Pergamon

European Journal of Cancer Vol. 31A, No. 4, p. 428, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00005-4

Recent Advances in Clinical, Cellular and Genetic Analysis

A.E. Evans

THE TOPICS addressed in this Special Issue cover a wide range, and are of interest for both the investigator and the clinician. In the past, the attention of both has focused on the malignant neuroblastoma cell: on the processes involved in oncogenesis and tumour progression, and how these findings can be manipulated to change the course of disease. Great efforts have been made to escalate therapies, including bone marrow transplantation or the use of biological response modifiers to increase the cure rate, with what can only be called modest results. Until now, relatively little attention has been paid to those extraordinary events that neuroblastoma demonstrates naturally and almost uniquely in oncology. Spontaneous regression of widespread lesions is a characteristic feature of the disease, as is, less often, maturation to ganglioneuroma. It has therefore been heartening to see a shift towards these aspects of neuroblastoma in recognition of its exceptional natural history. It is the belief of many, myself included, that neuroblastoma therefore is the most promising tumour to study these processes. Such research will not only explain the basic nature of the mechanisms involved but also, in so doing, show the way towards their exploitation for clinical purposes. Many of the papers presented here address these issues. Not only do they help identify the patient with the highly malignant tumour who requires the most aggressive treatments available, but equally important, help identify the patient with a predictably favourable tumour requiring no adjuvant treatment, thus sparing the patient the unfortunate side effects of intensive chemotherapy, irradiation and major surgery.

Approximately half the papers in this Special Issue identify various genetic abnormalities in tumour cell lines and fresh tumour specimens. The largest single focus involves the deletion of the short arm of chromosome 1, and the consistent site of the deletion in the region of p36. The belief is that this chromosome carries a suppressor gene, the loss of which permits uncontrolled cell growth. Some studies attempt to identify the actual site of the deletion and others examine the normal or extra chromosomes in the lower stage tumours associated with a more favourable prognosis. Several groups address various aspects of *MYCN* in relation to prognosis, i.e. amplified *MYCN* increases neuroblastoma metastatic potential in animals. An inverse association between CD44 and *MYCN* amplification is demonstrated, with CD44 loss seen in *MYCN* amplified cells, while the presence of CD44 expression is a strong predictor of favourable outcome, and up-regulation of CD44 is obtained when differentiation is induced. The function of *TP53* in primary neuroblastoma tumours is addressed, and the results show that mutations are uncommon, and suggest that the gene plays little part in the pathogenesis of neuroblastoma, except perhaps a few cases in which the *MDM2* gene is amplified. Investigations of the role of *BCL-2*, a gene which is thought to prevent cells from undergoing apoptosis if over expressed, shows that *BCL-2* expression in tumour samples is most intense in poorly differentiated neuroblastoma, and that apoptosis is most evident in *BCL-2* negative cells.

One of the hopes of the clinician is that undifferentiated neural tumours can be made to differentiate, and thus become less aggressive. In this Special Issue, some *in vitro* studies comparing 13-*cis* retinoic acid (RA) with all-*trans* and 9-*cis* RA show that all three RA isomers inhibit proliferation to a similar extent, although 9-*cis* RA is more effective in inducing differentiation. However, 9-*cis* RA is also shown to be less effective than all-*trans* RA at low concentrations, but more effective in causing inhibition at high concentrations. The results suggest that 9-*cis* RA may be of therapeutic value if sufficient concentrations can be maintained *in vivo*. Another observation suggests that neuroblastoma-associated Schwann cells are normal rather than tumour derived, and are attracted by the tumour from the surroundings. It is possible that these cells exert an antiproliferative effect on the neuroblastoma cell.

Several papers deal with the presence of cell surface markers, such as *TRKA*, and the association of these cell surface receptors with a favourable outcome. Some investigators report the presence of multiple factors grouped together that identify tumours likely to undergo spontaneous regression, and conversely those that are very aggressive. The presence of receptors for *TRKA*, hyperdiploidy and a normal chromosome 1 are shown to be associated with low-stage tumours; in contrast, 1p deletions, diploid chromosomes and oncogene amplification are shown to be associated with more aggressive tumours.

In the area of treatment, many papers on the use of [^{131}I]MIBG include both laboratory and clinical studies. The radioactive agent is being used as primary treatment combined with chemotherapy, even in patients with marrow involvement, without unacceptable myelosuppression. An innovative approach is to potentiate the effects of irradiation by placing the child in a hyperbaric oxygen chamber.

Those of us who attended the second European Symposium on Neuroblastoma, at which many of the results included in this Special Issue were first presented, left with a feeling of excitement, challenged by the promising areas that had been identified, and eagerly anticipating the day they can be applied clinically.

Correspondence to A.E. Evans at Oncology Research, Children's Hospital of Philadelphia, Philadelphia 19104, U.S.A.