Care for Rare Cancers: Improved Care Requires Improved Communication

Die erfolgreiche Behandlung seltener Tumorerkrankungen erfordert verbesserte Kommunikationsstrukturen für den Wissens- und Erfahrungsaustausch

D. T. Schneider[1]
I. B. Brecht[1]

[1] On behalf of the GPOH Rare Tumor Working Group

A high incidence and prevalence of a specific disease strongly facilitate clinical and biologic research. Thus, clinical studies, even single center studies may recruit significant patient numbers within a reasonable period of time. Moreover, clinical hypotheses can be tested by genetic or molecular-biologic experiments on abundant tissue probes. Vice versa, the rapid advances in modern molecular biology and biostatistics now allow for a better detection of new therapeutic targets that may then be tested in large clinical trials. Thus, molecular genetic research may be translated into clinical therapy in a moderate amount of time. As a consequence, we are currently experiencing a revolution of anti-cancer therapy, bringing a broad panel of biologically targeted drugs into clinical application.

On the other hand, patients suffering from rare cancers benefit from these dramatic advances to a far less extent. In general, clinical data of rare tumors are less frequently collected in large prospective trials or registries [12,18]. Biologic research on rare cancers is additionally hampered by both the limited availability of tissue samples and limited financial funding. Furthermore, the recently more restrictive guidelines for clinical trials have also increased the bureaucratic and financial burden for clinical research, making clinical trials for rare cancers (financially) unattractive or even impossible [13].

Nevertheless, rare tumors may unmask clinical and biological phenomena that may also apply to other, more frequent tumors. In this context, the treatment of gastrointestinal stromal tumors with imatinib or the helicobacter pylori eradication therapy of mucosa associated lymphomas constitute milestones in innovative translational cancer research and treatment [23,25]. Therefore, careful documentation of patients with rare cancers is worthwhile and may stimulate clinical research beyond this particular diagnosis.

Compared to adult cancer, all pediatric cancers are rare diseases, summing up to a total of approximately 2000 new diagnoses per year in Germany [21]. Of note, the pediatric cancers are highly heterogeneous and according to histologic and immunologic typing fall in at least 60 different categories. This heterogeneity causes that even in large oncologic centers, some diagnoses will occur only in large time intervals, and many pediatric oncologists might diagnose some rare entities only once or twice during their career. In order to keep the clinical community alert to such rare diagnoses, some of the rare and very particular patients are reported in scientific journals. Thus, this very particular experience is shared with other colleagues. For instance, some articles recently published and some included in the current issue of the *Klinische Pädiatrie*, specifically report on rare syndromes [4,7], whereas others focus on rare therapeutic experience in very specific situations [1,2]. Accordingly, also other German and international pediatric journals include a variety of case reports that illustrate the fascinatingly broad spectrum of pediatric oncology during infancy, childhood and adolescence [16,17]. This illustrates that the exchange of clinical experience using the scientific reporting of instructive patients is a vital part of the academic discussion in pediatrics. In fact, the scientific work-up of such patients has also a substantial impact on clinical research and clinical management, since new syndromes may be detected or simply, clinical guidance is provided to others confronted with similar problems.

In the current edition, several articles covering hemostaseologic themes focus on rare disorders such as neonatal aortic thrombosis (see pages 134–139, one of the few rare neonatal hemostaseologic emergencies [15], or inherited platelet disorders e.g. Glanzmann thrombasthenia (see pages 150–153). Among the oncologic articles, one report describes germ cell tumor metastases to the central nervous system in children (see pages 140–144). This analysis is drawn from the world-wide largest registry of pediatric germ cell tumors, but only 15 patients were identified in more than 2000 patients. Nevertheless, specific recommendations for follow-up diagnostics and hypotheses for potentially successful therapeutic management can be developed for these rare situations. Other articles specifically focus on rare diagnostic situations such as an uncommon clinical course of a very slowly growing nephroblastoma (see pages 190–191) or a very peculiar course of a family, in which two children were affected by a complex disorder mimicking osteopetrosis with progredient bone marrow failure associated with neurological deterioration (see pages 180–183). This article nicely illustrates that in some patients with a progredient hematological disorder underlying multi-system disorders should be excluded, in particular in case of positive family history. Furthermore, a young infant is reported

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Correspondence
Prof. Dr. Dominik T. Schneider
Klinik für Kinder- und Jugendmedizin
Klinikum Dortmund
Beurhausstraße 40
44137 Dortmund
Tel.: +49/231/953 21680
Fax: +49/231/953 21047
dominik.schneider@klinikumdo.de

that presented with an apparently aggressively growing tumor, that was ultimately diagnosed as an inflammatory myofibroblastic tumor, i.e. a lesion with borderline dignity (see pages 192–193). This illustrative report underlines the importance of careful differential diagnosis, distinguishing neoplastic disorders e.g. from congenital malformations [14], as well as histopathologic diagnosis, which should also include central pathologic review, in particular in rare disorders.

Last, experience in rare therapies is also shared in this current issue. A child is reported, who suffered from a large cranial mixed malignant germ cell tumor that was successfully treated with protons (see pages 175–179). Another article illustrates a stunning side effect of treatment with the tyrosine kinase inhibitor sunitinib, leading to necrosis of a skin autograft (see pages 184–186). Such observations may thus provide important information if therapeutic strategies have to be chosen in individual therapeutic attempts for relapse patients. In summary, the current issue of *Klinische Pädiatrie* includes a variety of reports on rare but illustrative and very instructive clinical situations, ranging from aspects of differential diagnosis to problems of differential therapy.

Nevertheless, there are several obstacles to be overcome before such a rare patient will be published, resulting in a significant gap between the numbers of such rare situations experienced in clinical practice and those communicated to the scientific community. First, it takes a considerable effort to report a patient within a short scientific presentation. Often, this task falls to "young" colleagues so that they may gather experience in preparing scientific presentations. The scientific review process may rather frequently result in a rejection of the manuscript, if a rare disease is reported but comparable reports have already been published before. Last, many scientific journals may hesitate to publish case reports since these are usually cited less frequently than original articles and may therefore decrease the citation index of this particular journal.

As a consequence, the scientific work-up of this particular patient may remain futile and the scientific input is not shared with colleagues at other hospitals that may be confronted with a comparable patient. As a consequence, future patients presenting with this rare diagnosis will remain the "first" patient and will not benefit from experience and scientific work-up performed elsewhere.

In this context, clinical journals such as the *Klinische Pädiatrie* may play a significant role as a communication platform for the exchange of experience and knowledge. By providing a forum for the presentation of unique patients to the scientific community e.g. in the "Pictorial Eassy" or "Short Communication", experience can be shared and the scientific input laid in the treatment of this particular patient is made available to others. Moreover, the scientific review process also ascertains the quality of the presentation and sound discussion of the presented data.

Nevertheless, not every single patient presenting with a rare diagnosis or with particular therapeutic problems deserves a case description in a scientific journal. In order to avoid that journals degenerate to a letter box for peculiar diagnostic and therapeutic constellations, some form of abstraction is absolutely necessary. For this purpose, clinical registries for rare diagnoses provide a significant benefit to the clinical and scientific society [3,10,22]. In these registries, clinical experience is collected, shared and evaluated. In addition, by national and international networking, information can also be shared within a greater forum, so that patients will benefit from experience gained at other hospitals confronted with a comparable situation [3,19, 20,22].

In common pediatric oncologic diagnoses the treating physician relies on proven diagnostic and therapeutic algorithms. Thus, diagnostic assessment and risk-stratified treatment are highly standardized. Nevertheless, optimal treatment requires a significant amount of experience. In contrast, a patient presenting with a rare disease does not fall into the usual diagnostic and therapeutic algorithm. Therefore, diagnostic assessment and treatment are not standardized, which may lead to incomplete (or too elaborate) assessment on one hand as well as under- or (over-) treatment on the other. Here, the development of diagnostic and therapeutic guidelines may provide a significant assistance to the treating physician that may also increase quality of care. Such guidelines may be developed on the basis of other documented patients with this particular rare disorder. For instance, more than 15 girls with the rare small cell ovarian carcinoma of the hypercalcemic type, a diagnosis made once or twice each year in Germany, have been documented within the MAKEI registry [9]. Based on these few patients, a diagnostic and therapeutic guidance has been developed which is made available to future patients.

On the other hand, guidelines may also be developed on the basis of scientific evaluation of the experience gained in comparable tumor entities. Thus, a guidance for the assessment and treatment of pediatric malignant melanoma has been developed by the GPOH Rare Tumor Working Group [3], which is mainly based on the corresponding guideline for adult patients with malignant melanoma [11]. Such guidelines must be scientifically updated based on the experience from patients treated according to these guidances. Therefore, a prospective documentation of these patients within a rare tumor registry is mandatory, which should be comparable to the documentation of patients within prospective therapy optimization trials.

In addition to this disease specific elaborate documentation, other rare diseases should also be documented at least with regard to the most essential clinical data so that consultation of other colleagues confronted with this diagnosis becomes possible. This would allow for easy clinical and scientific networking with low obstacles. As an example, the GPOH Rare Tumor Working Group is currently registering all patients with solid tumors that do not fall into the GPOH prospective therapeutic trials [3]. To date 77 patients have been registered within the last two years. Among these, the malignant melanomas, epithelial tumors of the salivary glands, and gastrointestinal carcinomas constitute the largest subgroups. Based on the work of the working group, physicians can now be provided with clinical advice based on the experience gained with previous rare cancer patients, or a direct contact between different hospitals can be mediated by the working group. In addition, specifically rare and problematic patients can rapidly be discussed in a forum including colleagues from international rare tumor groups. Thus, the rare tumor working group will significantly support communication but also allow for scientific evaluation of comparably larger groups of rare tumors. This will help to allow patients with rare diagnoses access to the clinical and scientific network that has achieved the continuously developing advances in pediatric oncology [3,6,10]. In the future, this network should also include patients with more common diagnoses treated with uncommon strategies e.g. in relapse situations [5,8]. In analogy, it has already been documented that consultation by a reference institution such as a study coordinator may significantly increase

quality of therapy [24]. Thus, the development of good communication networks may also have a significant impact on optimal clinical management by optimizing diagnostic assessment e.g. by excluding unnecessary investigations and therapy, ultimately leading not only to better patient care but also better use of medical economic resources [13].

In summary, in order to provide optimal care to patients with rare diagnoses, it is necessary to share information, both through networking of national and international registries and through scientific publications.

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