer.fr/

than 80 000 samples per year since 2011, including about 20% of tumours in the rare cancer category in addition to the selection of patients for routine treatment (the primary aim of these platforms). This strategy enabled the inclusion of these patients in academic clinical trials testing targeted drugs directed against the proteins encoded by the genes altered in these tumours. The ACSE (Accès Sécurisé aux therapeutiques innovantes) trials of crizotinib in cancers with *ALK*, *ROS1*, and *MET* mutations of all histotypes, and *BRAF*-mutated cancers of all histological types have included more than 100 patients with rare cancers or rare molecular subsets of frequent cancers in one year in France.[28]

Importance of reference and research networks

Although in theory the same rules should apply for the definition of standard treatments for rare tumours as for those for more common tumours, in practice that is not the case. For rare tumours, standard treatments are often established on the basis of results from historical studies done without control groups or from randomised controlled trials (sometimes only one trial) in small numbers of patients.

For example, meta-analyses[29] showing the usefulness of adjuvant chemotherapy for breast cancer included more than 100 000 patients, whereas the two trials[30,31] showing the usefulness of adjuvant chemotherapy for osteosarcomas included 36 and 59 patients, respectively. The trials that allowed the validity of conservative surgery with breast cancer to be established included several thousand patients,[32] whereas the one trial[33] in which amputation and limb preservation surgery in soft-tissue sarcomas were compared included only 43 patients. Once again, the development of clinical research on rare cancers necessitates a subtle coupling between reference and research networks, for the definition of the standard group, and to ensure feasible accrual.

For the **International Rare Cancers Initiative** see http://www.IRCI.org

Because standard therapies for rare cancers are thus often based on weak evidence, scientific societies are essential to define by consensus the standard treatment in these disorders. Since 2008, the European Society for Medical Oncology has been organising consensus conferences for treatment of common and rare tumours.[10,11] In the case of rare tumours, these meetings and their subsequent reports gather experts from active clinical research groups and consortia, which results in the production of consensus statements that are used to identify questions later addressed by clinical trials done by the consortia. The EORTC has developed this expertise during the past 50 years and has helped to define standard treatments for several rare cancers, such as Hodgkin's lymphoma, sarcomas, melanomas and brain tumours. Because rare cancers are increasingly being grouped into even rarer subentities with the progress of molecular biology, most large trials in a subset of rare cancers will now necessitate intercontinental collaborations to achieve accrual within reasonable timeframes.

Numbers: methods for clinical trials

All phases of drug development—and particularly phase 3, which is designed to determine treatment efficacy—are challenging when only small contingents of patients with rare tumours are potential candidates. For common cancers, many patients (often more than 1000) can be included to uncover small (but significant) differences between the new strategy and the standard treatment. Historically, the general perception used to be that randomised trials are simply not feasible in rare cancer populations. However, with the growth of consortia and their assistance with accrual, a growing number of randomised clinical trials are being done in patients with rare cancer (figure 2B).[34–43]

For example, the Children's Oncology Group did a randomised trial[34] investigating the addition of the immunomodulator muramyl tripeptide (MTP) to standard chemotherapy in a series of 662 patients with osteosarcoma; results showed improved overall survival in the MTP group. These results led to the approval of MTP by the European Medicines Agency, and to drug reimbursement in some but not all countries.[34]

International consortia have been particularly useful in accruing large numbers of patients for randomised trials. A notable example is the EURAMOS study, which was done by a single intercontinental cooperative group that included US and European cooperative oncology groups. The aim of EURAMOS was to determine the effect of changing postoperative chemotherapy on the basis of histological response on event-free survival, a question that necessitated a large sample size to answer. The EURAMOS trial successfully completed accrual with 2260 patients with osteosarcoma and has shown the feasibility of large intercontinental trials for rare diseases, although final results are still under analysis.[35] Another example of international collaboration is the International Rare Cancers Initiative, which incorporates the US National Cancer Institute, Cancer Research UK, and the EORTC, among others. Eight trials in very rare cancers have been begun by this initiative.

The degree of rarity affects the choice of accrual method for clinical trials of rare cancer—eg, well organised national research groups or international consortia. National networks can be efficient when the cancer is not excessively rare (eg, GIST, with an incidence of 1–1·4 per 100 000 per year). For tumours with a lower incidence—eg, osteosarcoma, for which the incidence is closer to 0·2 per 100 000 per year—international networks remain indispensable. The need for international collaboration in clinical and translational research is associated with several challenges, however, including high costs, delays, and administrative burdens to initiate and maintain the study. Experts in clinical trial legislation are needed to oversee this complexity.[26] The level of activity of the trial treatment can affect study design: in the case of treating GIST with imatinib, or treating pigmented villonodular

synovitis with CSF1R inhibitors,[44–47] small-scale phase 1–2 studies were sufficient to demonstrate outstanding clinical activity.

Novel statistical and trial designs for rare cancers

Clinical research groups and consortia are central to the development of innovative methods for clinical research in rare cancers.[45] The International Rare Cancers Initiative published an important report[48] of original methods applied in clinical trials open in several rare, previously unexplored cancer types. Bayesian methods allow a research question to be investigated by taking into account previously obtained information. Although rarely used in oncology, Bayesian methods have useful applications in trials of rare tumours. Several phase 2 trials (including some randomised trials) that have demonstrated the activity of treatments in rare cancers have been based on Bayesian methodologies.[49]

Phase 0 trials, in which microdoses are used, and particularly phase 2 trials with biological proof-of-concept research, allow demonstration of biological activity of a new drug on a given target and establishment of a broader biological rationale. Such trials are currently being developed[50] and are especially suited to work in rare tumours when a main target has been characterised. Phase 1 trials specifically aimed at tumour subtypes that are selected on the basis of their molecular properties equally allow rapid proof of concept, thereby leading quickly to pivotal studies with the potential to show activity of an entity in a selected population.[51]

Rare tumours and rare molecular subsets of frequent tumours often offer opportunities to test innovative clinical and translational research strategies. Basket studies are good examples of the innovative strategies for clinical research dedicated to rare tumours. These clinical trials allow for the exploration of a specific inhibitor in new indications for various tumour types (including rare tumours) that contain the same molecular aberration—eg, NCT01524978 is investigating a BRAF inhibitor (vemurafenib) in several tumours,[52] NCT02034110 (the ROAR study) is investigating the use of dabrafenib and trametinib (a BRAF and a MEK inhibitor, respectively) in a range of rare cancers. The EORTC also supports this approach with the CREATE study (NCT01524926), a phase 2 trial of crizotinib in various tumours, including rare tumours, with MET or ALK activation. Basket trials are also being used to replace non-informative compassionate use programmes that allow use of novel therapies outside clinical trials in some countries such as France.

Randomised studies with a similar approach that are overseen by academic research consortia are underway: in the RegoSARC (NCT00867113) and RegoBone (EudraCT2013–003910–42) studies, patients are randomly assigned to regorafenib or placebo in four independent groups, each defined by histological and molecular subsets of soft tissue and bone sarcoma. The novel format of the studies will better achieve the aim of providing rapid information about molecular subsets of cancer, and are associated with reduced costs and administrative burdens.

Interactions with stakeholders

Pharmaceutical industry

Research networks and consortia are essential to improve interaction with stakeholders, including the pharmaceutical industry, patient advocacy groups, primary care doctors, and some heath authorities. Previously the pharmaceutical industry was thought to be unwilling to do trials of new drugs for rare cancers because trials of new drugs in frequent tumours benefitted from faster recruitment and are more likely to provide better financial return for a similar investment. In the past several years, this notion has been challenged for several reasons. First, niche indications sometimes allow for rapid drug registration with regulatory agencies because of the absence of efficacious treatments. Second, in rare tumours with well identified driver mutations, tumour response and progression-free survival in treated patients are often increased, allowing demonstration of efficacy without randomised trials. Third, support from health authorities has enabled development of drugs to treat rare diseases.[53]

Finally, and most importantly, the feasibility of completion of the trial within a reasonable timeframe is important to ensure relevance and homogeneity of the trial population. A large proportion of the key clinical trials enabling the approval of novel drugs in the past 10 years were collaborations between a pharmaceutical company and cooperative research groups.[36,41] Successes achieved in the registration of novel active drugs in selected rare tumour types, such as lenvatinib and pazopanib for thyroid cancers and sarcomas, respectively, and rapid accrual within basket studies provide favourable signals to the pharmaceutical industry that rare tumours are good models for drug development.

However, challenges remain that will need to be solved in the coming years. Fragmentation of cancers into small, discrete entities could lead to an increase in the number of trials, which might not be advantageous when the cost of clinical research is already increasing substantially. Development of research methods that cost less after agreement with health authorities about simplified methods will be necessary. Overcoming these issues is crucial to ensure that research into rare cancers is not discouraged. Discussions about the global cost of research and return on investment need to take place with all stakeholders: there is a risk that the rising costs of drug development, together with the stringent pressure of health technology assessments for drug reimbursement, might discourage the pharmaceutical industry from investment in drug development in rare cancers, at a time when most newly identified molecular subsets of cancers are rare.

Search strategy and selection criteria

We searched PubMed with the terms "rare cancer" and "rare tumors" cross referenced with "clinical research", "clinical practice guidelines", "patients", and "patient advocacy groups" for work about research consortia for rare cancers published in English between Jan 1, 1990, and June 20, 2015. We also searched the websites of known research consortia (eg, the European Organisation for Research and Treatment of Cancer, Gynecologic Cancer InterGroup, national sarcoma groups), networks of expert centres (eg, the French National Cancer Institute, Scandinavian Sarcoma Group), networks of excellence dedicated to rare cancers, and patient advocacy groups with activity in the field of rare tumours. Only papers and webpages published at least in part in English were reviewed. We chose the final reference list on the basis of originality and relevance to the broad scope of this Series paper. In general, clinical research is organised within national or international networks of clinical research centres. We use the term consortium to denote these networks, although it can also refer to intergroup structures.

Specific criteria must be agreed upon with the health authorities, which have been providing guidance for applications for approval of novel drugs for rare cancer indications. Orphan indications received special attention from both the US Food and Drug Administration and the European Medicines Agency, and are recognised to necessitate specific criteria for assessment of the benefits of novel drugs. Identification of the mode of action of the drug and the magnitude of benefit ("outstanding") are crucial in series recruiting few patients.

Communication with patients and doctors

Unsurprisingly, treatment of rare cancers is perceived as being more complex than that of other tumours, by both patients and primary care doctors. A focus group of academics, industry members, patients, patient advocacy groups, and health professional societies that all worked on rare tumour issues were surveyed (by phone, internet, and postal questionnaire).[54] The survey included 169 patients treated for a rare tumour, and 102 patients treated for a common tumour. 74% of the primary care doctors had dealt with fewer than ten patients with rare tumours during their careers. Disease complexity, rarity, and lack of knowledge were cited as the most common difficulties by primary care doctors. Difficulties when diagnosed or at treatment initiation were reported by more than 50% of patients with rare cancers. Before diagnosis, the mean number of doctors consulted was higher in patients with rare tumours than in those with other tumours (3·25 *vs* 2·6; p<0·05).

For the **Rare Cancer Europe Network** see http://www.rarecancerseurope.org

For the **European Commission Expert Group on Rare Diseases** see http://ec.europa.eu/health/rare_diseases/expert_group/index_en.htm

Patient advocacy groups

Reference networks and research consortia need to improve dissemination of information to potential patients, the general public, and the primary care community. Patient advocacy groups are the main source of information for patients, on par with the internet. Accordingly, research projects funded by the European Commission (including Eurobonet, Conticanet, and EuroSARC) and at a national level have all included patient representatives on their steering committee. Some patient advocacy groups emerged after meetings within these networks of excellence (Sarcoma Patients Euronet and Conticanet, for instance). In general, the propagation of information about treatment strategies and research questions is efficiently achieved by these patient advocacy groups. Passing the information onto primary care doctors is more challenging.[55,56]

Patient advocacy groups are also key partners for research consortia: they sometimes contribute to generation of tumour banks and create rare tumour databases, and financially support basic and translational research. The involvement of patients in obtaining tissue samples is novel and also shows direct self-empowerment by patients for poorly supported diseases. Publications about the characterisation of genomic characterisation of diffuse pontic glioma of children, or fibrolamellar hepatocellular carcinoma are good examples of the emerging roles of patient advocacy groups.[57–59]

Regulatory bodies

Academic research into rare tumours has also been affected by increased cost and administrative burden. An analysis of the effect of the European Union Clinical Trials Directive on clinical trials in Europe was reported by the Impact on Clinical Research of European Legislation (a European Union project).[60] Investigators looked at a wide range of stakeholders—pharmaceutical companies, academic groups, ethics committees, health bodies—and compared activity data before and after the establishment of the directive. Results showed a small effect on the total number of studies, with a slight increase in clinical trials from commercial sponsors, but a possible fall in the number of academic studies. The implementation of the European Union Clinical Trials Directive seems, however, to have increased procedural homogeneity and the quality of some multi-country trials. However, all participants underscored the increased costs of trials since implementation of the directive.[60] None of the analysis was specific for rare tumours, but similar findings can be reasonably assumed, with the additional difficulty of funding for academic studies for these rare tumours and the specific need to reread the histology and international accrual and expertise.

In this context, interaction with health authorities and political bodies to provide information on the specific constraints of research in rare cancers is an important task for research consortia. Networks such as Rare Cancer Europe, the European Commission Expert Group on Rare Diseases, and scientific societies such as the European Society for Medical Oncology are currently engaged in interactions with key administrative bodies, such as the European Medicines Agency.[61]

Conclusion

Clinical research on rare tumours has long been hindered by difficulties linked to dispersal of patients and expertise. Progress in understanding the biology of these tumours and the advent of targeted therapies is leading to change. Research consortia need to associate with reference networks. Both have had key roles in the creation of novel clinical trials, which need to include systematically optimised diagnostic procedures and strategies to organise accrual, better define the standard treatments with the help of scientific societies, and be based on communication with key stakeholders in the rare tumour area, the pharmaceutical industry, patient advocacy groups, and health authorities.

Rare tumours are now models for research in the genomic era. As frequent tumours continue to be subclassified into discrete entities, each representing a small proportion of the total number of patients, it is clear that the issues of clinical research for rare tumours are in fact the issues of oncology research in general in the coming decades.

Contributors

J-YB, J-MC, and IR-C conceived the paper. J-YB and IR-C wrote the first draft, and FD oversaw data collection. All authors reviewed the paper and approved the final draft.

Declaration of interests

We declare no competing interests.

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