Review

Next generation neuro-oncology

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Abstract Neuro-oncology has evolved as a growing, but still small, highly specialised and multidisciplinary field at the interface of several diagnostic and therapeutic disciplines. The major challenge in the field of primary tumours is to translate the almost unique progress in deciphering the highly complex molecular genetic nature of many primary brain tumours, notably glioblastoma, into advances that allow for clinical benefit for affected patients. Furthermore, metastases to the central nervous system are an increasingly prevalent complication in many systemic cancers. Their diagnosis and management require major expertise, notably with consideration of several new systemic therapy options, such as targeted therapy and immuno-oncology approaches. These new treatments contribute to challenges within the third major domain of neuro-oncology, the diagnosis, treatment and prevention of nervous system toxicity of old and new anti-cancer treatments. All these considerations strongly argue for the development of specialised centres of excellence to improve care for patients with brain tumour across Europe.

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1. Introduction

Neuro-oncology today is a relatively small but expanding and increasingly complex area of oncology involving several diagnostic specialities, e.g. neuropathology, neuroradiology and nuclear medicine, as well as therapeutic disciplines, including neurosurgery, neurology, radiation oncology, general oncology and paediatric neuro-oncology. The updated World Health Organisation (WHO) classification defines an extensive spectrum of different primary brain tumours with age-specific incidences, highly variable outcomes and very different best practice strategies of management [1]. With approximately 20 new cases of primary brain tumours per 100,000 each year [2], all primary brain tumours are essentially rare
2. Diagnosis

Primary brain tumours are diagnosed mainly by histology, but the updated WHO classification of 2016 has integrated some molecular markers into the diagnostic algorithm, e.g. isocitrate dehydrogenase 1 and 2 mutations and deletion of chromosomal arms 1p and 19q for diffuse gliomas of adulthood, the histone H3 K27M mutation to define the new entity of diffuse midline glioma or the RELA fusion to define a subtype of ependymoma [1]. Meanwhile, specialised neuro-oncology centres increasingly make use of more extensive molecular testing, using e.g. their own gene panels for next generation sequencing or commercial platforms. In contrast to gene panel sequencing, transcriptomic or proteomic analyses have not assumed clinical relevance to date. Potentially, the most important new approach involves the assessment of methylation profiling which has been used, e.g. for the study of gliomas [3], ependymomas [4] and meningiomas [5], and has been developed into a self-learning algorithm that may in the future offer high-level, but still remote, molecular differential diagnosis [6]. Whether such high-throughput diagnostic tools will remain a complementary strategy to aid where histomorphology reaches its limits or take over the diagnostic process altogether remains to be seen. Importantly, at present, the debate of molecular genetics versus histomorphology should not be equalled to a machine-versus-man competition because histomorphological data can be subjected to new texture analysis approaches too and even methylation profiles will still need to be interpreted in the context of clinical parameters and histomorphology. In the area of metastatic brain tumours, progress in diagnosis is largely being made within the respective subspecialties of oncology.

Beyond molecular neuropathology, neuroimaging, mostly magnetic resonance imaging (MRI), remains the gold standard for diagnosis and monitoring during treatment and follow-up. The specific challenges associated with central nervous system imaging have been recognised and led to the formation of the Response Assessment in Neuro-Oncology initiative [7] which continues to provide guidance for standardisation of MRI techniques, for image interpretation and for the introduction of novel techniques such as positron emission tomography in various fields of neuro-oncology [8,9]. It has now become a common practice to include detailed guidance on how to perform and interpret neuroimaging data within clinical trials, and the criteria to define response or progression are continuously reevaluated within the cooperative clinical trial groups.

3. Therapy

A major proportion of intracranial tumours can be cured by surgery alone. For intrinsic brain parenchymal tumours, the clinical benefit of obtaining a gross total resection has to be weighed against the risk of permanent neurological deficits for each tumour and each patient. Radiotherapy can be used uniformly to improve local control and to delay progression, but is rarely curative, with notable exceptions such as germinoma. With improved survival for many brain tumour entities, timing and dosing of radiotherapy have become an area of debate, given that more and more patients are at risk of experiencing long-term sequelae from radiotherapy. Alkylating agent chemotherapy still plays an important role in the treatment of the common diffuse gliomas of adulthood, notably tumours with O6-methylguanine DNA methyltransferase promoter methylation, but more targeted therapies are being introduced into the standard treatment of some primary brain tumours, e.g. BRAF inhibitors for BRAF-mutant gliomas, mammalian target of rapamycin (mTOR) inhibitors for subependymal giant cell astrocytomas associated with tuberous sclerosis and sonic hedgehog pathway inhibitors in medulloblastoma. Current treatment of central nervous system metastases is less well standardised, and clinical practice varies widely across centres. Controversial issues concern the role of surgical
resection versus radiosurgery, the dosing and timing of radiooncological interventions, combinations of radiotherapy and systemic treatment, the overall role of local therapy in entities where increasingly active systemic options enter clinical practice and the role, if any, of intrathecal therapy for leptomeningeal metastasis.

4. Research

Neuro-oncology has been among the leading subspecialties within oncology with regards to in-depth high-throughput analyses to address important questions of cancer cell origin, tumour heterogeneity and tumour evolution [10,11]. Yet, these studies have had only minor impact on clinical practice so far, probably for several reasons. Some important brain tumours such as glioblastoma are probably never single-pathway diseases amenable to simple targeted therapy. Moreover, translating molecular genetic observations into effective therapies may remain challenging as long as the specific environment in which brain tumours originate and grow is not considered. Therefore, better animal models reflecting as closely as possible the human disease in a syngeneic (immune) microenvironment would probably be an important step towards more rapid and successful clinical translation, notably for treatments targeting immune system, angiogenesis, migration and invasion.

The rapid progress in molecular oncology has not only resulted in a better understanding of cancerogenesis and the delineation of more effective, targeted treatments at least for some types of cancer. It has also increased profoundly the challenges of conducting clinical trials because owing to the reasonable request for patient enrichment and homogenisation, accrual becomes more and more difficult, and national clinical trials are unlikely to be completed within reasonable timeframes. Moreover, the complex regulatory structures in Europe have profoundly contributed to a scenario where the most interesting new therapeutic concepts are explored outside, rather than with European participation. In this overall hostile clinical research environment, it is noteworthy how using the network of the European Organization for Research of Cancer (EORTC) Brain Tumor Group, Europe has nevertheless been able to contribute significantly to the definition of worldwide standards of care for newly diagnosed glioblastoma [12], anaplastic oligoden-drogioma [13] and anaplastic glioma without 1p/19q codeletion [14]. Finally, another EORTC trial on bevacizumab in recurrent glioblastoma interpreted as negative in Europe [15] has been instrumental in assuring access of US patients with glioblastoma to this drug that was never approved in Europe.

Given the huge diversity of mutations in human cancers and the cost associated with testing, one important step to facilitate clinical trials to be conducted in the future will be the set-up of molecular genetic screening platforms such as the Screening cancer Patients for Efficient Clinical Trial Access initiative of the EORTC.

5. Education and training

Education and training in neuro-oncology receive increasing attention. The complexity of diagnostic processes at the level of molecular neuropathology and neuroimaging and therapeutic clinical decision-making (Fig. 1) necessitate specialisation, but it remains open how much specialisation is needed and who should take care of patients with tumours of the central nervous system in which phase of the disease. Education and training in neuro-oncology needs to be comprehensive, that is, it must not be focused on tumour-specific therapeutic interventions alone but must integrate aspects of psycho-oncology, palliative care and patients’ and caregivers’ perspective [16]. One reasonable future strategy would be a European neuro-oncology curriculum that should be open to trainees from all disciplines involved in the daily care of patients with brain tumour.

6. Coordination of patient care

The present structure of patient care in neuro-oncology varies greatly by region of the world, by country and even within countries. Neurosurgeons are primarily responsible for most of the patient journey in many Asian countries. In North America and (Western) Europe, the efforts to implement multidisciplinary patient care, in some countries even within specialised cancer hospitals, are well advanced. Despite strong beliefs in its value, there is overall little data from prospective or even randomised studies to support a major impact of multidisciplinary care on outcome in neuro-oncology. Yet, we have observed an unexpected increase in median survival for glioblastoma on a population level in the Canton of Zurich after the introduction of multidisciplinary structures including a dedicated tumour board that was not otherwise explained and that was sustained thereafter [17]. While quality is probably best maintained in a team of specialists acting based on institutional or (inter)national standard operating procedures, in particular, patients with brain tumours and their caregivers value continuity of the team of healthcare professionals along the patient journey.

7. Vision

Patients with brain tumour should be diagnosed and treated at specialised centres of excellence that have access to state-of-the-art neuropathology and neuroimaging diagnostic procedures. Guidelines should not only provide guidance for best practice of
management but also include recommendations for diagnostic procedures. To improve patient care across Europe, preparation and updates of guidelines should evolve on an international, rather than national, level, reflecting the diversity of disciplines involved in care of patients with brain tumour and the diversity of nations and cultures in Europe. This will be best achieved under the umbrella of a multidisciplinary society such as the European Association of Neuro-Oncology, potentially in cooperation with other oncology societies. European regulations endanger the clinical trial landscape and thus progress for cancer patients, specifically in areas such as neuro-oncology where most entities are in fact orphan diseases. International collaboration of European expert centres in networks such as the EORTC is therefore the best strategy to improve outcome for our patients [18].

Conflict of interest statement

The author has received research grants from Abbvie, Acceleron, Actelion, Bayer, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, OGD2, Piqur, Roche and Tragara and honoraria for lectures or advisory board participation or consultation from Abbvie, BMS, Celgene, Celldex, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Orbus, Pfizer, Progenics, Roche, Teva and Tocagen.

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