A hallmark of neuroblastoma (NB) is heterogeneity, with a wide spectrum of clinical behavior which varies according to age at diagnosis, the stage of disease, and tumor biology (Brodeur 2003). This heterogeneity is most evident in the numerous transformation-linked genetic changes identified in cell lines and tumors. Some of these aberrations are predictive of treatment response and outcome (see Chap. 4). Nevertheless, it is increasingly clear that despite such tissue heterogeneity, the clinical biology of NB is generally predictable. By and large, patients with stage-4S and local–regional tumors are curable with minimal or no therapy, whereas children with distant metastatic disease pose an enormous clinical challenge. Only small subsets of patients have elusive risk identities at diagnosis. Modern treatments stratifying patients according to both clinical and biological factors are now the standard (see Chap. 7). At the present time, because of disparities in classification and treatment approaches, it remains difficult to compare the results of clinical trials conducted in different regions of the world; however, efforts are currently underway to develop an International NB Risk Group (INRG) System.

All of the current risk grouping systems utilize age at diagnosis (≤ vs >1 year), INSS stage, and tumor MYCN status. The COG Risk Classification System also includes tumor histology and ploidy, whereas other cooperative groups have incorporated the pattern of metastatic disease, tumor resectability, and the presence or absence of threatening symptoms (see Chaps. 7 and 11). As currently defined, each of the risk-classification systems has limitations. Small subsets of patients classified as low- or intermediate-risk at diagnosis have acted clinically as aggressive
disease, whereas other children, currently classified as high risk, have favorable outcomes and may not require the dose-intensive therapeutic approach presently prescribed. Some genetic abnormalities and molecular markers not utilized in the current classification schemas may help refine the definition of risk groups (see Chap. 4–5), and prospective studies investigating their clinical significance are ongoing. In addition, new techniques, such as comprehensive gene expression profiling, are being utilized to molecularly classify NB tumors (see Chap. 9). These studies are likely to lead to a refinement of the current risk-group classification systems and an improvement in risk-group based treatment strategies.

Although substantial progress has been made in the treatment approach toward patients with low- and intermediate-risk NB, the cure rate for metastatic NB in children remains unsatisfactory. As described in Chap. 11, most low-risk patients are successfully treated with surgery alone, and some infants do not require any treatment because their tumors have a high frequency of spontaneous regression (Chap. 2). Even for infants with stage 4 NB, >90% long-term survival is typical if the tumor \( MCYN \) oncogene is not amplified. Similarly, among patients with intermediate-risk tumors, >90% survival is expected following moderate-dose chemotherapy and surgery. In contrast, outcome remains poor for children older than 1 year with metastatic NB, with or without \( MYCN \) amplification, and during the past decade there has been only a modest improvement in cure. This small gain is due to intensification of induction chemotherapy, megatherapy consolidation, biological/immunological therapy and improved supportive care. Several clinical trials, including the large prospective randomized CCG-3891 study which demonstrated superior outcome for patients randomized to myeloablative therapy and bone marrow transplant vs chemotherapy during consolidation (Matthay et al. 1999), support the hypothesis that dose intensification is an important component to achieve successful treatment of metastatic NB (Cheung and Heller 1991). Whether intensification is most beneficial during induction or during consolidation remains controversial. Although promising results have also been observed in recent pilot studies testing tandem cycles of high-dose therapy plus stem-cell rescue (Grupp et al. 2000; Kletzel et al. 2002) (Chap. 11), further dose escalation is likely to be unacceptable. In addition, despite achieving complete clinical remission, the majority of children with high-risk disease will relapse due to drug-resistant residual disease. Eradication of refractory microscopic disease remains the most significant challenge in the treatment of metastatic NB. The paradigm of “more is better” should be questioned and additional high-risk trials testing biological and targeted agents need to be designed (Chap. 11).

Recently, the differentiation agent 13-cis retinoic acid was shown to be clinically effective when administered in the setting of minimal residual disease in the randomized CCG 3891 clinical trial (Matthay et al. 1999) (reviewed in Chap. 15). This seminal study demonstrated that a biological agent was capable of impacting outcome in high-risk NB. The COG is currently conducting a randomized prospective study comparing the efficacy of anti-GD2 ch14.18 antibody plus cytokines and 13-cis retinoic acid vs 13-cis retinoic acid alone in the setting of minimal residual disease. Clinical trials have also been developed in Europe to test immunotherapy in high-risk NB, and a single-arm study investigating the efficacy of the anti-GD2 antibody 3F8 plus GM-CSF, is ongoing at Memorial Sloan-Kettering Cancer Center. Additional phase-I and phase-II studies are testing other targeted therapies (see Chap. 12). As outlined in Chaps. 14–17, preliminary studies suggest that several immunotherapeutic molecules, new retinoids, anti-angiogenic agents, and other experimental therapeutics have activity against refractory disease.

As reviewed in Chap. 18, a variety of acute and late complications from NB and its treatment may occur; these include late effects of chemotherapy, radiation therapy, and surgery. High-risk patients are at greatest risk because of the intensive multi-modality treatment strategies that are currently utilized. Reliable identification of the subset of patients currently classified as high risk who do not require intensive therapy would significantly decrease long-term morbidity and treatment-related mortality for these very young patients. For example, data from both the POG and CCG indicate that toddlers 12–18 months of age
with favorable biology stage-4 tumors may not require the current intensive high-risk treatment regimen to be cured (Schmidt et al. 2003; George et al. 2003); however, ultimate improvements in survival and reductions of late effects may require more targeted therapies. Research aimed at discovering new genes and pathways critical to NB tumorigenesis and drug resistance should be prioritized. It is hoped that these biologically based treatment approaches will prove to be more effective and less toxic than the current regimens.

We have learned important lessons from NB. The clinical biology of stage-4S and local-regional NB, when combined with the findings of the screening study (Chap. 2), have challenged accepted oncological principles. If clinical progression from local-regional small NB to metastatic disease does not generally occur, adjuvant cytotoxic therapy is probably not necessary for the majority of these patients. On the other hand, despite general sensitivity of NB to chemotherapy, curing minimal residual metastasis remains difficult. Research focused on its measurement, control, or eradication should be emphasized. Most important of all, with the growing list of promising therapies, efforts devoted to their timely and effective integration into an overall curative strategy should have high priority.

References