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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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Randomised therapeutic trials are difficult to undertake in retinoblastoma not only because of the small numbers of children affected, but also because there are two forms of the disease, genetic and non-genetic and, for children with bilateral disease, there is wide variation in tumour size and location at presentation. As Professor Zucker's informative and succinct update points out (pp. 1045–1048), the Reese–Ellsworth grouping is not a satisfactory classification on which to compare new therapies and an international group has been established to derive a more appropriate intra-ocular staging system on which treatment decisions can be based. From the experience gained by various groups throughout the world, it should be possible to achieve a consensus of opinion on the optimum management of certain groups of patients.

Without question, the one modality of therapy which has led to the improved survival rates seen in the U.K. over the past decade [1], has been the use of adjuvant therapy in children with adverse histological factors, so that, fortunately, the child with metastatic disease is now rarely seen. The importance of an experienced histopathologist in this regard is paramount.

The considerable attraction of chemotherapy as the primary modality of therapy or intra-ocular retinoblastoma is, predominantly, because it avoids all the adverse cosmetic effects which result from the use of radiotherapy in a young child. However, it is likely to be successful as the sole modality of therapy in only relatively small tumours. Unfortunately, larger tumours can rarely be cured by chemotherapy alone and most will need additional therapies such as cryotherapy, laser or scleral plaque. The use of cyclosporin-A, as advocated by the Toronto group, to enhance the effectiveness of certain chemotherapeutic agents by overcoming the p-glycoprotein expression which is common in retinoblastoma, is an attractive idea but needs to be the subject of a randomised study before being accepted as standard therapy. An international study with the aim of determining the role of cyclosporin-A is now in progress.

With the increasing parental pressure for conservative ocular treatments, including patients with unilateral tumours, care must be taken that such an approach does not compromise survival. The fight to save an eye for what, ultimately, may be minimal visual benefit, must not result in a life being endangered from CNS (central nervous system) or distant dissemination. Very often, a better cosmetic result can be achieved by enucleation and insertion of a good prosthesis, than the painful, red, photosensitive eye which may be the final result of whole eye radiotherapy. In general, external beam radiation for unilateral tumours should be avoided. In addition, as Professor Zucker and colleagues point out, it must not be forgotten that most anti-cancer drugs are potentially mutagenic and, like radiotherapy, may increase the risk of second malignant neoplasms in patients with the genetic form of retinoblastoma. If possible, alkylating agents, which comprise the most mutagenic group of cytotoxic drugs, should be avoided in the standard treatment of children with the genetic form of retinoblastoma.

Many groups are involved in mutation analysis of the retinoblastoma gene and it is now possible to define the mutation in at least 80% of the known hereditary cases [2]. The main challenge is to identify the patients with unilateral disease who have the genetic form of the disease. In the past, some of these patients were led to believe that there was no risk of their offspring being affected, with consequent delay in diagnosing the disease in their children, whilst other patients may have decided not to have children when in fact, they had the non-genetic form of the disease. As Professor Zucker points out in his paper, those children with unilateral disease diagnosed during the first year of life are more likely to have the genetic type of retinoblastoma and should be counselled accordingly. With the increasing sophistication of laboratory techniques for mutation analysis, the laborious task of sequencing the retinoblastoma gene will be made easier and more families will able to benefit from the genetic information to be gleaned. Professor Zucker states that there appears to be a lack of correlation between the mutation and phenotypic course of the disease. Although this may be true for many patients, this is not the case for children with spontaneously regressed tumours where a consistent missense mutation has been identified in some families [3, 4]. The lack of correlation observed to date may be due to the small numbers of patients who have been fully analysed and clearly this is an important area for further study, particularly with regard to identifying those patients most at risk of developing second neoplasms. Close collaboration between the clinician and the laboratory scientist will continue to be an essential component of good clinical practice.

In summary, children with retinoblastoma have an excellent and increasing chance of survival, whilst new methods of therapy offer cure with less morbidity. However, the current enthusiasm for conservative therapies must not be allowed to compromise survival. As Professor Zucker and colleagues wisely point out, once spread to the CNS occurs, few children can be salvaged and CNS dissemination is a real risk from over zealous attempts at conservative therapy. The introduction of national and international protocols for the management of patients with retinoblastoma combined with modern computerised digital retinal photography will greatly assist clinicians in making the correct therapeutic decisions in an increasingly complex field.

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