EDUCATIONAL REVIEW

Embryonic tumours of the central nervous system

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INTRODUCTION

There are more and more cerebral tumours being diagnosed in the population under 18 years of age i.e., the paediatric age-group (although in some centres in our country the paediatric population cut-off age is 14 years). Firstly, new technologies, especially neuro-imaging, help early detection of cases and, secondly, advances in treatment of childhood cancer, particularly those used in multi-centred and multinational protocols, have contributed to an increase in the survival of the affected children; albeit not in all cases, since not all the histopathology types are the same.

Embryonic tumours represent around 25% of all brain tumours and constitute the group of most frequent solid tumours observed in children under 15 years of age. These embryonic tumours derive from the multi-potential progenitor cells of the central nervous system (CNS) with similar morphological and biological characteristics. They are considered tumours of high grade malignancy and are classified by the World Health Organisation (WHO) as having Grade 4 malignancy.

Among the embryonic tumours of this WHO classification, is the group of primitive peripheral neuro-ectodermal tumours (PNET) which is the most frequent and can be supratentorial and infratentorial, the pinealoblastomas and ependymoblastomas. When the tumour originates in the cerebellum, which happens in 85% of the cases, they are termed medulloblastomas (MB). Other primitive embryonic tumours are very rare but all belong to the grade 4 malignancy; rhabdoid tumour (RT) and atypical teratoid tumour (ATT) of different histogenesis and also medulloblastoma (MB). The genetic expression of the tumour and their high frequency and their high risk, there are no specific protocols for their treatment.

Currently, we are able to classify the tumours on the genetic-biological risk characteristics and we need to plan the treatment by taking into account the predisposing and genetic factors that have contributed to the development of the tumour in specific risk families. For example, molecular markers expressed by the tumour can indicate that their response to the conventional treatments may not be what had been expected. The genetic expression of the tumour and the design of microarrays are not accessible to all the centres nor to all countries involved in the treatment of childhood brain tumours and it is for this reason that well-designed, multi-centred studies have the responsibility of providing tumour samples that can be analysed in reference centres. With more research facilities and transport resources the results can be generated rapidly so that the optimum treatment strategies can be planned.

In this article we review the current characteristics of the embryonic brain tumours which make up the most numerous group; the PNET/MB.

EMBRYONIC TUMOURS OF THE BRAIN

These tumours are defined according to the pathogenesis factors. The mechanism by which proliferation of the abnormal cells are produced are considered to be of genetic origin, or are the consequence of a molecular aberration that favours the inactivation of the tumour suppressor genes. Nerve growth factors (NGF) and their protein receptors Trk A, B and C are expressed by the tumour and indicate their biological behaviour, differentiation and prognosis. Environmental factors play a slight role in the development of these childhood tumours and there are still controversies regarding the histopathological classification. More studies are needed for a more definitive molecular classification.

Epidemiologic data on the incidence of childhood brain tumours in Spain

According to recent publications summarising the data from the 9 European registries, the incidence is 14 cases/100,000 children in Europe.

In 1980, the National Registry of Childhood Tumours (Registro Nacional de Tumores Infantiles; RNTI) was founded in Spain under the supervision of a scientific committee of the Spanish Society of Paediatric Oncology (Sociedad Española de Oncología Pediátrica; SEOP). Since then, all paediatric tumours diagnosed...
in the public hospitals of the National Health Service, as well as in those hospitals that are privately funded, have been registered and is estimated to cover about 95% of cases. This has provided us with data on incidence and survival distributed by age, gender, tumour types, site, together with the follow-up of survival at 5 years from diagnosis of various cohorts (figs. 1 and 2).

Tumours of the CNS constitute the second group of the childhood neoplasias (17.9%) following the acute leukaemias (23.5%) and are the group of solid tumours most-frequently encountered in the paediatric population. Their incidence in our population is comparable to other international statistics (fig. 1).

MEDULLOBLASTOMA

MB is the most frequent malignant tumour of the brain in the paediatric population. Its annual incidence is estimated at 0.5/100,000 children below the age of 15 years. This represents 20% of the total brain tumours and 4% of tumours of the posterior fossa. The incidence peak is between 5-7 years of age, and predominating in males. The classical MB originates in the cerebellar vermis and the desmoplastic in the cerebellar hemispheres; the desmoplastic are more typical in adolescents and young adults.

The MB or cerebellar PNET is located in the vermis in 80% of the cases and the remaining 20% in the cerebellar hemispheres. The tumour is disseminated with higher frequency in the fourth ventricle and through the Silvio aqueduct, it can reach the cerebral trunk across the floor of the fourth ventricle. Dissemination into the cerebrospinal fluid and leptomeninges is frequent and can also reach the subarachnoid space, the supratentorial area, and the spinal canal. Distant metastases to the brain and spine are less frequent. Much rarer are the extra-neural metastases, particularly in bone and bone marrow, and implants in the abdominal cavity from the ventriculo-peritoneal shunts of the cerebrospinal fluid with tumour component. Histologically, the MB belongs to the group of round blue small cells with hyperchromatic nucleus and scant cytoplasm. It forms neuroblastic rosettes, that along with the tumour nodules, express different grades of synaptophysin, according to the histology subtype. It is subdivided into classical MB, desmoplastic MB, MB with extensive nodular involvement and greater neuronal differentiation, and large cell MB that has an unfavourable prognosis with a high grade of anaplasia, and which represents around 4% of cases. The desmoplastic, hyperdiploid tumours with a high degree of apoptosis and with lower index of cellular proliferation (evaluated by the grade of expression of the immunohistochemical marker Ki-67/MIB-1) and those that express Trk C are associated with better survival.
Recently, genetic profile studies with microarrays have demonstrated that the medulloblastoma consists of an entity clearly distinguished, at the molecular level, from the other embryonic tumours such as PNET and other brain tumours such as the RT/ATT or malignant gliomas. Among the genes that correlate with the MB are the transcription factors ZIC and NSCL1 (or in their activated transcriptional state) which are specific for the cells of the granular cerebellum. Further, these same authors demonstrated that the MB could be derived from the cells of the granular cerebellum via the activation of the Sonic-Hedegoc route. This adds to the hypothesis that the deregulation of the Sonic-Hedegoc activation route could play an important role in the pathogenesis of MB.

Diagnosis via clinical signs and symptoms at presentation

Headaches, morning vomiting and lethargy are produced by the increase in the intracranial pressure (ICP) due to the obstructive hydrocephaly caused by the tumour mass, that may not be marked and which can contribute to the delayed diagnosis of greater than 4 weeks in 50% of cases. Sometimes the child presents changes in character and bad school performance but these do not cause diagnostic suspicion until more typical signs and symptoms of the tumour appear. Ataxia or instability in walking and strabismus as a result of the involvement of the VI cranial nerve are frequent, as well as dysarthria, dysphonia and dysphagia. In infants there is a delay in development, irritability and macrocephaly with “sundown eyes” indicating the presence of ICP.

Diagnosis by imaging

Computerised tomography (CT) and magnetic resonance imaging (MRI) have contributed over the last decades to a revolution in the diagnosis of brain tumours. The techniques have facilitated early diagnosis and the detection of relapse and tumour progression prior to the appearance of the clinical signs and symptoms. Also, they have enabled the detection of residual tumour post-surgery, allowed for stratification of treatments according to risk, helped to measure the response to treatment, and helped to detect secondary effects due to brain damage (atrophy, vascular alterations, leuka-encephalopathies...). Pre-operative complete craniospinal MRI, with and without contrast, is the method of choice for the initial diagnosis of the tumour. Post-operative MRI within 24-72 hours seek evidence of residual tumour, since assessments conducted later than this time are difficult to interpret. This is the best assessment of the isolated MB. This needs to be a complete craniospinal study since the upper cervical area and the thecal sac are the two zones of metastatic invasion whose investigation is, sometimes, missed.

In the 21st Century, we need to mention the group of techniques collectively known as Functional Imaging. Positron emission tomography (PET) using radionuclides (the most frequently used being 18F-fluorodeoxyglucose because the MB has a high glucose metabolism) and 14C-methionine, that identify the active tumour and can measure response to therapy, discriminate in cases in which MB is doubtful, identify presence of tumour and, more recently, measure drug uptake by the brain. Advanced MR (AMR), which includes spectroscopic MR (SMR), studies of diffusion and microvascularity can identify the macroscopic alterations of the brain structure produced by the tumour as well as its metabolic status and vascular irrigation. These techniques are still only available in a few centres and, although they can assess potential malignancy of the tumour and can predict subsequent abnormalities that correlate directly with future neurological damage of the child, the results are difficult to interpret at the moment in a brain such as that of an infant in the course of maturation and development.

Additional complementary explorations

The fundoscopical examination and the visual acuity indicate not only the initial presence of the ICP by the presence of the papilloedema, but the assessments need to be conducted prospectively post-surgery and post-radiotherapy to monitor for response to treatment as well as potential sequelae. Audiometry needs to be conducted periodically or auditory-evoked potentials since radiotherapy as well as platinum derivatives can provoke neurogenic deafness following from accumulative toxicity. Cranial radiotherapy can provoke endocrine disturbances particularly in growth hormone, thyroid hormones and gonadotrophins resulting in alterations in puberty and growth. For this the basal status of the child needs to be evaluated together with the clinical stage of development because these deficiencies usually appear two years after radiotherapy is given. Neuro-cognitive disturbances are more difficult to evaluate in younger children. However, several tests exist, and scales of evaluation such as the Health Utility Index and the Ped Qol are available in the current protocols.

Staging system of Chang11 in medulloblastoma

1) M0: absence of metastases.
2) M1: cytology positive for blasts in cerebrospinal fluid.
5) M2: meningeal metastases dissemination in the posterior fossa or supratentorial area.
4) M5: metastases in the spinal column.
5) M4: metastases outside of the CNS (extra-neural).

The classification of these tumours based on their extent and initial dissemination according to clinical criteria has been improved by the Chang system and which, together with the classification of Zelzter14, continues to form part of the design of all current protocols of treatment. Obtaining cerebrospinal fluid needs to be via lumbar puncture, and preferably within 15 days of the surgery so as to determine M0 stage.

Medulloblastoma risk groups
1) Standard risk: children greater than 3 years of age with residual tumour of less than 1.5 cm² post-surgery and with no evidence of metastases (M0).
2) High risk: any residual tumour greater than 1.5 cm² post-surgery, or presence of metastases (M1-M4).

In the current survival analysis, the initial extent of tumour into the brain stem has lost prognostic significance, but the M0 stage and children younger than 3 years of age remain high risk cases.

Molecular genetics in the diagnosis of the primitive neuro-ectodermic tumours/medulloblastoma group of tumours

Nowadays it is possible to study the pattern of expression of many of the genes in one group using the microarray system for DNA. These patterns of expression of many of the genes in one group using the microarray system are known as signature genes and are useful for identifying patients that are likely to respond to treatment and have a better outcome. These genes may be used to design new therapeutic strategies and to identify patients who are likely to respond to treatment.

New data are continually appearing that, to-date, have not been shown to correlate with clinical characteristics. Recently, Gajjar et al.15 concluded that multi-centred studies with frozen samples are possible and, in 97 cases the results indicated that the tumours of younger children, the cases in which complete resection was not achieved, the presence of metastases at diagnosis and the aneuploid tumours with high index of cellular proliferation and anaplastic cell morphology subtype, are those tumours that present the greater incidence of molecular alterations and unfavourable prognosis. The studies of profiles of gene expression using microarrays, as well, can contribute to the diagnostic discrimination, independently of other criteria. Genetic characteristics of cerebellum differentiation, and genes coding for the extra-cellular matrix correlate with a better survival. On the other hand, the genes associated with proliferation and cellular metabolism are markers of therapeutic failure. There is a need to conduct these sophisticated analyses within collaborative studies with large numbers of patients so as to confirm these promising results. In the near future, studies of this type could contribute to define, and to further amplify, the group of patients who, using current clinical criteria, are considered as having high risk and, as such, contribute to a more aggressive therapeutic strategy.

Treatment

The affected children should be diagnosed, treated and evaluated periodically over the long-term by multi-disciplinary teams in centres qualified to obtain optimum results. There has been a great advance in the diagnosis of these tumours thanks to the neuroimaging technology and, more recently, with the methodology of image fusion of CT and MRI with PET. However, although detection has improved and diagnosis can be made earlier due to the new technologies, we can not, as yet, talk of great advances in treatment. The stratification of treatment based on the clinical characteristics, histology type, immunohistochemistry, and gene and protein expression, which are already in progress in some centres, could be the key to the future.

The three classical arms of treatment of MB surgery, radiotherapy and chemotherapy will be commented upon, separately.

SURGERY

Complete resection of the tumour is the major factor that impacts on survival, irrespective of the adjuvant treatments whether radiotherapy, chemotherapy and, even high doses with haematopoietic stem cell transplant. The mortality due to these tumours, especially
in the cases in which the surgery is incomplete, continues to be high; of the order of 50%.

RADIOTHERAPY

MB are, in the majority, radio-sensitive. Due to its tendency to disseminate along the neuroaxis, the consensus recommendations are the treatment with craniospinal radiotherapy, including those cases in which the tumour is localized at diagnosis and completely resected. It is necessary to check, using contrast resonance performed within 72 hours post-surgery, that the resection is complete and with an absence of residual tumour. The appropriate planning for radiotherapy needs to include the whole neuroaxis and the meninges. This is very important because previous studies have shown that some deviations have an important impact on the survival due to relapse in non-treated zones.

The standard dose of radiotherapy is 55-56 Gy craniospinal, with a “boost” in the posterior fossa up to a complete dose of 54-55 Gy, in fractions of 1.8 Gy. In the patients with better risk status, the survival at 5 years has reached 50%. The reduction of the radiotherapy dose, in European as well as American studies, impacts negatively on survival if not combined with appropriate chemotherapy, as has been demonstrated in the CCG-9892 with survival at 5 years of 79% with a 23.4 Gy craniospinal dose and 55 Gy to the tumour.

In the decade of the 90s, studies on the sequelae of craniospinal radiotherapy, especially with regard to neuro-cognitive and endocrine capacity, were published and indicated that poorer survival occurred in children whose tumour resection was incomplete. This caused a redesigning of protocols with reduced doses of radiotherapy with the objective of reducing the sequelae.

Chemotherapy as adjuvant to radiotherapy, induced greater survival rates in the decade of the 90s and, currently, forms part of the most-used protocols. In Europe, the protocol HIT SIOP-PNET 4, is a randomised study of standard-risk patients using two treatment arms based on the radiotherapy schedule. In the standard arm, conventional radiotherapy was used and, in the other treatment arm, a hyper-fractionated dose was administered in 2 doses/day. The chemotherapy consisted of weekly dose of vincristine during the radiotherapy, and a subsequent maintenance dose that included 8 cycles of vincristine, cisplatin and CCNU.

Current radiotherapy comprises different techniques: hyper-fractionation, accelerated radiotherapy and proton radiotherapy. The radiotherapy confined to the tumour bed, avoiding radiating all of the posterior fossa, has the objective of causing the least possible damage to tissue adjacent to the tumour and to avoid subse-quent toxicity in the young. The new protocol of the CCG, in a randomised trial, reduced the RT to the neuroaxis to 18 Gy in the cases of low risk. These combination schemes with regimens of chemotherapy could reduce the undesirable long-term morbidity in these children. However, we will not have satisfactory results without randomised, multi-centred, well-designed studies with greater numbers of patients included, than had been the case in studies conducted to date.

CHEMOTHERAPY

Initially, chemotherapy was used in the treatment of the medulloblastoma to improve the prognosis achieved with the surgery and craniospinal radiotherapy, using drugs capable of crossing the blood-brain barrier. The efficacy was tested in cases with sub-total surgery and residual macroscopic tumour, and in cases with disseminated metastases.

In the decade of the 80s, parallel studies commenced in Europe (SIOP) and the USA (POG/CCG). In the randomised SIOP protocol, isolated radiotherapy was used versus radiotherapy followed by vincristine/lomustine. In the POG study, radiotherapy versus radiotherapy/MOPP indicated a slight initial advantage for the chemotherapy arm, 56% and 59% but which was not maintained for more than 5 years of survival. In the SIOP-2 trial, the “sandwich” modality of chemotherapy pre-radiotherapy (procarbazine, vincristine, methotrexate 2 g/m²) was introduced but without benefit in survival (59% at 5 years). The regimen of radiotherapy versus carboplatin, cyclophosphamide, etoposide, vincristine before the radiotherapy demonstrated the advantage of combining the chemotherapy by improving the survival to 73% in the PNET-3 study.

With the regimen of pre-operative chemotherapy of “8 drugs in one day” of the CCG-921 trial, the event-free survival at 5 years was 43% compared to 65% of the CCG-942 trial which administered chemotherapy subsequent to the radiotherapy. Other studies, not only European (HIT 91) but also the American (POG-9031) had not been able to demonstrate differences between the administration of the chemotherapy before or after the radiotherapy. It is of note that delaying the radiotherapy more than 50 days in the patients with standard risk impacted negatively on the survival if regimens of intensive chemotherapy had not been employed.

As a result of these findings, there was intent to reduce the doses of radiotherapy from 50 Gy to 25.4 Gy in the CCG-9892 trial combining 8 courses of vincristine, cisplatin and lomustine at 6 weeks of conclusion of the radiotherapy with weekly concomitant vincristine. For the 65 children of better risk status, the schedule obtained an event-free survival of 78% at 5 years, levels which have not been bettered to date.

This strategy had sequelae that included im-
The long-term survival of children with MB has not conformed radiotherapy to the posterior fossa. The efficacy and toxicity that can be achieved with the intra-ventricular and intra-thecal chemotherapy using malofnmamide, methotrexate, etoposide or topotecan in these patients requires further analysis, although the data of the German protocols look promising[26,27,29,31]. For MB in those children under 5 years of age, the POG trial applied alternating cycles of vincristine/cyclophosphamide with cisplatin/vincristine over 2 years for those under 2 years of age and over 1 year for those above 2 years of age followed by radiotherapy. The results showed overall survival and event-free survival of 59% (60% in those with complete resection) and 31% at 5 years[32,33]. Other groups using the 8 drugs/day regimen obtained poorer results. Regimens using greater dose intensity of systemic chemotherapy with intra-ventricular methotrexate obtained good results with a survival of 77% if there was no residual tumour. But these outcomes were lowered to 27% if disseminated disease was present. Although omitting radiotherapy is an option to decrease morbidity, toxicity to the white matter that can be produced by the intraventricular administration of methotrexate, remains unresolved[34]. In the majority of current studies in progress, high-dose chemotherapy is used followed by haematopoietic stem cell transplant and radiotherapy reduced to 18 Gy, or conformed radiotherapy to the posterior fossa.

**SURVIVAL**

The long-term survival of children with MB has not advanced much over the past decades, up to 50%-60% at 10 years from the time of diagnosis. The major cause of mortality for this group of tumours is relapse, or tumour progression, such that the overall survival and the event-free survival are almost equivalent at 5 years of follow-up (fig. 5). Currently with the improved technologies of neurosurgery and radiotherapy, survival can reach levels > 60% at 5 years (fig. 5). If we add chemotherapy, in the children whose tumours are localised and completely resected, the survival is even more favourable and reaches levels of 80%-82% [27,28]. This improvement in the survival comes at a high price due to the serious sequelae resulting from the tumour and the treatment used. The derangements are principally neurocognitive, endocrine and neuropsychological, and are much more severe in the younger age-groups of children and, especially, if craniospinal radiotherapy is administered[15]. Current treatment protocols in European and American trials are designed with the objective of increasing survival and reducing the sequelae. To achieve this, the biology of the tumour, its clinical profile, metabolic and molecular differences need to be taken into account in stratifying the cases in groups of risk. However, there is a dearth of such studies with long-term survival data. For example, in this typical tumour there have been relapses occurring at 10 years post-diagnosis[15,16].

**Supratentorial tumours primitive neuro-ectodermal tumours**

This group constitutes 2% of the brain tumours, and 60% of them occur in children below 5 years of age. Localisation is, usually, in the frontal and temporal lobes of the cerebral hemispheres. Localisation in the pineal gland (pinealoblastoma) has the best prognosis. They are large tumours of aggressive behaviour that present with leptomeningeal or spinal dissemination in 40% of the cases, and with poorer prognosis in the younger age groups of patients. In 22 patients recorded by Reddy et al[15], the localisation of the tu-
The role of high-dose chemotherapy with stem cell support in children with high-risk medulloblastoma/primitive neuro-ectodermal tumours

Although in the past few years there has been an increase in the disease-free survival (60%-70%) in the children affected with MB of standard risk, for the patients diagnosed as having advanced disease such as the other malignant brain tumours (especially in the absence of complete tumour resection), the prognosis continues to be poor despite the surgery, radiotherapy or conventional chemotherapy. For these patients who present recurrence of the disease despite the initial therapy, the prognosis is even more ill-fated than usual.

Hence, in an intent to improve the prognosis of the patients affected with brain tumours with poor prognosis, the use of high-dose chemotherapy together with autologous haematopoietic stem cell rescue, has constituted a line of investigation of high interest. The data available to-date highlights promising results with this strategy in patients diagnosed as having MB, PNET supratentorial or high-grade astrocytoma.

Specifically, in MB and PNET, this strategy could prolong survival of those patients with controlled tumours, with evident chemosensitivity, and in younger children. Nevertheless, there appears to be no evidence of efficacy in the management of the recurrent tumours.

For objective and reliable evaluation of survival benefits and the risks of treatment, the most important studies are meta-analyses, multivariate analyses of large series of patients, and the randomised trials. Hence, the design and conduct of molecular analyses of brain tumours of the patients included in the prospective randomised studies with high-dose chemotherapy will become the ideal line of investigation in this field in the coming decades.

Data generated in our country is, as yet, slight. In a study published recently, and which collected the experience of the Hospital Niño Jesús de Madrid, there were 19 of 55 children with CNS tumours who were undergoing procedures for the treatment of MB/PNET. In 14 cases (9 primary, 5 relapses) the tumour site was the posterior fossa, and in the 5 remaining, it was supratentorial. The event-free survival was good with reported levels of 57% for the primary tumours and 71% for the group of children under 4 years of age. The median follow-up for the overall group was 18 months (range 5-65 months). However, we need to highlight that not only the prior treatment schedules as well as the pre-transplant conditioning were not uniform and that the period of follow-up in the study was short.

The American experience with the Head Start II scheme for this group of very high-risk disseminated MB, indicated an 81% response with an intensification of the induction chemotherapy with high-dose methotrexate in addition to the Head Start I scheme (vincristine, cisplatin, etoposide, cyclophosphamide). The toxicity continued being high, especially, haematological, infectious and gastrointestinal side-effects.

The event-free survival was 49% at 5 years. Although it is accepted that there is a need to avoid, or postpone craniospinal radiotherapy in younger children, there is also a need to investigate to determine the best scheme of conditioning using autologous transplant of marrow stem cells.

Future directions

The stratification of the tumours by risk groups in relation to their biological conduct using the expression of molecular markers, would complement the design of treatment protocols in the future. Other aspects that require attention are: the optimisation of the radiotherapy confined to the tumour bed in children with standard-risk tumours; the use of protons or techniques of hyper-fractionation which, with the addition of chemotherapy, has the objective of reducing the morbidity without losing efficacy.

Recent studies with postoperative chemotherapy alone are also promising. Topoisomerase I inhibitors and in-hibitors of tyrosine kinase form a part of the new protocol designs. Finally, of considerable promise is the use of pharmaceutical products directed towards target molecules. This would be an effective substitute for conventional treatments which do not discriminate between healthy cells and those of the tumour, and which leads to undesirable adverse effects in the children.

References


