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Paediatric Update

Retinoblastoma

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INTRODUCTION

RETINOBLASTOMA (Rb) IS the most common malignant intra-ocular tumour in childhood, with an incidence of 1/15 000–20 000 births. Two-thirds of these tumours are unilateral, mostly non hereditary, with a median age of 2 years at diagnosis. One third are hereditary and bilateral, with a median age of 1 year at diagnosis [1].

This cancer, although curable for many years, still poses major problems in terms of:

(1) The prognosis related to the tumour itself: Rb is rarely a life-threatening disease in economically advanced countries, but remains a major concern in developing countries because of the frequency of orbital and metastatic extension.
(2) The prognosis related to the hereditary type: these Rb patients also have a pleiotropic genetic predisposition to other types of tumours—rarely, an ectopic intracranial Rb, arising in cells of photoreceptor origin in the pineal gland and suprasellar area (trilateral retinoblastoma) and, more frequently, secondary tumours, usually sarcomas and mostly bone sarcomas.
(3) The visual prognosis: there are major difficulties planning therapy which will allow eye preservation as well as a useful central or peripheral vision.
(4) The limitations of the current available genetic information given to the parents of affected children and to cured adult patients treated for Rb during childhood.

If an early diagnosis, essential for an effective treatment, is still based upon full attention paid by the paediatrician and/or the ophtalmologist to the description by the parents of an unusual appearance of the eye, some traditional concepts concerning this disease have now become more sophisticated. We shall focus on current staging procedures, new therapeutic strategies leading to revision of the indications for so-called 'reference' treatment and persistent genetic uncertainties making counselling of affected families often difficult or limited.

STAGING PROCEDURES

The best staging procedure in intra-ocular disease is ophtalmoscopic examination under general anaesthesia. A qualified ophtalmologist is needed to determine the size and the location of the tumour(s) and its closeness to the most important structures of the fundus: the macula and the head of the optic nerve. The tumour's dimensions and extension should be clearly defined at diagnosis by sketches and clinical photographs, which will be the basis of a close and long-term follow-up. The classification of Reese and Ellsworth is still useful but may be insufficient. It was designed in 1969 [2] in order to predict the likelihood of tumour control and preservation of vision with a conservative approach using external beam radiation therapy, but it does not take into account the difficulties of the treatment of posterior pole tumours when using new conservative techniques. The examination under general anaesthesia must also be completed by an ultrasonographic examination of the eye, which is useful for measuring the size of the tumour(s) and evaluating tumour response when a conservative treatment is indicated.

Computerised tomography (CT) scan or magnetic resonance imaging (MRI) of the orbit and brain is mandatory for almost all patients, but can be avoided in young children with small tumours which are not close to the optic disc. In these children, often early diagnosed because of a familial disease, the only staging procedure may be the examination of the eye and ultrasonography.

Other staging procedures have selected limited indications [3–7]. CSF cytology and bone marrow cytology are required when enucleation has been necessary and has shown histopathological risk factors. Brain and spinal axis MRI and bone scan are mandatory in case of orbital involvement, pre-auricular and/or submandibular lymph nodes, and/or distant metastatic disease.

Finally, there is no standard commonly agreed staging system for Rb which could, as in other paediatric malignancies, be predictive of survival, but an international Rb party is currently attempting to come to an agreement on the basis of the well-established prognostic factors in this disease.

NEW THERAPEUTIC STRATEGIES

Adjuvant treatments after enucleation

Rb is most often unilateral and diagnosis is usually established after the tumour has already spread intra-ocularly, with a combination of endophytic growth from the inner surface of the retina towards the vitreous and exophytic growth from the outer layers of the retina causing retinal detachment. Thus,

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the possibility of conservative treatment is, unfortunately, unrealistic for many cases and enucleation must be performed by a qualified surgeon following precise guidelines:

(1) Removal of a long section of the intra-orbital optic nerve and preservation of all of the eyeball.
(2) Insertion of an implant which improves the quality of the subsequent prosthesis.
(3) Collection of tumour samples, in collaboration with the pathologist, for genetic studies.

Histopathological examination must be performed by an experienced pathologist, examining the site of tumour spread in the retina, vitreous, choroid, sclera, optic nerve (by studying the relationship with the cribriform plate and meninges) and the anterior chamber of the eye. Rb cells resemble primitive photoreceptor cells and possess photoreceptor cell-associated proteins such as rhodopsin and S antigen. The degree of differentiation is also defined according to the abundance of 'rosette' cell groups, classically observed in neuroectodermal tumours. Histopathological investigations can define prognostic criteria indicating the need for adjuvant treatment after enucleation [8–10]. Some risk factors have been clearly established (for example, dysruption of the sclera with microscopic invasion of the orbital soft tissues, invasion of the optic nerve resection margin). Such patients require not only irradiation of the orbital cavity but also adjuvant chemotherapy. The need for complementary treatments for patients with other types of extraretinal invasion (selective choroidal and optic nerve retrolaminar invasion) is much more controversial [11], although in our experience these criteria justify the use of postoperative chemotherapy [8]. Finally, there is a consensus that chemotherapy is necessary when choroidal invasion is associated with optic nerve invasion [9, 12]. Ultimately, new molecular prognostic criteria could prove useful in the future to indicate adjuvant treatment [13].

Antimitotic drugs which are efficient against Rb are those which are active in other embryonic neuroectodermal tumours, including alkylating agents (cyclophosphamide), platinum compounds (carboplatin), vincristine, anthracyclines (doxorubicin) and epipodophyllotoxins (etoposide) [14–16].

Treatment of orbital and metastatic forms

The objective of adjuvant treatment after enucleation is to prevent the development of orbital recurrence or metastases (metastases occur usually in bone, bone marrow and central nervous system). The prognosis of these forms, considered until recently to be almost always fatal, has been improved by the use of new chemotherapy modalities and, maybe, high-dose chemotherapy with haematopoietic stem cell rescue [17, 18]. Today, there is no standard treatment for extra-ocular retinoblastoma. The use of an intensive chemotherapy regimen allows the cure of some patients with orbital disease [17], lymph node metastases [16] and even distant metastatic disease [18]. The prognosis of patients with CNS metastases is still very poor. Embryonic tumours in the pineal gland, which is structurally and functionally a photoreceptor organ, are known as pinealoblastomas or 'trilateral retinoblastomas'. They arise from optic vesicle cells [19, 20], can occur in the context of hereditary retinoblastomas and their clinical and radiological symptoms may precede the discovery of the eye tumour; these have a particularly poor prognosis.

Conservative ocular treatments

Conservative treatments must be performed in specialised centres, with close cooperation between the ophtalmologist, the radiotherapist and the paediatric oncologist. Such treatments are usually indicated in bilateral forms of Rb, although they can sometimes be used in selected unilateral diseases. Such situations include:

(1) Diagnosis following screening in children with a family history of retinoblastoma: the tumour is thus often diagnosed at an early intra-ocular stage and a high risk of developing a metachronous lesion of the other eye is to be taken into account.
(2) Young age at diagnosis: even if there is no family history, young age suggests an hereditary form and, therefore, a risk of subsequent development of a tumour of the contralateral eye.
(3) The tumour not affecting the most important structures (macula, optic disc): the chance of preserving vision in the affected eye may be possible.

The gold standard conservative treatment is still, until recently, external beam radiotherapy which achieves tumour control in the great majority of cases [1]. However, its use should be increasingly limited in view of its late adverse effects (Table 1).

Classical conservative ophthalmological treatments are highly effective, but can generally only be used when the tumour is located anteriorly to the equator of the eye. These treatments include cryotherapy and radioactive iodine or ruthenium disc brachytherapy, avoiding any irradiation of the muscles and bones of the orbit. Photocoagulation can usually only be used in the posterior pole for tumours not exceeding 2 mm in diameter. In 1992, Murphree described the use of thermochemotherapy for posterior pole tumours up to 8 mm

Table 1. *Side-effects of external beam radiotherapy for retinoblastoma*

Ophthalmological hazards	The commonest is posterior cataract which may require subsequent surgical operations; Dry eye and photophobia require tedious replacement treatments. Other less common complications include keratitis, maculopathy, optic neuropathy, radiation retinopathy.
Cosmetic effects	Temporal bone undergrowth after use of a lateral beam is frequent, leading to facial assymmetry in the case of unilateral irradiation; use of an anterior beam for all or part of the irradiation carries a risk of palpebral retraction, loss of eyelashes and enophthalmos.
Endocrine effects	Pituitary irradiation, beyond the threshold of 25 Gy, can lead to subsequent growth hormone deficiency, possibly requiring replacement therapy [21].
Secondary tumours	A major long term danger in hereditary forms of Rb is the predisposition to secondary sarcomas [22]. Irradiation actually potentiates the spontaneous predisposition associated with the constitutional anomaly of the *RB1* gene.

in diameter [23]. This treatment is based on the synergy between platinum-based chemotherapy, such as carboplatin, delivered by intravenous injection and hyperthermia induced by a diode laser with a direct impact on the tumour. This new technique has made posterior pole tumours even more often accessible to conservative treatments other than external beam radiotherapy [23, 24].

Demonstration of the efficacy of chemotherapy in the rare forms of Rb with orbital involvement or metastases [25] has also encouraged the use of 'neoadjuvant' chemotherapy for ocular tumours [24, 26–28]. In order to make tumours accessible to conservative treatment in order to avoid enucleation; to make tumours accessible to conservative treatment other than external beam radiotherapy; and to improve the visual prognosis by decreasing the area of the retinal tumour and, sometimes, by decreasing macular and/or optic disc involvement or overlapping,

Preferred drugs for neoadjuvant chemotherapy of intra-ocular Rb are epipodophyllotoxins (etoposide more often than teniposide) associated with carboplatin and, for some, vincristine.

The use of cyclosporin, a multidrug resistant blocker, combined with chemotherapy, has been described to improve tumour response and to increase the chances of success of a non-radiotherapeutic conservative treatment [26]. However, there are two essential points which should not be forgotten when considering these new conservative modalities (1) very extensive intra-ocular tumours do not appear to be accessible to conservative treatments other than external beam radiotherapy: all other conservative approaches are limited in terms of accessible tumour volume; and (2) most anticancer drugs are potentially mutagenic and, in the context of hereditary retinoblastoma, the risk of an increased incidence of sarcoma by the simple use of chemotherapy is not negligible [29–31].

PERSISTENT GENETIC UNCERTAINTIES

Retinoblastoma is a 'model' disease for the development of tumours due to loss of an anti-oncogene. In the great majority of unilateral, unifocal forms, the two anomalies of the *RB1* gene are situated on retinal somatic cells. The other forms (bilateral, unilateral multifocal) correspond to a combination of a constitutional anomaly of the *RB1* gene and a second event occurring on retinal somatic cells. The *RB1* gene, situated at 13q1.4, has been cloned [32] and analysis of its structure and expression in retinoblastoma has confirmed its anti-oncogene activity [33]. Despite this detailed knowledge about the *RB1* gene, genetic counselling of patients and their families is still difficult for a number of reasons:

(1) Some unilateral unifocal forms are hereditary [34];
(2) Even exhaustive analysis of the *RB1* gene in clearly hereditary forms only reveals a causal constitutional anomaly of the *RB1* gene in less than 30% of cases [35, 36];
(3) Interpretation of anomalies detected on non coding sequences of the *RB1* gene is still hazardous;
(4) The *RB1* gene mutation can occur at a late stage of embryogenesis, resulting in variable expression depending on the tissue. This mosaicism may prevent detection of the constitutional anomaly in blood lymphocytes;
(5) Penetrance is classically high, but rare spontaneously involuted forms ('retinomas') [37], or even skipped generations in hereditary forms have been reported;
(6) There is little established correlation between the type of genetic anomaly detected in the *RB1* gene and the phenotypic course of the disease [38, 39], and no established correlation with the development of second tumours;
(7) Paternal gametogenesis confers a higher mutation rate on the *RB1* locus [40]; and finally
(8) Exhaustive analyses of the *RB1* gene are expensive and complex and, at the present time, cannot be performed routinely in all patients and their families.

CONCLUSIONS

Current therapeutic strategies of adjuvant chemotherapy after enucleation should be able to reduce the incidence of high risk Rb with orbital and metastatic involvement, which are frequent in developing countries. New strategies of conservative treatment, avoiding external beam radiotherapy, tend to be more effective the smaller the intra-ocular tumour volume. It is, therefore, essential to promote retinoblastoma screening and early diagnosis by seriously considering symptoms reported by parents (leukocoria, strabismus) which are still too frequently neglected.

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Commentary

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RETINOBLASTOMA IS an eminently curable childhood cancer with survival rates in excess of 90% [1]. However, cure is often achieved at a cost, particularly in terms of visual impairment and psychological morbidity. Approximately 1 in 10 children with bilateral disease eventually require bilateral enucleations or have such severely limited vision that an independent existence is hard to achieve, whilst the facial deformity resulting either from enucleation or shrinkage of the bone and soft tissues of the face following external beam radiotherapy, may have a major deleterious psychological impact. Many patients with the genetic form of the disease live under a constant cloud of anxiety, engendered by the knowledge that they have a cancer susceptibility gene and, therefore, are at considerable risk of a second malignancy, a risk which increases with time. In addition, they also have to face the prospect of passing this potentially lethal gene on to their offspring.

Notwithstanding, the last decade has seen a remarkable and exciting change in the management of retinoblastoma, primarily with the intention of avoiding many of the long term complications seen with previous standard treatments. The spectrum of therapeutic options now available, including cryotherapy, chemotherapy, infra-red and green light lasers, scleral plaques, external beam radiation and surgery, has made the management of retinoblastoma very much more complex than previously. No longer is the ophthalmologist able to work in isolation. Close liaison between ophthalmologist, paediatric oncologist, radiotherapist and geneticist is now essential.

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