

Current Management of Neuroblastoma

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ABSTRACT

Neuroblastoma is one of the more common pediatric cancers. Although there have undoubtedly been major advances in therapy over recent decades, there is still room for significant improvements in outcome to be made. Neuroblastoma is a disease with a variable outlook, encompassing a spectrum—from patients with disease which may undergo spontaneous regression, through those who may be cured with limited treatment, to others whose disease is refractory even to the most aggressive management strategies. Great progress has been made toward understanding the basic biology of the disease, which allows reliable allocation of individual patients to good, intermediate, or poor prognostic groups

and aids selection of appropriate therapeutic approaches. Unfortunately, attempts to improve the outcome of patients with adverse prognostic factors have been less effective.

This paper reviews the clinical and biological features of neuroblastoma which determine outcome, and outlines current management policies. Some experimental approaches involving translational research which seek to exploit the unique biology of neuroblastoma are discussed. Although currently unproven, such new treatments are undergoing clinical evaluation and may yet offer new hope for patients with this enigmatic disease. *The Oncologist* 1998;3:253-262

INTRODUCTION

Neuroblastoma, the most common extracranial solid tumor of childhood, is an embryonal tumor of the sympathetic nervous system. It accounts for about 7%-8% of all pediatric malignant disease [1]. It is the most common tumor in infancy and becomes less frequent in each succeeding year. About half the cases occur under the age of three years. Neuroblastoma in adult life is well recognized but very rare. The male:female ratio is equal.

PATHOLOGY

Neuroblastoma, along with rhabdomyosarcoma, Ewing's sarcoma, and lymphoma, is one of the "small, round, blue cell tumors of childhood." It is a highly cellular tumor, with masses of small, round, or occasionally ovoid cells with scanty cytoplasm and darkly staining nuclei. Typically, rosettes containing a tangle of neurofibrillary material are visible. Immunohistochemical techniques are used to distinguish neuroblastoma from other tumors. It is preferable if a panel of antibodies is used for diagnosis [2], as none of the antigens expressed (Table 1) is completely specific

for neuroblastoma. Some tumors, called ganglioneuroblastoma, also contain mature ganglion cells in addition to undifferentiated neuroblastoma cells. These are usually treated in the same way as pure neuroblastoma. The benign variant, called ganglioneuroma, is more often encountered in older children, and more commonly in the thorax. Histological subtype, as described in the Shimada and Joshi classifications, is of prognostic significance [3, 4]. There is now an International Neuroblastoma Pathology Classification [5]. Over the last ten years, International Criteria have been developed for the diagnosis, staging, and assessment of response to treatment [6, 7]. More recently, the same international study group has achieved consensus on the need to develop stratification of patients into prognostic groups—the International Neuroblastoma Risk Groups (INRG)—on the basis of pathology and other biological markers [8].

Table 1. Some antigens expressed on neuroblastoma cells

- ▲ Neural cell adhesion molecule
- ▲ Neuron-specific enolase
- ▲ Neurofilament proteins
- ▲ Ganglioside G_{D2}

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BIOCHEMISTRY

Like the postganglionic nerves of the sympathetic nervous system and adrenal medullary cells, neuroblastoma cells have the ability to synthesize and release the catecholamines epinephrine, norepinephrine, and dopamine. In addition, neuroblastoma cells possess a mechanism for the re-uptake of catecholamines. The physiological functions of this are to terminate the neurotransmitter action of norepinephrine and the hormonal action of epinephrine. This mechanism is exploited therapeutically in the targeted radiotherapy of neuroblastoma by meta-iodobenzylguanidine (mIBG).

The principal catecholamine metabolites (Table 2) are valuable tumor markers in the diagnosis and surveillance of patients with neuroblastoma. They can be detected and quantified in urine. Urinary catecholamine metabolites may be used for screening healthy babies for neuroblastoma. Unfortunately, screening programs cannot be recommended as they have not led to a reduction in neuroblastoma mortality [9, 10].

Table 2. Catecholamines and their metabolites

Catecholamines	Metabolites
Epinephrine and norepinephrine	4-hydroxy-3-methoxymandelic acid (HMMA) also known as vanillylmandelic acid (VMA)
Dopamine	2-hydroxy-3-methoxyphenylacetic acid (HMPA) also known as homovanillic acid (HVA)

MOLECULAR BIOLOGY

In some instances, neuroblastoma may have a genetic basis, but this is unusual [11-14]. Chromosomal abnormalities, principally affecting chromosomes 1 and 17, are often found in tumor cells [15], but identifiable constitutional aberrations are unusual [16, 17]. The most common abnormality on chromosome 1 is a deletion of the distal region of the short arm. This 1p deletion suggests that loss of a tumor suppressor gene (or genes) may be responsible. The location of the deletion breakpoint varies between 1p31 and 1p36 [18-20]. Loss of heterozygosity in this region is often associated with poor prognostic factors such as advanced stage and *N-myc* amplification [21-23]. Recently, chromosome 17 gain has been shown to have adverse prognostic significance [24].

Amplification of the *N-myc* oncogene located on chromosome 2 at 2p23-24, is one of the more powerful prognostic indicators in neuroblastoma [25, 26]. It is found in between one-quarter and one-third of patients, more commonly in association with advanced disease. A relationship has been found in cell lines between *N-myc* amplification and sensitivity to treatment [27]. It is possible that *N-myc* may exert its effect through the regulation of expression of the multidrug resistance-associated protein gene (MRP) [28].

Assessment of DNA ploidy by flow cytometry can also be of significance. Patients under two years of age whose tumors are hyperdiploid or aneuploid appear to have a better outcome than those with diploid characteristics [29].

Lack of expression of the cell surface glycoprotein CD44 is also associated with a poor prognosis. CD44 expression seems to correlate with *trk-A* expression in patients with a favorable outcome [30], but appears to be independent of *N-myc* amplification [31].

DIAGNOSIS

The gold standard for the diagnosis of neuroblastoma is examination of tumor tissue by histopathology and immunohistochemistry. However, as initial surgery is not indicated in patients with advanced disease who require systemic therapy, International Neuroblastoma Diagnostic Criteria (INDC) have been established which permit a reliable diagnosis to be made without a biopsy [6]. A diagnosis of neuroblastoma is established if bone marrow contains unequivocal tumor cells (e.g., syncytia or clusters of cells positive on immunocytology) and urine contains increased urinary catecholamine metabolites. This may be defined by urinary VMA and/or HVA levels greater than three standard deviations above the mean per milligram creatinine for the age of the patient. The age is important here, as normal levels are highest in neonates and gradually diminish over the first two years of life. Both the VMA and HVA levels should be measured. Normalization per milligram of creatinine makes a timed collection unnecessary and avoids potential false negatives due to dilute urine.

Although histopathological confirmation may not be essential in these circumstances, it is still desirable to obtain tissue for biological studies. This is because biological information is not merely of prognostic relevance [8], but may, more importantly, be used to guide treatment [26]. In those patients for whom the diagnosis of metastatic neuroblastoma is certain before biopsy on the basis of bone marrow examination and urinary catecholamine metabolite studies, tumor tissue can be obtained for biological studies, including histopathological assessment, at the time of insertion of an indwelling venous access catheter. This is a reasonable way of maximizing valuable prognostic information while keeping the number of anesthetic sessions to a minimum.

CLINICAL FEATURES

Most patients with neuroblastoma present with symptoms caused directly by the primary tumor or metastases (Table 3). Only about one-third of patients have localized disease at presentation; two-thirds have metastases. Some may have symptoms caused by excess catecholamine production or by the nonspecific effect of disseminated malignancy. A significant minority of patients with no symptoms are detected

Table 3 Clinical features of neuroblastoma

Neck primary tumor
▲ Palpable cervical swelling
▲ Horner's syndrome
Thoracic primary tumor 14%
▲ Respiratory problems
▲ Dysphagia
Retroperitoneal tumor 62%
▲ Abdominal pain
▲ Palpable mass
▲ Anorexia and vomiting
Pelvic primary tumor 5%
▲ Urinary dysfunction
▲ Constipation or fecal incontinence
Paraspinal tumor
▲ Back pain
▲ Scoliosis
▲ Spinal cord compression
▲ Sphincter dysfunction
Liver metastases
▲ Hepatomegaly
▲ Jaundice
▲ Abdominal pain
Bone metastases
▲ Bone pain
▲ Palpable bone swellings
▲ Proptosis
Bone marrow infiltration
▲ Anemia
▲ Purpura
Lymph node metastases
▲ Palpable lymphadenopathy
Skin metastases
▲ Subcutaneous nodules
Neurological effects
▲ Cord compression
▲ Ataxia
▲ Opsomyoclonus ("dancing eyes")
Metabolic effects
▲ Hypertension
▲ Flushing
▲ Irritability
▲ Sweating
▲ Diarrhea

during a routine examination or because of screening. Neuroblastoma may be congenital and may occasionally be detected antenatally.

STAGING

Tumor stage is one of the more important prognostic factors in neuroblastoma. The International Neuroblastoma Staging System (INSS) (Table 4) is the currently used classification [7].

PROGNOSTIC FACTORS

The survival of children with neuroblastoma has improved over recent years (Table 5) [32], largely because of the development of effective chemotherapy. Can we distinguish reliably between those patients who are destined to do well and those in whom the disease will prove fatal?

Various clinical, histological, biochemical, and molecular features can be used to give some idea of prognosis and as a guide to treatment (Table 6). The principal clinical features, age and stage, retain their pre-eminent position as prognostic indicators. Patients older than one year fare worse. Five-year survival figures for children diagnosed in 1983-1985 are: for those aged less

than one year, 77%; aged one year, 39%; aged two, 28% and from three to nine years, less than 25% [33]. After age comes stage: the outlook for patients with INSS Stages 1 and 4S is much better than in those with more advanced disease.

The adverse significance of elevated serum levels (when compared with the normal value for a particular age) of the markers ferritin [34, 35] neuron-specific enolase [36, 37], and lactate dehydrogenase [38, 39] has been recognized for some years. The clinical use of serum markers is, however,

currently waning because of the increasing interest in more specific molecular markers, histology, and INSS staging. Advances in molecular biology have shown that factors such as *N-myc* amplification [26, 40] and 1p deletion [41, 42] correlate with a poor prognosis. Tumor cell ploidy is a powerful discriminating factor, but only in children under two years of age. Patients with aneuploid tumors usually do well, whereas those with diploid tumors are likely to fare badly [29, 39, 43].

Recently, the significance of the family of tyrosine kinase receptors for nerve growth factor and other neurotrophic factors has been recognized. mRNA expression of *trk-A*, *trk-B*, and *trk-C*, among others, can be quantified and correlated with outcome [44-46]. *trk-A* and *trk-C* expression is more common in infants and low-stage patients, and is related to a favorable outcome. In contrast, *trk-B* expression is associated with *N-myc* amplification, and related to a poor outcome.

It is clear that while the principal clinical risk indicators, age and stage, predict much, a good deal more can be gained by the incorporation of molecular factors into risk assessment [47]. As, however, many of the poor prognostic factors are not independent but go hand in hand, it is not necessary to measure every possible factor. A judicious selection from among those available should be sufficient to provide a good indication of the likely clinical outcome.

To provide reliable data on the relative importance of the many biological prognostic features in neuroblastoma, it is necessary to perform a multivariate analysis of all of these features and their relationship to treatment and outcome in many thousands of patients. This will require international collaboration. Unfortunately, although all collaborative pediatric oncology groups currently measure some factors routinely at presentation, there are insufficient complete data sets for that analysis to be performed now. The same international group [6] which formulated the INSS and the International Neuroblastoma Response Criteria (INRC) is working toward the creation of INRG [8]. The hypothesis for the INRG study is that, when coupled with INSS stage and age, select biological variables will define three distinct risk categories, each requiring different therapy. The objectives of the INRG study are first to determine by multivariate analyses which and what combination of biological variables are most powerful in changing predictive outcome of INSS stage- and age-related categories, and second to establish an international cooperative network for re-evaluating the INRG when new biological features with prognostic potential or newer therapy become available.

Finally, in relation to prognosis, it should not be forgotten that treatment is one of the most important prognostic variables. Certain biological factors which seem to be of significance in relation to the outcome of one type of treatment may no longer have any significance if newer therapies prove to be more effective.

Table 4. The International Neuroblastoma Staging System (INSS) [34, 35]

Stage 1:	Localized tumor* with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).
Stage 2A:	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
Stage 2B:	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
Stage 3:	Unresectable tumor infiltrating across the midline** with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage 4:	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined in Stage 4S).
Stage 4S:	Localized primary tumor (as defined for Stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow*** (limited to infants less than one year of age).

* Multifocal primary tumors (e.g., bilateral adrenal primary tumors) should be staged according to the greatest extent of disease, as defined above, and followed by a subscript "M" (e.g., 3_M).

** The midline is defined as the vertebral column. Tumors originating on one side and "crossing the midline" must infiltrate to or beyond the opposite side of the vertebral column.

*** Marrow involvement in stage 4S should be minimal, i.e., less than 10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The mIBG scan (if done) should be negative in the marrow.

Table 5. Improving survival in neuroblastoma

1977-1981	1982-1986	1987-1990	1991-1994
33%	46%	49%	54%

Three-year actuarial survival rates for successive cohorts of United Kingdom Children's Cancer Study Group patients.

χ^2 (1df) for trend 27.2; $p < 0.001$.

Table 6. Adverse prognostic factors in neuroblastoma

Older age
Advanced stage
Unfavorable histology
Elevated serum markers
▲ lactate dehydrogenase (LDH)
▲ ferritin
▲ neuron-specific enolase (NSE)
Diploid DNA content
N-myc oncogene amplification
1p deletion
17q gain
trk B expression
Lack of CD44 expression

TREATMENT POLICIES

Stage at diagnosis is the principal criterion for determining treatment policy. Other factors, however, such as age and biological features, should be taken into account when planning treatment.

EARLY DISEASE

Patients with stage 1 and stage 2A disease have localized tumors which are usually suitable for curative surgery. Adjuvant treatment with radiotherapy or chemotherapy is not indicated, even if there is micro-

scopic residual disease [48, 49]. Unfavorable histology and diploidy predict for local recurrence [50]. Careful follow-up is therefore necessary, as local recurrence or distant metastasis may rarely occur and require salvage treatment.

MORE ADVANCED OPERABLE DISEASE

Treatment of patients with lymph node involvement, that is, stage 2B and some stage 3 cases, is again principally surgical. The need for adjuvant treatment depends on age. In infants younger than six months, chemotherapy is controversial. In older children, chemotherapy is definitely warranted, using a schedule such as "OPEC," which comprises vincristine, cisplatin, etoposide and cyclophosphamide [51]. In these patients, it is often preferable to use chemotherapy as the initial treatment with the aim of reducing the tumor bulk, making complete removal more likely and the operation safer. Data from the Pediatric Oncology Group (POG) in patients with stage 2B and 3 disease have shown that while complete resection is not associated with a significantly better event-free survival than incomplete resection, patients with favorable Shimada histology have a significantly better event-free survival rate at two years—92%—compared with only 58% for unfavorable cases [52].

Irradiation of the tumor bed to eradicate residual disease is controversial. In a retrospective review of patients with Children's Cancer Study Group (CCSG) Stage II disease, no significant benefit was seen in irradiated patients [53]. A POG randomized trial was designed to evaluate the place of radiotherapy in addition to chemotherapy in patients over one year of age found to have nodal disease at resection of the primary tumor [54]. In irradiated patients, significantly improved local control and survival rates were seen. The chemotherapy schedule used in this study was less intensive than that now considered standard, and it remains possible that results with more intensive chemotherapy might be as

good as those in the combined modality arm of the trial. As patients with biologically favorable tumors generally have a good prognosis [53, 55], even in the presence of residual disease, it is reasonable not to give radiotherapy to patients with biologically favorable stage 2B and 3 tumors, with or without residual disease after chemotherapy and surgery. Despite the adverse effects in young children, radiotherapy should be considered in the management of patients with biologically unfavorable stage 2B and 3 tumors with residual disease [26].

STAGE 4S DISEASE

Infants with stage 4S disease have, in general, a good prognosis, and treatment is not always necessary, as the tumor may regress spontaneously as a result of programmed cell death. If the disease is not causing distressing or life-threatening symptoms, it is possible to follow a policy of observation in the hope of spontaneous regression due to apoptosis. Sometimes limited, nonintensive chemotherapy is called for if there are major symptoms such as massive hepatomegaly causing respiratory distress. Alternatively, low-dose irradiation may precipitate regression. Rarely, tumors in such patients may be found to have adverse biological features such as *N-myc* amplification. In these circumstances, the prognosis is poor, and full, intensive treatment is indicated.

INOPERABLE DISEASE

Patients with advanced disease, that is, those with stage 4 or inoperable stage 3 disease (Fig. 1) should receive initial chemotherapy with "OPEC" or a similar schedule. If chemotherapy has rendered the stage 3 tumor operable, it should be removed. In stage 4 patients, surgery to remove residual primary tumor should also be considered if there has been a complete remission at metastatic sites.

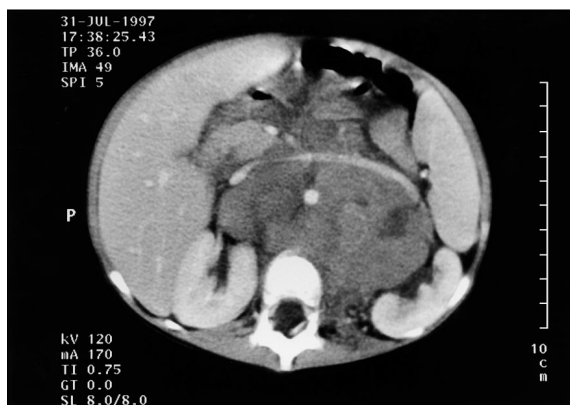


Figure 1. Contrast enhanced CT scan of a child with stage 3 abdominal neuroblastoma at presentation, showing a large leftsided retroperitoneal tumor crossing the midline and encasing the aorta.

Dose intensification strategies, designed to achieve a greater degree of cytoreduction and to circumvent the development of resistant clones by using a larger number of non-cross-resistant drugs in higher doses over a shorter period, are feasible but have not yet proved significantly superior to OPEC [56, 58]. The European Neuroblastoma Study Group (ENSG) trial 5 compares a standard, three-weekly chemotherapy regimen of carboplatin, cisplatin, vincristine, cyclophosphamide, and etoposide with a more dose-intensive regimen combining the same total doses of the same drugs given fortnightly regardless of hematological recovery. So far, this trial, which is due to close later in 1998, has recruited more than 200 randomized patients with stage 4 disease over one year of age. The results of this trial are awaited with interest.

MEGATHERAPY

Intensive treatments, or "megatherapy," combining high-dose myeloablative chemotherapy and/or total-body irradiation (TBI) with either autologous bone marrow transplantation (ABMT) or peripheral blood stem cell reinfusion are often used in advanced disease. The rationale is that if undetectable minimal residual disease can be eradicated, then the otherwise inevitable relapse is prevented. Residual cells which have survived initial chemotherapy may be resistant to drugs at conventional doses, but still sensitive to similar drugs which at higher dose levels can bypass inadequate membrane transport and saturate detoxification pathways and DNA repair mechanisms. Single-agent high-dose melphalan, which was evaluated in ENSG trial 1, is one of the more commonly used schedules [59, 60]. Although radiation, usually in the form of TBI, has been investigated with high-dose chemotherapy and ABMT for neuroblastoma, the results are no better than when chemotherapy alone is used, yet the acute and late side effects are greater. Allogeneic transplantation is not associated with improved results.

It is difficult to be certain of the true value of megatherapy. It certainly seems to prolong time to relapse; whether it truly improves long-term disease-free survival is less clear. The European Blood and Marrow Transplant Group has registry data on more than 1,000 patients with neuroblastoma who have received myeloablative therapy [61]. Overall, survival at five years is 33%, but relapses may still be seen later. When patients relapsed after initial ABMT, salvage was not possible, but ABMT did salvage 15% of patients in second or subsequent relapse who had not previously undergone ABMT. The principal factor indicating a poor outcome for transplantation in stage 4 patients over the age of one year is persistent skeletal or bone marrow involvement.

TARGETED THERAPY

Targeted radiotherapy involves the use of compounds labeled with radionuclides which preferentially localize in or around tumor deposits. Biological differences between normal and malignant cells are exploited to achieve the required differential distribution. Clinical results of radioimmunotherapy using the labeled monoclonal antibody UJ13A [62, 63] and the anti-GD2 antibody 3F8 [64] in neuroblastoma have been disappointing. Targeting with nonradiolabeled antibodies may also be used [65]. While not necessarily improving bulky disease, such treatment may have a role post-megatherapy with the aim of controlling minimal residual disease and thus improving long-term event-free survival.

The pharmaceutical mIBG, an analog of the adrenergic neuron-blocking drugs guanethidine and bretylium, is taken up into neuroblastoma cells and normal tissues of sympathetic nervous origin by an active transport process [66] involving the epinephrine transporter molecule [67]. When radiolabeled, mIBG can be used for both imaging and treatment of neuroblastoma (Fig. 2) and other neural crest tumors.

The use of ^{131}I -mIBG as part of the initial treatment of advanced neuroblastoma must still be considered experimental, although encouraging results from Holland have led to

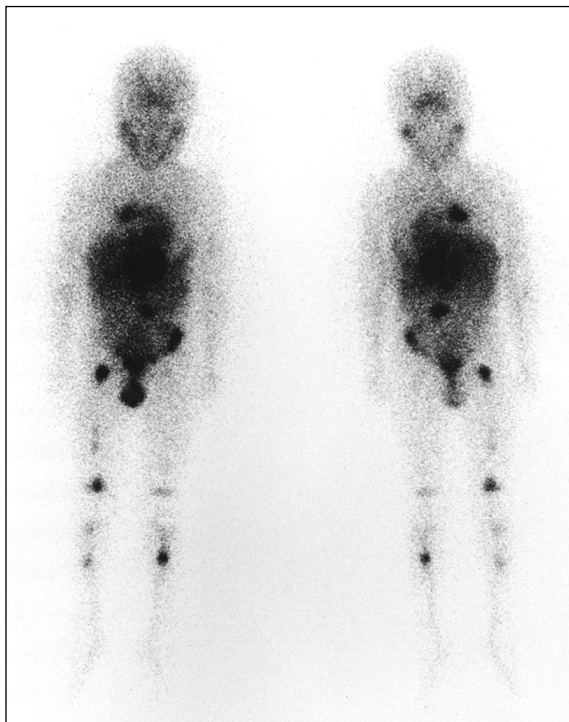


Figure 2. Post-therapy ^{131}I -mIBG scan (right: anterior view, left: posterior view) of a child with stage 4 neuroblastoma showing uptake in the left adrenal primary tumor and in multiple bone metastases.

the initiation of several prospective studies of its use in this setting [68]. The principal side effect is myelosuppression, particularly thrombocytopenia. ^{131}I -mIBG has also been evaluated in conjunction with high-dose chemotherapy as part of myeloablative regimens prior to ABMT [69-71].

DIFFERENTIATING AGENTS

A variety of agents have been shown to have noncytotoxic biological effects on neuroblastoma cells in vitro. For example, drugs such as interferon and retinoids [72, 73] may induce differentiation, and betulinic acid [74] can cause apoptosis. These agents offer possible therapeutic pathways for control of neuroblastoma. In the randomized Children's Cancer Group study CCG-3891, 255 high-risk patients were randomized after completion of conventional therapy to receive 13-*cis*-retinoic acid or no further treatment. The three-year event-free survival rate for those receiving retinoids was 47% compared with only 25% ($p = 0.013$) for those receiving no treatment [75]. In the ENSG trial 4, 177 patients with advanced neuroblastoma in complete or good partial remission were randomized to receive either 13-*cis*-retinoic acid or a placebo as maintenance therapy. This trial has now closed, and results will be analyzed in 1998 when follow-up data are more mature. Other isomers of retinoic acid may be suitable for clinical evaluation [76].

PALLIATIVE CARE

Sadly, despite advances in treatment, the majority of patients with advanced neuroblastoma are still destined to die from their disease. While those patients who relapse after minimal initial treatment for early disease may still be salvaged, patients relapsing after intensive therapy for advanced disease are very rarely cured by second-line treatment. Nonetheless, judicious use of chemotherapy and radiotherapy can be beneficial in terms of symptom control and prolongation of life, and supportive measures can often enhance the quality of life of terminally ill children.

PALLIATIVE ANTICANCER TREATMENT

The use of oral etoposide, given daily for three weeks with a seven-day interval between courses, can sometimes produce disease stabilization even in heavily pretreated patients, although the response rate is disappointing [77]. As the capsules are very large and may be difficult to administer to children, the liquid intravenous preparation is preferred, although its unpleasant taste must be disguised. The principal side effects are myelosuppression and alopecia.

Some new cytotoxic drugs are always undergoing evaluation in the pediatric setting in phase I and II clinical trials. The likelihood of benefit for an individual patient is small, and these drugs are most often tried when a family,

unwilling to accept the grave prognosis, is desperate for every avenue to be explored. The anti-DNA-topoisomerase I drug irinotecan is due to enter clinical studies in patients with neuroblastoma in the United Kingdom soon [78].

External beam radiotherapy can be valuable in the care of terminally ill children with recurrent or refractory neuroblastoma. It is most widely used for the relief of pain from bone metastases. A single 8Gy fraction usually results in a rapid and lasting benefit. In some cases, however, symptoms may recur at the same site, in which case retreatment can be considered. A fractionated regimen, such as 20Gy in five daily treatments, may be considered preferable in some circumstances, such as for the relief of spinal cord compression or extensive orbital disease.

Over the last decade, ¹³¹I-MIBG therapy has found a definite place in the palliation of symptoms of advanced neuroblastoma. Response rates varying between 16% and 58% have been reported [79-81]. While many patients show no objective tumor reduction, pain relief is often dramatic, making noncurative treatment worthwhile [82].

CONCLUSIONS

Much progress has been made in the management of neuroblastoma over recent decades, yet there is still scope for improvement. We know more about the peculiar biology of neuroblastoma than we do about any other childhood cancer. We are on the threshold of an era in which determination of the biological characteristics of the tumor in an individual patient not only allows us to make an accurate estimate of the prognosis in that case but can guide us to select the best treatment schedule for that particular patient. A greater understanding of the underlying biology of neuroblastoma is opening up new therapeutic horizons where treatments are specifically tailored to attack cells with certain molecular features.

Further progress in the introduction and evaluation of new treatments depends critically on continuing collaborative translational research led by the various national and international groups such as CCG, POG, SIOP, SFOP, and the UKCCSG, which have already achieved so much [28, 83].

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