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Rare cancers: Challenges & issues

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Rare cancers account for about 22 per cent of all cancers diagnosed worldwide, disproportionately affecting some demographic groups, with an occurrence of less than 6 per 100,000 individuals annually. Many rare cancers in adults, adolescents and children are not curable, and patients and care providers have little option to take therapeutic decisions. The epidemiology of rare cancers is a challenging area of study but is inadequately addressed. Despite efforts mainly in some European nations, a few improvements have been observed in the management of rare cancers. Reasons for this obvious stagnation are multifactorial and are mainly inherent to logistical difficulties in carrying out clinical trials in very small patient populations, hesitation of the pharmaceutical industry to spend in small markets and complexity in creating adequate information for the development of cost-effective drugs. Rare cancers also face specific challenges that include late and incorrect diagnosis, lack of clinical expertise and lack of research interest and development of new therapies. The utilization of nationally representative study findings for the patients' evaluation may possibly offer chances to find out pathogenesis and prevalence, and this will eventually lead to control and prevention. Currently, advancing targeted therapies offer a great opportunity for the better management of rare cancers. Conducting clinical trials with small patient population, innovative clinical trial approach, prevailing controlling obstacles for international cooperation and financial support for research are the present challenges for rare cancers. The International Rare Cancers Initiative functions as a main platform for achieving new international clinical trials in rare tumours. This review delineates the current challenges and issues in the interpretation, management and research scenarios of rare cancers.

Key words Diagnostic issues - haematological rare cancers - International Rare Cancers Initiative - management issues - rare cancers - rare childhood cancers

Introduction

Rare cancers are any tumours that involve a small percentage of the population in any age groups[1]. In the United States (US), the National Institute of Health (NIH) describes a rare disease or otherwise called orphan disease, as one with a prevalence of less than 200,000 persons per year (*https://rarediseases.info.nih.gov*). Rare cancers, when projected as a separate entity, impose a major burden to human race in both developed and developing countries[2]. These diseases may occur in any age group, gender or organ. Aetiologic data on rare cancers are limited, and the pathological and molecular patterns are still obscure. The dilemma with these rare tumours is that their entire burden on population has not been effectively assessed[3]. Even when defined more predictably by considering peculiarities of pathogenesis

and patient outcome, rare tumours constitute about 22 per cent of all reported cases of cancers, comprising all tumours occurring in childhood and adolescents[4-6]. This is higher than any single frequent cancers such as breast cancer (16%), colorectal cancer (13%), lung cancer (13%) and prostate cancer (12%)[5]. Rare cancers in adulthood, adolescence and childhood including haematological tumours are usually improperly interpreted and treated due to lack of understanding and medical expertise[7]. Therapeutic options for rare cancers are still poorly documented and remain essentially empiric. Europe has initiated efforts[8,9], and it is hoped that other countries, particularly developing countries such as India and other resource-limited countries, will see the importance and potential benefit of studies on rare cancers. The International Rare Cancers Initiative (IRCI) has selected nine rare cancers in adults that include anaplastic thyroid cancer, small bowel adenocarcinoma, fibrolamellar hepatocellular carcinoma, gynaecological sarcoma, salivary gland cancer, thymoma, penile cancer, relapsed/metastatic anal cancer and ocular melanoma[10]. The selection of these cancers by IRCI was based not only on the rarity of the disease but also ensuring that there were no existing randomized controlled trials and international trial group for these diseases.

Cancer incidence varies significantly from one continent to another. The incidence is fast increasing in developing countries, where nationwide prevalence is fast mounting those accounted in Western Europe and North America[4,11]. Figures from population-based cancer registries from India[12] and China[13] indicate that actual occurrence of cancer is low in Asia as compared to Western Europe and North America. Further, the pattern of cancers is different based on the aetiological factors. Certain cancers related to human papilloma virus infection such as cervical cancer, penile cancer and anal cancer are more common in developing countries[14,15] compared to the developed ones. In addition, a few cancers (*e.g*. gall bladder cancer) considered rare in western part are prominent in northern part of India and in some other parts of the world[16]. There are many differences in population demographics in resource-limited countries leading to improper recording of cancer incidence data[17]. The distribution, incidence rate and types of rare cancers are also different in various regions. Currently, rare cancers are of public attention but not certainly a health priority in many countries, and hence, definite guidelines feasible to each country should be made based on their resources. The Orphan Drug Act of 1983 from the US and EC141/2000 and 847/2000 from the European Union (EU) legislation became effective to encourage for the improvement of therapies for rare cancers[18-20]. Such programmes have been recommended as key steps to encourage integrity in the development of drug practice for cancers with distinct occurrence.

Definition of rare cancers

A correct definition for rare cancer does not exist. In European nations, orphan diseases are often designated as those with a frequency of <50/100,000 per year[18]. The problem with this definition is that it is grounded on incidence, which does not accurately reveal the health burden of disease events such as malignancy. Rare malignancies are usually categorized in the group of rare diseases, which are defined in the EU as diseases with a frequency of less than five cases out of a population of 100,000[5]. According to this definition, rare cancers are recognized as those with a prevalence of less than 6/100,000 persons per year. Use of this definition would help minimize the risk of mistaking a rare cancer such as testicular carcinoma, which is frequently cured and thus has a rather high prevalence, for a common cancer, or a frequent cancer such as small cell carcinoma of lung, which has a low life expectancy and thus a low prevalence, for a rare cancer[19]. It should be remembered that the study of rare cancers is not limited to rare histologic variants, but also it includes sub-groups that can be difficult to study in common cancers (*e.g.* T4N0 breast cancer). Conversely, rare cancers can be rare episodes of common cancers that present in uncommon hosts such as male breast cancer[20]. A list of rare cancers in adults has already been published (*www.rare-cancer.org/info/raw-adult-list.php*).

In the United States, the Orphan Drug Act described orphan diseases as those affecting <200,000 persons[21]. The Office of Rare Diseases provides a searchable list of almost 7000 rare diseases with information sources. The Rare Disease Act of 2002 and the US Orphan Drug Act clarify a rare disease as one that '(*i*) affects <200,000 persons in the US or (*ii*) affects more than 200,000 persons in the US, and for which there is no reasonable expectation that the cost of developing and manufacturing a drug for such disease, available in the US, will be get backed from sales in the US of such drug'[21]. A study of rare tumours in the US used the definition of <15 incident cases per 100,000 annually, roughly corresponding in the US to 40,000 new cases annually or fewer[4]. To support the progress

of international comprehensive clinical trials for those diagnosed with rare tumours, IRCI has generally defined rare cancers as a prevalence of <2/100,000[10].

To evaluate the epidemiology of rare tumours as a whole in a large and heterogeneous population, the project Surveillance of Rare Cancers in Europe (RARECARE)[22] collected data on cancers from 89 population-based cancer registries in 21 EU countries[23]. Working from this database, a RARECARE working group generated a new list of cancers (186 rare cases) and formulated a new definition of rare cancers. The list was developed by a team of oncosurgeons, oncopathologists, haematologists, physicians and epidemiologists and materialized after a discussion during which the developing list and its validation were made available (*http://www.rarecare.eu*). Based on the definition of RARECARE (incidence <6/100,000/year), the projected annual prevalence of all rare tumours in Europe was about 108/100,000 in proportion to 541,000 new diagnoses yearly[23]. Five-year relative survivals were more or less worse for rare cancers (47%) than common cancer types (65%). More than 4,400,000 people diagnosed with rare cancers live in the EU, 24 per cent of the total cancer prevalence[23].

Most rare cancer epidemiology studies involve people living in Europe[1,5,8,23], North America[4], Australia[24], Japan[25], Italy[5,26,27], Turkey[28], *etc.*, which constitute a small portion of the global population. Definite descriptions of such data from other countries are still limited mainly because of the uncertainty in the definition of rare cancers. The National Institutes of Health (NIH) has elucidated that subtyping within a rare disease could also be regarded as rare (*https://rarediseases.info.nih.gov*). With this delineation, when compared to cancers of childhood, frequent epithelial cancers that are diagnosed in adults would be regarded as a 'rare' disease. An example is cancer of prostate gland which, despite more than 200,000 new diagnoses annually in the US, has been selected a 'rare' disease. Cancers such as hepatocellular carcinoma or ovarian malignancies are also designated as rare. This is because malignancies of ovary occur only in 21,000 US women annually. As the total incidences are fewer than 40,000 annually, it is considered a rare incidence. It is evaluated that worldwide gynaecological cancers account for about 19 per cent of cancers in females[29]. This comparatively large number is mostly accounted for the high prevalence of cervical cancer in the developing countries, particularly in India[30]. On the other hand, in the UK, uterine and ovarian malignancies account for only 5 and 4 per cent of gynaecological cancers, respectively (*www.cancerresearchuk.org/cancer-info/cancerstats/incidence/commoncancers*), and the occurrence of cancers of the vagina and vulva are significantly reduced. Carcinosarcomas, germ cell, gestational trophoblastic and stromal ovarian neoplasms are less frequent, but as a group, rare gynaecological neoplasms are relatively common[23]. Until in recent times, the three most frequent forms of gynaecological cancers (epithelial ovarian, cervical and uterine) have been considered as individual entities with a few changes for histologic subtype. The term 'rare tumour' was mostly reserved for non-epithelial tumours. However, there are distinctive pathologic behaviour patterns for histologic epithelial subtypes of ovarian, endometrial and cervical cancers, placing many more of these neoplasms into a rare group (*www.rarecare.eu*). Overall, rare gynaecological tumours include over 50 per cent of the total number of gynaecological tumours, with about 80,000 new cases annually in Europe, involving more than 30 different histologic diagnoses, with a very limited number of patients in each diagnostic category[23].

With the RARECARE definition of rare cancers in India, as per the Delhi Cancer Registry (DCR) data[31], approximately 60.9 per cent of males and 46.4 per cent of women fall into the category of rare cancers. Correspondingly, taking IRCI definition, the DCR data showed rare cancers in 19.4 and 23.0 per cent males and females, respectively[32]. The prevalence of some type of cancers in India and their rarity in western countries may be due to the extensive diversity of dietary, geography, lifestyle and environmental exposures, as well as the genetic variation among people[33]. As a result of the variation in the rare cancers' incidence and type in different parts of the world, the aetiology of many of these malignancies is still obscure.

Challenges in rare cancers

Rare cancers in general get less scientific consideration and financial support than their more frequent counterparts[34]. Hence, patients with rare cancers pose particular challenges due to their low prevalence, including mostly incorrect and often late diagnosis, difficulty accessing clinical skill and proper treatments, lack of confidence in clinical decision-making, possible indifference in developing new drugs, and shortage of accessible cancer registries and tissue banks. Further, investigators face difficulties in carrying out clinical studies because of the small number of sample population. All these factors affect the average

outcome of patients diagnosed with a rare tumour[23]. Scientific understanding of rare tumours is usually gained from case reports or anecdotal evidence, single-institution case series or, at best, small multicentre series[35]. Observations from such selected studies may be confusing as these do not reveal the characteristics of the underlying population of all similar cancers[36].

Many rare tumours can be incurable, but with limited substantiation support for patients and healthcare takers, it becomes difficult to conduct clinical planning[37]. International collaboration is necessary to carry out clinical trials of adequate statistical power to answer significant questions in a reasonable timeframe. Improved research on rare cancers can make possible developments in diagnosis, treatment and prognosis[38] and can also lead to significant observations about pathogenesis of these diseases[39].

Only a few treatment modalities have been developed for rare tumours and this has contributed to the problem that while survival rates have considerably improved for common cancers, there has been very little, if any, development in the prognosis of patients with rare cancers[40]. Although research initiatives in rare cancers have witnessed important development, but these are still comparatively incompetent and need progress immediately. Comprehensive epidemiological studies on rare cancers are scanty and such investigations should be performed in each developed and developing country. Finally, basic research centring on unusual cancer types is also likely to pay off in the long term due to lower competition when compared to cancers with higher prevalence and issues related to the cancer biology[11]. However, there is no easy solution in this context, but several components and potential explanations have to be formulated to increase the knowledge on rare tumours.

Diagnostic issues of rare cancers

Rare cancers are usually interpreted based on histopathological examination. Although tissue diagnosis is mandatory for cancer treatment, the possibility of interpretational errors remains considerably high, ranging from 25 to 40 per cent, in regular practice[41,42]. Important factors influencing diagnostic accuracy comprise specialist subjectivity and lack of expertise, intra- and inter-observer variability and submission of inadequate tumour samples. Though better treatments have been proposed for rare cancers, death rates have not yet been reduced[39,43,44] and the cost of management of rare cancers remains one of the healthcare financial burdens worldwide[45,46]. There is an urgent need to expand methodologies for improving diagnostic accuracy so as to minimize interpretational errors and, thus, guide successful treatment options. Diagnostic accuracy coupled with appropriate treatment policies would ultimately help patients with rare tumours improving survival and quality of life, while simultaneously maintain healthcare expenditures at a reasonable level.

The study of rare cancers is complex at various stages. First, to make sure that sufficient diagnostic sample is obtained and that specimen is handled properly. Second, the tissue collected in the biorepository should be of the best quality[47]. Accurate diagnosis and classification of the cancer are possible only by receipt of high-quality specimens. The traditional tumour classification and diagnostic practices of staining with haematoxylin and eosin, immunohistochemistry (IHC), conventional karyotyping, and fluorescence *in-situ* hybridization have virtually attained their potential maximally. Using these traditional diagnostic methods, it is hard to predict with definitely the pathogenesis, tumour type, metastatic potency, genomic and proteomic variation, treatment response, prognosis and survival rate of most of the rare cancers. Immunohistochemical markers are also usually inconclusive as several IHC markers have established to be tumour sensitive but not tumour specific[48]. There is a need to exploit methylation analysis, copy number variation analysis, single nucleotide polymorphism arrays, signalling pathway analysis, whole-genome sequencing, *etc*., to develop distinct tumour classification for rare cancers on the basis of their molecular/genetic makeup. Limited efforts have been done to formulate new policies for developing healthcare facilities for individuals suffering from rare tumour[49]. Promising results can be established by teaching and training of physicians and pathologists[50], telepathology as a result of synergistic consensus effort of several specialists[49] and decision support systems using quantitative features extracted by image analysis[51-53].

Management issues of rare cancers

Because of the rarity of disease, the management of rare cancers in the adults pose a problem. Published data about optimal approaches for diagnosis and treatment of rare tumours are limited[54-56]. Although the treatment modalities of rare cancers are improving, clinicians still face many challenges. In this context, it

is important to highlight rare cancers of genitourinary (GU) tract to explain the challenges faced by the clinicians during the management of these diseases[56]. Rare tumours of the GU tract comprise cancers of the male and female urethra and a range of renal malignancies, including collecting duct cancer, penile cancer, testicular cancer[57,58], sarcoma[59] and many others. In testicular cancer, the treatment of poor-risk and relapsed metastatic disease, which includes only 10 per cent of incident cases, presents a challenge[60]. In penile cancer, better prognoses have been revealed in primary tumours and lymph node metastases, but visceral and distant disease remains an incurable problem requiring further study[61]. Urethral carcinoma, with a different natural history in male and female, is the least frequent of the cancers discussed and suffers from a paucity of Level 1 data[62]. Anatomy governs management with superficial cancers treated with surgery and/or radiotherapy and with more progressive cancers sometimes showing advantage from combined modality therapy.

Absence of adequate clinical information on rare cancers translates to no definite treatment protocol, and defining a strategy is not as simple as looking at published guidelines that are supported by sufficient research[63]. Lack of treatment guidelines and published research often leave clinicians with no obvious approach to treat patients diagnosed with rare tumours. A treatment approach that has been applied for one patient with rare tumour will not necessarily be effective for other patients. Information from early-phase clinical trials also can lead to hypothesis of possible therapy in rare tumours. Another approach is to search for the underlying mechanisms involved in the histogenesis of the rare cancers in laboratories and through translational studies.

Very rarely adult cancers develop in adolescents and children. Lung cancers, head and neck cancers, breast carcinomas, gastrointestinal cancers, melanomas cause many deaths every year. However, these are exceptionally unusual in children and adolescents[64]. In this context, the following questions need to be addressed: (*i*) do adult-type tumours found in children have the same biology and behaviour of same cancer in an adult?, (*ii*) are epithelial cancers in children and adult the same?, (*iii*) why and how do children develop adult cancer in a very short time period compared to prolonged development in adults?, (*iv*) do they have precancerous stages as in multistep carcinogenesis?, and (*v*) how many of these tumours arise in the obvious absence of environmental carcinogens? One hypothesis is that such paediatric cancers (*e.g.* adenocarcinoma of the colon) may not be biologically comparable to the histologically identical cancer in adult patients[64]. In certain neoplasms (*e.g.* gastrointestinal stromal tumour), this concept may be supported by different response rate to chemotherapy[65]. In this situation, compared to adult patients, it is expected to have decreased response rates in paediatric patients. Similar studies need to be done for other adult cancers infrequently developing in children. Analyses based on molecular genetics have been hampered by the limited accessibility of suitable tumour samples of such rare cancers. Thus, centralized collection of tumour samples from rare cancers in central registries should be encouraged. Such actions would offer scientists with the chance to improve the understanding of the molecular mechanisms of rare cancer types, with immediate impact on clinical diagnosis and follow up[66].

International Rare Cancers Initiative (IRCI)

It has been observed that the average outcome for patients with a rare cancer is inferior compared to more frequently occurring cancers[4-6]. International clinical trials in rare cancers are possible with appropriate funding, planning and support to develop treatment strategies. In an attempt to address this issue and encourage the development of international trials for rare cancers, the IRCI was established early in 2011[10]. IRCI is a joint initiative by the National Institute for Health Research Cancer Research Network (NCRN), Cancer Research UK (CR-UK), the National Cancer Institute (NCI) and the European Organization for Research and Treatment of Cancer (EORTC).

The aim of the IRCI is to facilitate international clinical trials for rare tumours to enhance the improvement of new therapies for these diseases. IRCI brings together international professionals and experts in rare cancers and associated groups that have the competence to carry out clinical trials across national boundaries. It also provides an environment for associate groups to prioritize global rare cancer policies, organize discussion of clinical trials in cancers that otherwise lack international organizing infrastructure, aid evaluation of ideas and procedures by associate groups, work to lower barriers to performance of international clinical trials in cancer and offer a public support for clinicians with academic interest to approach industry for international cooperation in rare cancer clinical trials[10]. So far, IRCI has exempted rare molecular subtypes of frequent cancers; however,

a rare molecular subtype can be considered if it is a distinct, prospectively identifiable rare sub-group with a strong rationale for separate research, rather than inclusion as a molecular stratum in a mainline trial. Importance has been given to cancers with potential for an interventional trial (usually randomized) rather than an audit, registry or non-trial tissue collection. This programme is expected to boost the practice of advanced approaches, such as Multi-Arm Multi-Stage (MAMS) trial designs and Bayesian statistics, to exploit the prospective for addressing research questions and to ascertain and break obstacles to permit approved IRCI trials to conduct efficiently[10,67].

IRCI organizes face-to-face discussions and teleconferences to initiate possible clinical trial proposals to be discussed and developed. Developing relationships with industry is also a key objective[68].

Rare childhood cancers

Unlike in adults, childhood cancer is seen rarely, with prevalence usually between 70/million and 160/million at the age of 0-14 yr annually[69]. As a result of improved survival, the cancer mortality rates have also decreased for children all over the world. However, in childhood and adolescence, a wide range of rare cancers can develop with particular biological and clinical characteristics although great variations are seen between populations for some specific tumour types[70]. In addition, frequent cancers can occur with unusual histologic patterns or can present in uncommon atypical locations[71]. Rare cancers in children constitute <1 in 30 of all childhood tumours. According to the TumoriRari in Eta Pediatrica (TREP) project, a nationwide Italian cooperative project, rare tumours were defined as those malignancies described by an annual occurrence of <2/million children and teenagers up to 18 yr of age[26,27]. Cancer incidence and survival data have indicated that rare cancer incidence rate is about 15 per cent of all childhood tumour in the US[72]. Turkish Pediatric Oncology Group (TPOG) observed that 8889 children were diagnosed with cancers between 2002 and 2008 in their country and 3.7 per cent of them were diagnosed as rare cancers[28].

The TREP project was initiated to expand basic research on childhood rare cancers and generate diagnostic and therapeutic policies for each of the rare cancers. Pleuropulmonary blastoma and other lung tumours, nasopharyngeal carcinoma, adrenocortical tumours, renal carcinoma, thyroid carcinoma, breast carcinoma, carcinoid tumours, cutaneous melanoma, salivary gland tumours, gastrointestinal tract carcinoma, gonadal non-germ cell tumours (ovary/testis), pheochromocytoma, paraganglioma, pancreatoblastoma and other pancreatic exocrine and thymus carcinoma were enrolled in their study group[26,27,73]. TPOG study list was different from TREP list and included the rare cases such as hepatoblastoma, renal primitive neuroectodermal tumour, adrenocortical carcinoma and synovial sarcoma[28].

Thyroid carcinoma (19.2%), carcinoma of appendix (18.8%) and gonadal non-germ cell tumours (10.3%) were the larger groups in the TREP project[70,71]. Another study[28] also reported that most frequent cancer forms among adolescents in their rare tumour cases were thyroid carcinomas (11.6%) as shown in TREP list. Although incidence seldom exceeds 1.5/million, the most common carcinoma in children is the thyroid carcinoma in many regions of the world[74]. Considering this situation in children, the UK Children's Cancer Study Group and the US Children's Oncology Guidelines suggest annually thyroid palpation, followed by ultrasound or fine needle aspiration if there is an abnormality[75]. Tacyildiz *et al*[28] have explained most of the rare malignant, borderline and benign tumour types among children and adolescents in their study.

On the contrary with the present situation in highly incident cancer types, little development has been attained in the management of most of the childhood rare tumours. The reasons for this obvious stagnation are mostly inherent to logistical difficulties in performing large clinical trials in rare diseases. In spite of multi-modal therapies and technical development for diagnostic intervention, management of rare cancers in paediatric cases is difficult in developing nations owing to their variation. Diagnosis of rare tumours can be difficult, particularly in children and adolescents. Adult cancers which are predominantly epithelial, vary considerably from paediatric cancers. Once an interpretation of the disease is established, management becomes difficult because of the lack of evidence to guide therapy in children. Further, some of the drugs or combinations of drugs given to adult patients may not be suitable for children as toxicity of these drugs in children has not been investigated. Therefore, it is essential to make policies for the management of children and adolescents with rare cancers. There are comparison groups which may be helpful[76]. First, there are cancers that are very frequent in adults. Second, uncommon childhood cancers that are frequently seen in adults may also aid as a comparison group. For adult-type cancers in children, one strategic option would be

to refer to an adult oncology facility. This might be more suitable in an older adolescent[77].

Rare haematological cancers

Generally, rare haematological malignancies are a dilemma to medical practice, and treatment experience, even in leading oncology centres to which these types of diseases are usually referred. Ansell[78] described that various rare haematological malignancies, which include primary myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myelomonocytic leukaemia, chronic eosinophilic leukaemia/ hypereosinophilic syndrome, hairy cell leukaemia, the 5q-syndrome, rare acute leukaemias and Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma. In the past, the diagnosis of many rare haematological malignancies was often exclusionary diagnoses; at present, it is made more confidently as a result of the molecular aberration detected in these disorders[79,80]. This breakthrough has had a major impact on tumour classification, interpretational approach and in designing research policies in these diseases. A major progress was in understanding of the pathogenesis of myeloproliferative disorders[81]. Revealing the molecular basis for such diseases has, in turn, led to the development of semi-molecular classification systems for grouping patients based on recurrent genetic alterations. It will be of curiosity to watch how the recent molecular genetic studies become incorporated with conventional histopathological standards in setting up a practical roadmap for physicians who take care of patients with these diseases[82]. Moreover, several medicines have been developed and manufactured for the treatment value of rare haematological disorders. In spite of such development, treatment in rare cancers yet becomes suboptimal in terms of both patient survival and quality of life[83,84]. To maximize and probably personalize cancer treatment, it is essential to develop and validate risk evaluations and apply a risk score for evaluation to clinical trial studies.

Most of patients with new therapies for haematological diseases experienced life-threatening septicaemia during the treatment course. Thus, the treatment must only be employed by haematologists with ample experience and the patients should be observed vigilantly for cytopenia[85]. Usually, patients with indication of minimal residual disease (MRD) had a shorter relapse-free survival[86]. Policies to further improve early response rates, to accomplish maximum disease-free stage and to devise a curative protocol have been developed. In spite of the efficient therapeutic choices, the treatment outcome remains obscure due to the frequent occurrence of MRD even in complete responders[87]. Prospective research using combination therapies targeting complete suppression of MRD will confidently get better relapse-free survivals and also overall survival and may even suggest the prospect of cure[88]. Setting up of comprehensive databases should promote constant assessment of the significance of clinical features of disease in response to treatment protocol and prognosis.

Randomized clinical trials in rare cancer

Rare cancers are diverse and can be very different from each other; this can be a real challenge for clinicians and researchers to find enough patients to be included in clinical trials testing new treatments for developing orphan drugs. Randomized controlled trials are considered as the standard when comparing a new treatment with the standard treatment for a particular cancer[89]. Even for common cancers, trials usually have to be multicentric to guarantee sufficient numbers of subjects being selected in a reasonable period. However, to be considered clinically useful in patient trials, toxic regimens are normally essential to display relative declines in the risk of death of 20-30 per cent. For trails to have adequate statistical power (≥80%) to identify therapeutic outcomes of this magnitude, a substantial number of deaths need to be witnessed. This suggests sample population sizes that are idealistically voluminous for rare tumors[90]. However, because of the potential remoteness of the therapeutic resources, the patients' way of care remains unstudied[91].

An expert opinion, mainly concentrated in some establishments, is necessitated for rare tumours' management. Moreover, even if a considerably better therapeutic outcome could be anticipated, estimates obtained from the subsequent (small) randomized controlled trial would reduce the accuracy required for clinical judgments. It has been proposed that a Bayesian statistical approach would be helpful in planning and consequently summarize small randomized controlled trials[92-94]. Tan *et al*[89] have observed that treatments for rare tumours are not easily estimated in randomized trials as there are very few subjects to notice actual treatment differences[89]. Merging of earlier data with trial data by Bayesian techniques could overcome this issue[92]. The vital phase in a Bayesian approach is summarizing the data available before the trial[95]. This will usually be from single-arm clinical trials or trials of response rate rather than survival. However, a systematic analysis of clinical trials supporting rare

cancer drug approvals may identify concepts and terms that can inform the effective design of prospective clinical trials for rare cancers[96].

Several obstacles must be overcome while doing clinical trials in rare tumours. Especially, complex ethical and legal concerns have importance. Cancer genomic studies and molecular characterization of each rare cancer must be carried out to reach the final goal of an absolute cure for these diseases. To attain this goal, tumour banking is the essential[97]. For best possible use, the banked tissues need to be suitably consented, collected, annotated and stored. If any of the components are missing or spoiled, the research using these tissue samples are compromised[97].

Targeted molecular therapy (also known as genomic medicine) has led to considerable breakthroughs for many rare cancers[98]. A targeted molecular therapy is a biologic treatment that makes use of an activated oncogene as the Achilles' heel of the disease and employs this molecular entity as a target for treatment. NCI studies observed that targeted therapy on individuals with advanced forms of a rare type of pancreatic cancer may have new successful therapeutic alternatives[99]. Pierotti *et al*[100] elucidated the idea of 'one drug for different tumour types'. Novel trial design, overcoming regulatory obstacles for international cooperation and financial support of research in rare cancers by intellectual organizations with little, or no, pharmaceutical support are the main challenges while performing clinical trials with a small number of individuals. Most of these problems can be solved through the launching of robust international cooperation that harmonizes the approach to clinical trials. For effective implementation, we require robust data collection by national registries that can be managed to form international data sets. At last, assessment of novel therapeutic outcomes in these rare tumours may occur through audit, iterative learning and molecular analyses.

Conclusion

Rare cancers have not been much investigated because of their low prevalence. That is why epidemiological studies have difficulties in identifying indisputable aetiological risk factors. The resources to identify and explain rare cancer incidence, explore their aetiology and decide the possible methods for prevention, diagnosis and therapies have been suboptimal, leaving patients, specialists and policymakers with limited information. Low prevalence is a main barrier to conducting clinical trials to device efficient treatments. The incidence of rare cancers may also differ in different countries. In India, considering the population size, the number of patients with rare cancer may be high. There is a lot more to be done, with many other countries yet to contribute to the output. Enhanced multicentric experimentation on rare cancers can also aid in diagnostic accuracy, better treatment, prognosis and can guide to significant observations about cancer biology.

***Conflicts of Interest*:** None.

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