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Evidence-based data and rare cancers: The need for a new methodological approach in research and investigation

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ABSTRACT

Rare cancers are not so rare, their incidence is increasing and, as a group, they have worse survival than the common cancers. These factors emphasise the societal need to ensure sufficient focus on research into their biological basis, aetiological factors, new more effective therapies and organisation of healthcare to improve access to best practice and innovation. Accuracy of diagnosis is one of the first hurdles to be overcome, with around one third of tumours being reclassified – by type or risk group – when subject to a centralised pathology review process. Timely access to appropriate expert knowledge is a second challenge for patients – in Europe this is being addressed by the establishment of European Reference Networks (ERNs) as part of the EU cross border healthcare initiative. There are ERNs for adult solid and haematological cancers and childhood cancers, all of which are individually rare. These ERNs will facilitate creation of large databases of rare tumours that will incorporate knowledge of their molecular features and build an evidence base for the effectiveness of innovative, biology-directed therapies. With an increasing focus on 'real world' outcome data, research methodologies are evolving, to include randomised registry trials and data linkage approaches that exploit the ever-richer information held on patients in routine health care data. The inclusion of genomic analysis into cancer diagnosis, treatment and risk prediction raises many issues for the conduct of clinical research and cohort studies and personal data sharing. Sophisticated means of pseudonymisation, together with full involvement of affected and 'at risk' patients, are supporting novel research designs and access to data that will continue to build the evidence base to improve outcomes for patients with rare cancers.

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Introduction

The increasing incidence and effects of cancer have led to greater use of cancer registries to understand the opportunities for intervention and the development of screening and research programs for cancer prevention. These initiatives have resulted in improvement of cancer detection, diagnostics, treatment, follow-up and research. However, these advances have not been applied to the same extent across all cancer types and patient groups. For rare cancers, because the number of patients is low, there is insufficient focus on accurate and timely diagnosis, effective treatment modalities and evidence-based guidelines. Additionally, funds for research on rare cancers are limited and it is complex to perform clinical trials due to the lack of adequate sample sizes [1].

The principles of evidence-based medicine (EBM) are relevant to all types of diseases including uncommon and rare cancers. In EBM, there is a rather clear hierarchy of evidence in which the highest form is the randomised controlled trial – the RCT. The randomisation assures that both known and unknown confounding factors are evened out between groups, and the control treatment assures that the intervention is different than the natural progression. Despite the strong evidence that they create, RCTs are very expensive and generally cumbersome. The logistics of an RCT are challenging, the recruitment process complicated, staff need to be trained and the study sites monitored. Observational studies on the other hand, are less expensive, but create weaker evidence. They are generally placed much further down the evidence ladder as, without randomisation, tests of efficacy are deemed less credible.

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However, they have the advantage that they recruit a much broader range of patients who more closely reflect the 'real world' of clinical practice. Through collection of detailed data on treatment and outcomes, such observational studies have the potential to demonstrate population impact of new interventions. Such an approach can be of particular interest in rare cancers.

Until recently, no universal definition of rare cancer existed. The RARECARE group from Europe proposed a practical definition of 'rare' as a cancer with an incidence rate of <6 cases per 100,00 population per year [2]. This group produced a list of clinically relevant, histologically defined cancers (almost 200). The rare cancer list proposed is based on the International Classification of Diseases for Oncology (ICD-O, 3rd version), the classification of tumours recognised worldwide. Rare tumour entities are relevant for clinical decision-making and clinical research, while families of tumours are relevant for organisation of health care. In the era of molecular targeted therapies, the molecular profile will also be relevant. Indeed, genetic and molecular profiling of common cancers can partition these into rarer subgroups and international agencies that preside over such classifications are constantly updating them. However, these 'rare' subgroups of commoner cancers often have mechanistic evidence for a therapy based on the molecular target that defines them. Hence, their therapeutic and research needs are somewhat different to the individually rare cancers. The key figures of rare cancer burden in EU during 2000–07 were the following: 24% of all new malignancies and worse survival than common cancers [3]. In the US, approximately 20% of patients were diagnosed with rare cancers and 70% occurred in children and adolescents [4]. The worse 5-year relative survival (55% for rare cancers vs 75% for common during 2009–13 in USA and 49% vs 63.% during 2000–07 in EU) is more pronounced in adult patients and probably linked to a more advanced stage in rare cancers (59% 5-year relative survival for rare cancers vs 45% for common in USA) [3,4].

These data provide a clear picture of the global situation for rare cancers and emphasise the need to use detailed 'real world' data collected as a joint effort between national population-based cancer registries and clinical registries, and routine health care data. By merging all this information, we should be able to conduct clinical outcomes research in an efficient way and to provide results that are relevant to all patient groups affected by the selected cancer type, rather than just those eligible for entry into clinical trials.

Herein, we describe the barriers in the development of evidence-based medicine and the possibilities of strong development in research and clinical investigations by using rare cancer examples. These illustrations and modalities to develop research in rare situations should be considered for all type of cancers since the concept of rare cancer is evolving – the genetics/unique biological features of a tumour may reveal a rare subtype of an otherwise 'common cancer' (i.e. lung, breast, colon).

The following examples illustrate the heterogeneity of rare cancers, as well as the different clinical contexts, incidence rates (Fig. 1, Table 1) and the latest therapeutic progress:

- Childhood cancers: the care of children with cancer is based on decades of collaborative clinical trials, organised on a national or international level. All childhood cancers are currently defined as rare. This has led to long-term overall survival rates in excess of 80% in high income countries, but with variations ranging from 5% to >95% according to individual subtypes of childhood cancer [5]. Therein lies the challenge – further optimisation of therapy for those with a 'very good' prognosis on current standard therapies is increasingly difficult as the expected number of events reduces and sophisticated risk-stratification yields smaller subgroups [6].
- Haematological malignancies in adults (20% of incident rare adult cancer): a greater understanding of their biology and hence how they may be treated. Two rare leukaemia types (acute promyelocytic leukaemia and chronic myeloid leukaemia), which have poor prognosis when treated with cytotoxic chemotherapy, are now considered to have very favourable prognosis with targeted therapies [7].
- Sarcoma (5% of incident rare adult cancer): sarcomas can be classified into two broad categories soft tissue sarcomas (STS), and sarcomas of the bone. They account for only ~1% of all adult solid malignant tumours, yet represent more than 70 distinct tumour subtypes. Obtaining the correct diagnosis of specific subtypes of sarcoma is becoming increasingly important in delivering optimal medical care [8].

Uncertainty in the diagnosis, in the treatment: 'intrinsic lack or defect in evidence': limited patients and scarce high-level evidence literature

For most rare cancers, research to identify causes (aetiology) or to develop strategies for prevention or early detection is limited or non-existent [9]. Even when a specific molecular defect underlying a particular rare cancer is discovered, it can still be challenging to get a quick and certain diagnosis. Finally, standards of care derived from RCTs are not available for the majority of them and treatment options for the patient could be less effective, partly due to the non-availability of high grade evidence studies.

Several studies have reported the frequency of histological diagnostic inaccuracies in rare tumours. For sarcomas, the study carried out by the Conticanet network on three European regions quantified the problem. This study was carried out on a complete series of tumours, collected through regional networks. All the tumours diagnosed and tumours suspected of corresponding to a sarcoma were reviewed by a panel of national and international expert pathologists. Significantly, the centralised review corrected diagnostic inaccuracies in a significant proportion of cases. Fifty per cent of the cases for which the first pathologist was uncertain about the diagnosis and requested a second opinion, were assigned a classification. Discrepancies were related to benign versus malignant, diagnosis of carcinoma versus sarcoma, and the incorrect diagnosis of histological subtypes and grade [10]. Requests by the primary pathologist involved about 30% of patients. Of course, these diagnostic parameters have a major influence not only on the subsequent therapeutic management but also on the interpretation of clinical research and the evidence base. Indeed, without centralised review, up to 28% of patients with rare tumours included in clinical trials may be misclassified, as published evidence on this in sarcoma and lymphomas [11–13]. The centralised review of the diagnosis, implemented in clinical trials of rare tumours in many groups, including the European Organisation for Research and Treatment of Cancer (EORTC), is therefore an essential tool for obtaining quality data. Another consequence of this misclassification concerns etiological research in case-control studies (the most frequent design in rare cancers), and underlines the need to carry out new studies with a correct inclusion of cases after central review.

The particularities for rare cancer impact directly on the patients for whom no 'standard of care' treatment exists, and so the first objective should be to devise an optimal treatment plan. In theory, the same rules should apply for the definition of standard treatments in both rare and frequent tumours. For rare tumours, therapeutic standards have often been implemented from studies without a control arm or from RCTs whose small patient numbers mean they are underpowered to detect any differences [14]. The therapeutic standards are thus based on more 'fragile' criteria. It is not uncommon that no therapeutic standard is available in the absence of previous clinical studies.

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