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EORTC Brain Tumor Group: achievements and perspectives

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Abstract

The EORTC Brain Tumor Group has a long standing history of achievements. The activities of the Brain Tumor Group have recently been re-structured in order to face the challenge of large intergroup/intercontinental trials and be a reference address for early drug development needed for gliomas. Constant adaptation to higher quality assurance criteria and implementation of translational research studies are now priorities for the Brain Tumor Group. Due to such activities, the EORTC Brain Group has become a major player in clinical research. The number of centres and patients joining its trials have greatly increased over the past 2 years. Achievements and strategies are detailed in this article.

Keywords: Brain tumours; Gliomas; EORTC

1. Introduction and history of the EORTC Brain Tumor Group

The EORTC Brain Tumor Group (BTG) has a more than 30-year long history of expertise and activity in carrying out clinical trials in neuro-oncology [1–3]. This expertise has historically been growing side-by-side with the Radiotherapy Group, as both groups have largely contributed to the improvement of the therapeutic strategies for brain tumours. These efforts have also been extended through the cooperation set up with non-EORTC groups, such as North American groups, in order to improve accrual and cross-fertilise experiences. The last 10 years of the Group's activities have best illustrated these efforts. One of the first trials performed at that time brought a final position to the international community that there is no significant difference in terms of survival when low grade glioma patients were exposed to various doses of radiotherapy [4]. Another trial investigated whether patients with low-grade astrocytoma and oligodendrogliomas should be treated with radiation therapy early on or at the time of recurrence/progression [5]. Trials with long-term endpoints have proven that the BTG embodies an outstanding network for conducting trials that require longer follow-up and continuity. Since then, the EORTC BTG has provided a forum to enable large and medically relevant clinical trials even for tumour types that may appear relatively rare. A first trial addressing *dibromodulcitol* (DBD) *plus BCNU* showed efficacy in malignant gliomas [3]. This effect was mainly seen in the subgroup of patients with anaplastic astrocytoma. Now, a second trial on DBD and BCNU in anaplastic astrocytoma only is in its finishing phase of data analysis. Since then, the BTG has continued its initiatives to address major public health issues related to these tumour types. A large phase III trial addressing the role of *adjuvant PCV chemotherapy in combination with radiotherapy* in anaplastic oligodendrogliomas was started in 1996 and is completing accrual in 2001. Similarly, a trial addressing whether it is possible to avoid radiation therapy in patients over 60 years old with primary Central Nervous System (CNS) lymphoma is ongoing.

As of the late 1990s, the EORTC BTG has extended its activities to new drug development and launched two phase II trials looking at the activity of *temozolomide* both as first-line treatment and as second-line after PCV chemotherapy in oligodendroglial tumours. These trials are now closed to patient accrual and the protocol on second-line chemotherapy has been presented at the meeting of the American Society of Clinical Oncologists

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(ASCO) in 2001 [6]. The EORTC BTG group is presently conducting in cooperation with the National Cancer Institute (NCI) of Canada and the Australian TROG, a large phase III trial addressing the role of *temozolomide in a concomitant and adjuvant approach to radiotherapy* in newly diagnosed glioblastoma multiforme. The observed participation to this trial is impressive with almost 300 patients accrued in 1.5 years, confirming the visibility of the EORTC neuro-oncology network.

The BTG is now in the process of developing projects to optimise the treatment of oligodendrogliomas, and of addressing the issue of radiotherapy for newly diagnosed and recurrent meningiomas. Efforts are also dedicated to build a task force on more infrequent types of CNS tumours.

Since 1999, the group is enforced with a separate section of neuro-pathologists. This section aims at coordinating central neuropathology review and setting up consensus guidelines on the grading of low and high-grade gliomas. Besides, the neuropathology section plays a crucial role in setting up together with the clinical investigators translational research, mainly on identifying gene markers for different types of gliomas in relation to responsiveness to radio- and chemotherapy in patients participating in randomised controlled trials.

2. Current network and activities

The activities of the past few years have gradually brought the EORTC BTG to the forefront of clinical research, and presently the network of neuro-oncologists under the EORTC umbrella is more active than ever in preparing and conducting large and relevant studies addressing key questions for the treatment of brain tumours. Therefore, the EORTC BTG is now structuring its activities in four main major and complementary directions: (1) a continuous optimisation of the clinical trial network and investigational centres; (2) implementation of a quality assurance programme; (3) development of major activities for translational research; (4) a focus on early drug development in cooperation with the Early Clinical Studies Group.

2.1. Optimisation of the clinical trials network

From its long-standing expertise in performing clinical trials, the EORTC BTG has become skilled in applying rapidly changing requirements in testing new therapies and is sensitive to new international standards pacing the evolution of clinical research. The BTG also tries to ensure by adaptation of its membership rules that the investigational centres contributing to its activities would comply with the highest standards. In cooperation with the EORTC Data Center, central procedures have been set up to guarantee that participating centres provide the good quality data needed for the visibility of its network. Institutions are closely followed to ensure outstanding standards of submitted facts and figures and the timeliness of these data. As a rule, feasibility of clinical trials is investigated before initiation in order to avoid continuation of long-lasting, and therefore unproductive, clinical studies.

Last, but not least, the EORTC BTG is currently extending its international cooperation with other groups. The story of the collaboration with the NCI Canada illustrates the fruit of international exchange developed for the conduct of a study using temozolomide in a *concomitant and adjuvant approach to radiotherapy* in newly diagnosed glioblastoma multiforme. This study also provides an opportunity to initiate working procedures in cooperation with the Australian TROG.

Indeed, large international efforts will be needed to address in the future the conduct of clinical trials on more infrequent types of primary brain tumours. Part of the mission of such structured networks for establishing worldwide cooperation would facilitate the set-up of randomised clinical trials on tumour types for which Europe by itself cannot be expected to meet realistic requirements for evidence-based medicine. These would include primary cerebral lymphomas, ependymomas, medulloblastomas and other primitive neuro-ectodermal tumours, and the collection of germinomas.

Experts foresee that clinical trials on new modalities to treat these infrequent types of primary brain tumours would probably show substantial improvements in efficacy.

Over the period 1998–2000, the BTG has constituted a network of 48 centres in 12 European countries, which contribute to an average and steady participation of 140 patients on a yearly basis. In 2001, the benefit of the ongoing activities by the group are being observed. As of September 2001, more than 300 patients have been recruited in trials conducted by the BTG.

2.2. Quality assurance programme

The BTG has initiated a large quality assurance programme. The mission of this programme is to set up a close interaction between Group representatives and Data Center staff to ensure in depth control of the overall quality of the BTG. This would cover not only the general compliance to the protocols but would allow early recognition of deficient compliance or protocol violation and alert centres to ensure strict protocol adherence. In some instances, the quality assurance programme is also useful to detect unpractical aspects of protocols, which may lead to protocol amendments. Besides, the mission of the quality assurance

programme supports the EORTC Data Center in optimising the development of proper CRFs to ensure unambiguous recording of relevant scientific data. It upholds a comprehensive approach where a protocol and its contents may be used to raise meaningful queries and procedures for data monitoring. The overall activities and data-timeliness of the participating institutions are examined by the quality assurance committee, which may ultimately take appropriate action.

In a similar approach, during the performance of a trial, any question or deviation relating to a clinical trial protocol is thoroughly discussed with the study coordinator and the Data Center. This has been proven to tighten compliance to protocols. Therefore, it ensures an easier management of studies and a more rapid processing of data, while increasing quality. When more difficult subjects are discussed, the quality assurance subcommittee can be involved.

2.3. Translational research activities

Brain tumours do not all respond similarly to chemotherapy. While astrocytomas are generally chemo-resistant, about two-thirds of oligodendrogliomas respond to combination chemotherapy such as the *PCV (procarbazine, CCNU, vincristine) regimen*. Distinction between these two different subtypes of gliomas by pathological investigation alone is insufficiently reliable because of the absence of strict criteria, and the presence of so-called mixed oligo-astrocytomas, which are less sensitive to chemotherapy than oligodendrogliomas. Proper parameters to distinguish these clinically relevant sub-groups are lacking. However, recent studies indicate that oligodendrogliomas have different chromosomal lesions affecting mainly the 1p and 19q regions. Other chromosomes, such as 7 and 10, may also be involved. The EORTC BTG is now launching an extensive programme of translational research to investigate the significance of molecular cytogenetic abnormalities to predict the response to chemotherapy or other therapeutic modalities and to evaluate the value of histopathological criteria in relation to cytogenetic characteristics. Such activities can only lead to true advances if performed alongside randomised and well-controlled clinical trials ensuring reliable data. By virtue of the neuropathological section and the quality assurance programme, the EORTC BTG has the structure and expertise on the clinical and laboratory side to accomplish such a project. This translational research project is based on large phase III trials, but also takes part in the new drug development initiative and is expected to use the drug screening programme as well. This would allow the rational development of testing new drugs targeted at the appropriate population of neuro-oncological patients. Genetic characterisation of primary brain tumours in individual patients participating in clinical studies would enhance better understanding of aberrant molecular pathways and thus lead to avenues of how to improve therapeutic potential or efficacy.

2.4. Focus on new drug development

The BTG and the Early Clinical Studies Group (ECSG) have been setting up co-operation to create a specific network to screen potentially new active drugs in brain tumours. The formation of this network is possible due to the quality assurance programmes implemented in both of these EORTC groups. This initiative is also supported by the EORTC New Drug Development Program at the Data Center that serves as a platform to promote early drug development and to meet the requirements for the different types of brain tumours. Criteria have been selected both within the network of early drug developers and brain tumour specialists to select a number of high quality centres capable of managing phase I and II trials assuming close co-operation between clinical investigators on site, consisting of medical oncologists and neuro-oncologists supported by trained clinical research teams. So far, this has resulted in the creation of a network which has successfully conducted a series of three phase II trials of good quality and within a short time-frame. The network is dedicated to screening potentially active new drugs. Future studies will be targeted at drugs that show a promising therapeutic rationale and have shown sufficient evidence of activity. Panel reviews of computed tomography (CT) and magnetic resonance (MR) films have been systematically implemented in these trials in order to ensure unequivocal reliability control of recorded response rates.

3. Future directions

The EORTC BTG has taken a leading role on the international scene and has recently published an editorial on the current status of brain tumours [7]. Through its intergroup collaboration, the BTG and his partners constitute a unique network to undertake major clinical trials even in rare tumour types. In particular, the BTG is now initiating a collaborative effort to seek the feasibility of clinical trials in infrequent types of neurological tumours such as ependymomas and various PNETs in adults. In co-operation with the EORTC Data Center, the brain group addresses the necessity to revise clinical trial methodology. Indeed, response rates may not necessarily be an adequate parameter to assess drug activity. In aggressive tumour types, one needs to appreciate and assess the value of stabilisation that might be of clinical significance. This would impact on the methodology of phase II studies from which

decision rules may be set up as to whether or not to continue the development of specific agents or drugs and which would not only depend on the recorded responses. In the same spirit, there is a need to address the criteria used to assess the tumour response. Currently used Mcdonald's criteria are based on bi-dimensionally targeted lesions and the implementation of uni-dimensionality according to the RECIST proposal should be validated [8]. Mcdonald's criteria include the neurological status of the patient and the intake of glucocorticoids. Despite the relevance of such parameters, there is presently no consensus on the best way to assess the neurological status from a clinical point of view. Various scales do exist, but no rigid evaluation of these is available. The use and modification of the dose of glucocorticoids may vary from one centre to another, but are mainly indicated for the patient's well being and his quality of life. All this has a major impact on the assessment of the criteria that have previously been designed and may require re-evaluation in order to come to firm conclusions.

The EORTC BTG, in co-operation with the Data Center, is planning to initiate such a project with other academic partners outside Europe in order to develop international and commonly approved criteria with specific guidelines for proper application.

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