SMGroup

Neuroblastoma

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INTRODUCTION

Neuroblastoma is an embryonic malignant tumor of sympathetic nervous system originating from embryonic cell remnants; they occur mostly in infants and young children. It is the most common malignant tumor in infants. NB accounts for about 8 % of malignancies in patients younger than 15 years old and approximately 15% of cancer-related deaths [1]. On the other hand neuroblastoma is one of few malignant tumors that have been reported to regress spontaneously without intervention [2]; hence it is classified into main three categories: low, intermediate, and high risk, considered one of the most heterogeneous diseases [3].

Heterogeneity of NB helps to stratify patients and treatment approaches, the clinical parameters age, Stage and pathological features have been used to define different risk groups at the time of diagnosis. Those at high risk for disease relapse are given intensive multimodal therapy, in order to increase their survival rate while those at low risk are given less intensive modalities to ovoid associated toxicity. Previous studies [4,5] show important gene modifications, profiles and signatures that have been involved in classification of tumors patients; we aim from this review to focus in recent advances in understanding molecular basis of NB, different risk stratification treatment approaches that has been reported in previous studies.

HEREDITARY ASPECTS OF NB

Recent studies of NB genetic predisposition have been greatly contributed to current

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understand of NB oncogenesis, although Familial NB is rare and account only for approximately 1% of all NB cases [6], cases of NB occurring in association with familial tumor syndrome neurofibromatosis type 1 other RAS–MAPK syndromes suggest the underlying hereditary aspect of NB [7]. In this regard, powerful genome-wide association studies (GWAS) demonstrated a link between NB and genomic variations, mutations of PHOX2B on chromosome 4p were the first reported variations in NB [8]. Half of the familial cases have been found to have activating ALK mutations, on chromosome 2p23 [9], previous study [10] shows that common variation in BARDI is associated with some of aggressive types of NB. According to Maris JM and colleagues [11] NB patients with abnormalities on chromosome 6p22 are in risk of developing stage 4 NB and somatic amplification of MYCN.

NB RISK STRATIFICATION

Risk Values

By reviewing the Children's Oncology Group (COG) risk stratification and treatment approach, the most prominent biological variables for classification of NB patients are histopathologic classification [12]; the main genetic abnormalities include ploidy and MYCN status [5] with clinical variables of age and stage [13].

Stage

The current International Neuroblastoma Staging System (INSS) based on resection of primary tumor and involvement of ipsilateral and contralateral lymph nodes and the relation of a primary tumor to the midline. Stages include; stage 1 in which tumor can be completely removed without involvement of adjacent lymph nodes, stage 2A in which tumorcannot be completely removed during surgery and adjacent lymph nodes don't involve in tumor progression, stage 2B with lymph nodes involvement, in stage 3 tumor cannot be removed by surgery with local metastasis, stage 4 with metastasis in bones, bone marrow, liver, skin, and/or other organs. However, many difficulties limit the widespread application of INSS such the necessity of expertise present and erratically lymph node sample. . Montclair et al [20] proposed a new staging system based on tumor imaging, staging depend on absence (L1) or presence (L2) of one or more of 20 image defined risk factors (IDRFs), patients with stage L1 disease had a significantly 5-year event-free survival than those with stage L2 disease (90% ± 3% vs 78% ±4%, p = 0.001). Metastatic tumors are defined as stage M. Stage MS refers to disease with metastases limited to skin, liver and bone marrow.

Age

Children less than one year old have a better prognosis than older children with the same stage of disease [18], previous study [19] shows that patients with higher age than 18 month have a higher risk stage. So age represent an important clinical variable for stratification of disease and help in determine the intensity of treatment.

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Genetic Abnormalities

DNA content (Ploidy)

The DNA index is the ratio of the number of chromosomes to the normal one (46), approximately, 55% of primary NB are triploid or near-triploid, while the remaining 45% are near-diploid (35–57 chromosomes) or near-tetraploid [14]. DNA index has been described as vulnerable prognostic value, NB patients with near- triploid cells (DNA index 1.26 to 1.76) have promising prognosis and high survival rate in comparison with patients have near-diploid or near-tetraploid tumors [15], currently, ploidy influence the risk assessment of infants age 12–18 months with metastatic disease and infants with 4S disease in the COG risk stratification.

Amplification of the MYCN proto-oncogene

Amplification of the MYCN proto-oncogene is measured by more than 10 copies per cell. MYCN amplification has been found in 5% to 10% of patients with low-stage disease and 40%of patients with advanced stages [5]; it is associated with aggressive tumor stages and a useful prognostic tool for prediction aggressive tumor behavior.

Histopathology

The International Neuroblastoma Pathology Classification (INPC)which is a system based on a framework of the Shimada classification with minor modifications, developed classification system of neuroblastic tumors based on tumor morphology [16], according to the degree of surrounding Schwannian stroma, NB is classified as: neuroblastoma (Schwannian stroma-poor), ganglioneuroblastoma-intermixed (Schwannian stroma-rich), ganglioneuroblastoma-nodular (composite, Schwannian stroma-rich/stroma-dominant and stroma-poor), and ganglioneuroma (Schwannian stroma-dominant). Further classification of these tumors into favorable and non-favorable prognosis has been established, ganglioneuroma is considered a benign neuroblastic tumor. Despite this, ganglioneuromas can be quite large and infiltrative, and attempts at removal associated with significant complications [17]

TREATMENT FOR CURRENT COG RISK STRATIFICATION

Based on biological and clinical prognostic value, current COG risk stratification is categorized into; low, intermediate, and high-risk.

Current Treatment for Low Risk Stratification

Low risk group include; the presence of microscopic residual disease (stage 1), gross residual disease (stage 2A), or gross residual disease with ipsilateral lymph node involvement (stage 2B) that is not MYCN-amplified and stage 4 disease with DNA index greater than one and favorable histology. Current treatment include surgical resection with adjuvant therapy only, infants with small adrenal masses can be managed by biochemical and Ultrasound observation only [19].

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Current Treatment for Intermediate Risk Stratification

Intermediate risk group include; Stage 2 disease with non-amplified MYCN but less than 50% of the tumor was removed, patients age 0–1½ years with stage 3 disease whose tumors are not MYCN-amplified, Stage 3 disease with 18 months and non-amplified MYCN and favorable histology, infants with stage 4 disease whose tumors are not MYCN-amplified and patients age 1–1½ years with stage 4 disease whose tumors are not MYCN-amplified, have favorable histology and DI>1. Also included Stage 4S disease with non-amplified MYCN and either unfavorable histology or a DNA index of 1 [21]. According to current COG protocol patients with favorable clinical and biologic factors can have a reduction in therapy. However, chromosome 1p or 11q abnormalities show less free-event survival in patients with low and intermediate risk [22] and spare from this reduction. Treatment includes cycles of cyclophosphamide, doxorubicin, carboplatin with duration based on intermediate-risk groups a patient was placed in. surgical procedure aim to make complete resection possible, however primary residual adherent to critical anatomic structures must be left, delayed surgery is performed after number of prescribed cycles. Radiation is prescribed when there is possible organ impairment with no response to chemotherapy, especially in infants with 4S disease and respiratory insufficiency.

Current Treatment for High Risk Stratification

High risk neuroblastoma includes patient above 18 month age at the time of diagnosis withmetastasis to other sites in the body such as the bone or bone marrow, patients with MYCN amplified tumors (except stage 1)even if they do not have evidence of metastasis. Current treatment approaches for high risk group is accepted to be intensive, the main approach has included intensive chemotherapy, myeloablative consolidation therapy with stemcell transplantation [23], stem cell transplantation is done after two cycles of chemotherapy whileresection of the primary tumor and bulky metastatic sites is attempted after the fifth cycle. The current COG high-risk neuroblastoma protocol aim to compare the effect of different intensity myeloablative therapy on cure rate, it also aim to determine the necessity of additional radiation therapy even after complete resection of the tumor. The role of surgery is not clearly defined, studies conclude that patients with INSS stage 3 or 4 disease who undergo complete resection have an increase overall survival [24,25] while other conclude different results [26,27]. However the COG high-risk protocol recommends gross total resection of the primary tumor in patients with high-risk NB.

INRG Risk Stratification

In order to avoid the variety of current approaches to risk classification, The International Neuroblastoma Risk Group (INRG) proposed a new risk stratification system based on analyze The statistical and clinical significance of 13 potential prognostic factors. Stage, age, histologic category, grade of tumor differentiation, the status of the MYCN oncogene, chromosome 11q status, and DNA ploidy were identified to be the most relevant factors [28], study involve 8,800

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children diagnosed with NB between 1990 and 2002 and aim to develop a consensus approach for pretreatment risk stratification.

CONCLUSION

Neuroblastoma is one of the most heterogeneous diseases; it can undergo spontaneous progress or develop in rapidly fatal form, current classification categorize the disease into; low, medium and high risk disease. Different treatment approaches has been determined for each classification with less intensive treatment for low-risk disease which may require only surgery and observation. Hereditary aspects of NB have been concluded in many studies which may prompt early prediction and management of disease.

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