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The role of the EORTC pathologist in clinical trials: achievements and perspectives

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Abstract

The role of the pathologist in clinical trials (CT) is focused on three activities: pathology review, translational research, and participation in scientific committees. The primary goal of *pathology review* in CT is the quality control (QC) of the diagnosis and prognostic parameters. Important contributions have been achieved in the context of QC for CT such as new classifications of diseases or identification of new prognostic markers that are now widely used. Telematics implemented in some EORTC groups markedly facilitate the pathology review. The pathologist has a key-role in *translational research* for the identification of new targets in tissue specimens that may eventually lead to new therapeutics and for the understanding of the mechanisms involved in tumour progression. The gap between individualised prognosis and therapeutical possibilities has been considerably reduced by the development of drugs targeted on specific molecular defects. The paradigm of this is the treatment of stromal tumours by STI-571. For proper selection of patients to be treated, information on the expression of the molecules involved is needed, which is well suited for pathologists. The access to tissue resources from patients included in CT is a major goal to enhance translational research, both for brand institution and CT organisations. Active involvement of pathologists in *scientific committees* and interactions with the pharmaceutical industry is mandatory for an optimal design of CT protocols. In addition, translational research is a resource-consuming activity that necessitates an adequate financial flow to create a proper infrastructure at least for sponsored trials to the participating pathology departments and committees.

Keywords: EORTC; Pathology; Research; Quality control; Clinical trials; Oncology

Since the very beginning of the EORTC, the pathologists have been involved as experts in various disease-oriented groups to organise the quality control of the diagnosis and prognostic features [1–5]. This involvement of pathologists in the multidisciplinary context of large clinical trials and the access to follow-up data allowed important contributions that now belong to the 'state-of-the-art' pathology. Their effort to find new prognostic parameters that would allow better classifications of diseases set the scene for the modern translational research. The history of the EORTC illustrates the strength of the interaction between the quality control activity, the discovery of new prognostic markers and the progress in understanding the molecular basis of cancer. The breakthroughs in the 1990s in molecular oncology led the pathologist to be a key player in translational research and made the access to high-quality tissue resources crucial for the community of scientists. Therefore, an EORTC-Pathology Group was established in 1997 with the pathologists acting in the various disease-oriented groups to facilitate pathology review in clinical trials and to stimulate translational research in the EORTC and participating institutions. For these tasks, a common platform has been set up using telematics tools to facilitate the review of slides and a centralised tissue bank.

1. Pathology review and evaluation of predictive features (targeted trials)

The aims of the pathology review in the context of clinical trials are the quality control of the diagnosis and of the prognostic and predictive parameters defined in

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the protocol, and to assure the homogeneity of informations collected from different centres in the same clinical trial. This supposes that guidelines for pathology review are established for each protocol, and a strategy for the control is made explicit, allowing, in particular, the management of discrepancies. The organisation of quality control may have a major impact on the clinical management and the final results. This is especially the case when heterogeneity between the centres is expected [6–9]. The primary goal of pathology review in clinical trials is the quality control of the diagnosis. In a European review of 162 lesions diagnosed initially as melanoma in children before their 17th birthday, the initial diagnosis of melanoma was reviewed by the panel as nevus in 46% of the cases [10]. This argues against the inclusion of children in adjuvant trials for melanoma because of the frequent uncertainty of the diagnosis in this category of patients. The finding that two-thirds of the reclassified lesions contained a predominant spindle-cell population underlined the frequent overdiagnosis of spindle-cell nevi and allowed the educative sessions to be focused on this topic. The issue of doubtful diagnosis has been addressed for the patients with pleural mesothelioma. For these patients who are likely to be included in a EORTC trial, the slide is reviewed and the diagnosis is classified among several categories of certainty [11]. The patients with a lesion classified as doubtful mesothelioma are not included in the trial, but periodical reviews of their lesion are planned. This label of pending diagnosis is crucial in oncology: a diagnosis may be doubtful at the time of the first review, but may be more certain thereafter because of a better morphological recognition of the entity or new diagnostic tools that may appear in the future.

The evaluation of prognostic features represents a major part of the activity of the pathologist in the clinical trials. This has been at the origin of major progress made for the prognostic taxonomy of tumours. The grouping of lesions based on both morphology and follow-up data has contributed to the development of the EORTC classification of cutaneous lymphomas that is used worldwide and the recognition of new entities [12–16]. Several scoring systems developed by the pathologists in the context of the EORTC are now used by most of the pathologists as standards. These include identification of prognostic features for soft-tissue sarcomas [17–22], and reappraisal of the grading systems in breast [23,24] and thyroid [25,26]. Microstaging of melanomas and breast cancers has been drastically changed by the development of the sentinel lymph node (SLN) procedures. The evaluation of the SLN by the pathologist encompasses all aspects of their activities: the quality control of the diagnosis, the identification of prognostic features that may help to identify different subcategories of patients with SLN involvement and translational studies to evaluate the biological significance of the tumour cells in SLN. In the EORTC 18991 trial for stage III melanoma, a side study aims to evaluate the immune response and downregulation of dendritic cell functions in the positive SLN [27].

The classical view of the oncopathology is based on the grouping of patients according to various types of variables, basically morphological, but also histochemical, immunohistochemical or cytogenetic. A novel aspect of this approach is the emergence of the so-called targeted trials, where the crucial task for the pathologist is the semi-quantitative evaluation of a dominant single predictive variable. In most of the targeted trials, the immuno-expression in the tumour of the protein that is directly or indirectly linked to the target is a key factor in the inclusion of the patient. Overexpression or amplification of the human epidermal growth factor-receptor 2 (HER2) is needed to include a patient in most of the adjuvant breast cancer trials with Herceptin®. The standardisation of the immunohistochemical technique and the interpretation of images, as well as the strategy to manage the doubtful cases (cases rated + + for HER2 immuno-expression) were therefore a crucial objective for the overall quality of the trial. An international working group has been set up jointly by the EORTC and the US National Cancer Institute (NCI) to address the quality control and standardisation (QC & S) aspects of immunohistochemical tests for the transatlantic clinical trials. The EORTC 62005 intergroup phase III study with STI571 in metastatic gastro-intestinal stromal tumours (GIST) is an excellent demonstration of the involvement of the pathologist at all levels of the trial: in the initial diagnosis of GIST where the targeted molecular defect (KIT overexpression as revealed by CD117 antibody) is used as a key diagnostic element, the semi-quantitative evaluation of KIT immuno-expression and involvement in the design of translational studies. As for all multicentre targeted trials, the QC & S aspects of the pathological results imply that the pathologists meet to agree on standardisation of the techniques and semi-quantitative evaluation. This approach is based on 25 years' experience of external quality assurance in the context of EORTC trials for the measurement of oestrogen receptors [28–30]. The link between the evaluation of predictive factors for targeted trials and translational research is obvious. As reagents to analyse molecular endpoints are developed, these same reagents should be useful as diagnostic tools, as well as suitable candidates for treatment purposes.

2. Translational research

Translational research may be defined as the scientific evaluation of the application of new technologies and

fundamental insights in the clinic. In the context of the clinical trials in oncology, translational research should be viewed as an ethical and scientific obligation. The EORTC translational programmes include side studies that are described as a chapter of the trial protocols and create an added value to the EORTC trials. Alternatively, the goals are to provide 'proof of principle' for experimental hypotheses in a clinical setting, to study novel techniques in human cells and tissues and to detect and validate new markers for diagnostic, prognostic and therapeutic purposes. The development of molecular medicine targeting molecular defects has integrated 'diagnostic', 'prognostic' and 'predictive' aspects.

In the framework of the EORTC network and with the help of the EORTC Data Center, several multicentre studies have been undertaken by pathologists to develop consensual diagnostic strategies [31]. Other similar studies led to the identification of new prognostic markers [32–35]. However, by nature, the translational studies conducted in the EORTC framework are mainly focused on cancer treatment. It is therefore not unexpected that the main results were obtained in the evaluation of the molecular and cellular effects of new drugs and in the identification of new markers predictive of the therapeutic response. A side study of the EORTC 10854 trial that compared an adjuvant polychemotherapy (FAC) in breast cancers versus no further therapy showed that patients with p53-negative tumours had a significant benefit from perioperative chemotherapy, whereas patients who had p53-positive tumours did not [36]. It is noteworthy that, in this study, analyses for disease-free survival failed to show a prognostic value for p53 demonstrating as other EORTC studies have that prediction for the therapeutic response does not necessarily result in a prognostic value with regard to survival [22].

The elucidation of the mechanisms involved in the immune response to cancer and the characterisation of tumour antigen profiles with tumour progression has become critical with the recent availability of novel immunotherapeutical modalities. In a recent study conducted by the EORTC Melanoma Group, the expression of most of the melanoma antigens was present throughout various stages of tumour progression supporting the rationale for immunotherapy directed against these antigens [37]. Side studies aiming to analyse the molecular effects of treatment protocols provided also new options for therapeutic strategies. For instance, the histopathological and immunohistochemical studies of the effects of tumour necrosis factor (TNF)-alpha and melphalan in isolated limb perfusion demonstrated that hyperpermeability of the tumour vessels induced by TNF-alpha resulting in higher intratumoral concentrations of melphalan or a prolongation of its effect [38,39].

3. Participation of the pathologists in scientific committees and protocol design

In the past years, the development of telematics in pathology appeared as very promising in facilitating the pathology review for the EORTC clinical trials. In this context, an EORTC Pathology Group was set up to represent the EORTC pathologists in the European committees dealing with telepathology. Telepathology has been implemented in several cooperative groups to facilitate the pathology review and specific studies. Protocols for digitisation were developed that are now used in routine practice for some lesions [40]. Another major task for all large clinical trial organisations was to facilitate the access of the community of scientists to tissue with respect to the legal and ethical issues. Therefore, a comprehensive EORTC Tissue Bank Project was designed. This project aimed to organise a centralised repository of fixed material at the EORTC Data Center and a virtual tissue bank of frozen tissue stored in the participating institutions. As the legal issue and especially the heterogeneity between the countries in this aspect appeared as a serious problem with regard to the sharing of resources in an international context, a group of legal experts was set up in the context of the EORTC Tissue Bank Project. This unique platform connecting a repository of tissue specimens, all being histologically validated by experts, the Data Center clinical database and a network of European brand institutions should be an extremely powerful tool for the discovery and validation of new markers. Incorporation of posttranscriptional high-throughput technologies is the next step for the use of the tissue bank.

When looking back at 40 years of involvement of pathologists in the EORTC, it appears that the pathology review was the main area where pathologists were involved. This pathology review needed a permanent interactions of pathologists belonging to the EORTC participating institutions, as well as an exchange of knowledge and sharing of material. This functional network made possible the development of multicentre translational research programmes. It is likely that the development of predictive trials will reinforce the need to establish modality-oriented working groups focused around a marker rather than a disease, and the development of a common platform to facilitate the access to tissue and technologies should help in these studies. Optimal interactions will therefore be needed between tumour- and modality-oriented groups.

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