Neuroblastoma: An Overview

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Abstract

Neurons are known to stay in G0 once they are mature. So, it isn't expected for neurons to form tumors. But what if the cell starts to lose control during its differentiation process! The type of the tumor depends on the type and the location of the transformed cell. One of these tumors is neuroblastoma which infects from 700 to 800 humans in the United States annually. In that review, we will have a look at neuroblastoma. From the definition to the treatment passing by the causes, symptoms, clinical stages, and its different types, the various features that affect and are affected by the disease would be discussed.

I. Introduction

Neuroblastoma, which was first delineated within the 1800s, is the commonest cancer in babies and the third-most common cancer in children after leukemia and brain cancer. Around one in every 7,000 children is affected at some time; 90% of cases occur in children less than 5 years old, and it is rare in adults. Moreover, 15% of cancer deaths in children are due to neuroblastoma.

Neuroblastoma (NB) is a type of cancer that originates in certain types of nerve tissue. It most often starts from the adrenal glands and then develops in the neck, chest, abdomen, or spine. Symptoms embrace bone pain, a lump within the abdomen, neck, or chest, or a painless bluish lump underneath the skin. Neuroblastoma happens because of a genetic mutation occurring throughout early development or because of a mutation inherited from a person's parents. However, environmental factors are found to be not involved. Diagnosis is based on a tissue biopsy, in which a small sample of the tissue is taken so it can be examined under a microscope. Sometimes, it may be found in a baby by ultrasound during pregnancy. During diagnosis, cancer has usually already spread. The cancer is assessed into low-, intermediate-, and high-risk groups based on a child's age, cancer stage, and what cancer looks like.

Treatment depends on the severeness of the disease. It may include observation, surgery, radiation, chemotherapy, or stem cell transplantation. Low-risk disease in babies has good results with surgery or simple observation. However, in high-risk diseases, chances of long-term survival are less than 40%, despite aggressive treatment.

II. The Disease & Its Types

i. Definition

Neuroblastoma (NB): is cancer that originates in immature nerve cells(neuroblasts); it is the most common extracranial solid tumor of childhood. Neuroblastoma may be found in the adrenal gland and paraspinal nerve tissue from the neck to the pelvis [1].

ii. Clinical Stages

In an attempt to determine if the disease started to proliferate or not and if so, to which level it has spread! The staging process was the solution for that. There are two systems: The International Neuroblastoma Staging System (INSS) and International Neuroblastoma Risk Group Staging System (INRGSS). In that review, the considered one is (INSS) which takes into account the results of surgery to remove the tumor, it has 4 stages as the following:

Stage1: Cancer remains in its first location on one side of the body and it did not spread to the near lymph nodes, all visible tumor cells have been removed completely by surgery (although looking at the tumor's edges under the microscope after surgery may show some cancer cells).

Stage 2A: The cancer is still in its original area and on one side of the body, near lymph nodes are free of the tumor but it cannot be removed completely using surgical ways.

Stage 2B: Cancer may or may not be completely removed and it has spread to the near lymph nodes on the same side but not on the other side or any other part of the body.

Stage 3: it does not proliferate to distant parts of the body. But, it has crossed the midline and cannot be removed completely, it has spread to the relatively near lymph nodes, or it starts in the middle and grows towards both sides of the body.

Stage 4: Cancer has spread to distant parts of the body such as distant lymph nodes, bones, liver, skin, bone marrow, or other organs.

Stage 4s: It is a special case when the child is younger than 1 year old, cancer spreads to the lymph nodes on the same side of the tumor only, the neuroblastoma has spread to the liver, skin, and/or the bone marrow. However, no more than 10% of marrow cells are cancer cells [2].

iii. Different Types of Neuroblastoma

It is clear that clinical criteria are not always sufficient to predict disease outcomes, and the current international recommendation is that data regarding biological features should be collected on all patients so that new therapeutic groups can be defined. For example, genetic including diploid or tetraploid, *MYCN* amplification (oncogene), deletion of 11q and 1p chromosome and gain of chromosome arm 17q or the latter rearrangement, which can result from unbalanced translocation of 17q to more than 20 different chromosome regions. In addition, frequent loss of heterozygosity (LOH) has been reported for other chromosomal regions in neuroblastoma.

In an experiment to classify different types of the disease, Patients presented between October 1987 and December 1999 at any one of 11 United Kingdom and Republic of Ireland centers, with patient ages ranging from 1 month to 18 years. More than 80% of cases were diagnosed within the last 5 years of the study, from 1995 to 1999. Neuroblastoma diagnosis and staging were according to INSS the distribution of stages being as follows: stage 1 (11 patients), 2 (10 patients), 3 (18 patients), 4 (61 patients), and 4s (eight patients). Primary tumors from 108 patients were studied before therapy. Then, the following morphologic features were investigated: the amount of schwannian stroma, MKI (low, medium, and high being, 100, 100 to 200, and . 200 mitotic or karyorrhectic cells per 5,000 tumor cells, respectively), degree of differentiation based on presence or absence of neuropil, ganglionic differentiation (undifferentiated, poorly differentiated, or differentiating), and the presence or absence of calcification. Results of CD44 expression were already available for 35 patients and were

detected immunohistochemically using the CD44 antibody.

The genetic results detected by Fluorescence In Situ Hybridization (FISH) through the experiment showed different abnormalities through metaphase or interphase such as Chromosome 17q, 1p, and *MYCN* status was established in 73, 84, and 96 tumors, respectively, whereas 11q status was only established in 15 tumors. These results are numerically listed in table 1 below:-

Table 1. Histopathologic Characteristic of 108 Neuroblastoma Tumors

	Patients	
	No.	%
Single features		
Differentiation, as % of cells		
≥ 5%	4	4
< 5%	11	10
0%	90	86
NA	3	–
Differentiation, INPC		
Diff	2	2
Poorly	89	86
Undiff	13	12
NA	4	–
MKI		
Low	69	75
Medium	11	12
High	12	13
NA	16	–
Calcification		
Yes	38	37
No	65	63
NA	5	–
CD44 expression		
Yes	20	57
No	15	43
NA	73	–
Histopathologic risk systems		
Original Shimada		
FH	43	45
UH	52	55
NA	13	–
INPC		
FH	34	34
UH	66	66
NA	8	–
Modified grades		
1	33	36
2	50	55
3	8	9
NA	17	–
Modified Risk Group		
L	48	53
H	43	47
NA	17	–

NOTE. One hundred four of 108 tumors were stroma poor neuroblastomas. Among stroma-rich tumors three were of intermixed and one was of nodular type.

Abbreviations: diff, differentiating; undiff, undifferentiated; L, low; H, high; NA, not analyzed.

Table 1: Histopathological Characteristic of 108 Neuroblastoma Tumors

As a result of the genetic abnormalities, if these three genetic alterations were assorted randomly, it would be possible to identify eight genetically distinct subgroups. However, 92 out of the 96 tumors that were unambiguously informative for all three genetic alterations fell into the following four groups: group 1, structurally normal chromosome 17, no 1p deletion, and no *MYCN* amplification (29 patients); group 2, 17q gain, no 1p deletion, and no *MYCN* amplification (24 patients); group 3, 17q gain, 1p deletion, and no *MYCN* amplification (12 patients); and group 4, 17q gain, 1p deletion, and *MYCN* amplification (27 patients). The four remaining tumors had the following combinations of abnormalities: no 17q gain, 1p deletion, and no *MYCN* amplification (one tumor); no 17q gain, 1p deletion, and *MYCN* amplification (two tumors); and 17q gain, no 1p deletion, and *MYCN* amplification (one tumor). 95% of all tumors in the series were included in the first four groups so the rest groups are neglected in the analysis. There can be a comparison between the first group and the groups from 2 to 4 in table 2.

	No. of Patients		
	Group 1 (n = 29)	Groups 2-4 (n = 63)	Statistical Comparisons (P)
Genetics			
Ploidy			
3n	11	4	.001
2n/4n	2	38	
NA	16	21	
No. of numerical imbalances, median	6	1	.001
No. of structural imbalances, median	0	4	.001
Chr 3			
−3p	0	10	.03
−3	5	1	.007
NO	14	35	
NA	10	17	
Chr 4			
−4p	1	10	.15
−4	10	1	.001
NO	8	35	
NA	10	17	
Chr 9			
−9p	2	3	.6
−9	4	3	.2
NO	13	40	
NA	10	17	
Chr 11			
−11q	1	15	.05
−11	5	4	.1
NO	13	31	
NA	10	13	
Chr 14			
−14q	0	5	.3
−14	7	5	.03
NO	12	36	
NA	10	17	
Chr 1			
+1q	0	9	.049
NO	19	37	
NA	10	17	
Chr 7			
+7q	0	5	.3
+7	9	4	.002
NO	12	38	
NA	8	17	
Chr 17			
+17	22	0	NA
NO	7	64	
Histopathology			
Stroma			
Rich	0	3	
Poor	29	60	.5
Diff, % cells			
0%	22	54	
< 5%	5	6	.3
≥ 5%	2	1	
NA	0	2	

	No. of Patients		
	Group 1 (n = 29)	Groups 2-4 (n = 63)	Statistical Comparisons (P)
Diff, INPC			
Diff	2	0	
Poorly	27	47	.01
Undiff	0	10	
NA	0	6	
MKI			
< 100	26	36	
100-200	2	7	.03
> 200	0	10	
NA	1	10	
Calcification			
Yes	17	17	
No	11	42	.009
NA	1	4	
CD44			
Yes	4	11	
No	1	10	.4
NA	24	42	
Shimada original			
FH	26	14	
UH	2	41	.001
NA	1	8	
INPC			
FH	25	7	
UH	5	50	.001
NA	1	6	
Modified grade			
1	17	13	
2	11	32	.003
3	0	7	
NA	1	11	
Modified risk			
L	28	18	
H	1	35	.001
NA	1	10	
Clinical features			
Sex			
Male	15	37	.7
Female	14	26	
Age			
< 1 year	24	8	.001
≥ 1 year	5	55	
Median age, years	0.4	2.6	.001
Stage, INSS			
1	9	2	
2	5	3	
3	10	7	.001*
4	2	49	
4s	3	2	
Site			
Abdominal	14	50	
Other	15	13	.004

Abbreviations: Chr, chromosome; diff, differentiating; undiff, undifferentiated; L, low; H, high; NO, normal; NA, not analyzed.

*Stage 4 versus other.

Table 2: Comparison Of Group 1 With Other Groups Combined in Regard Ploidy and Chromosomal Imbalances, Single Histologic Features and Histologic Risk Classifications, and Clinical Characteristics (N=92)

The comparison between the three groups from 2 to 4 is shown in table 3.

Table 3. Association of Groups 2, 3, and 4 With Ploidy and Chromosomal Imbalances, Single Histopathologic Features and Histopathologic Risk Classifications, and Clinical Characteristics (N = 63)

	No. of Patients			Statistical Comparison (P)*
	Group 2 (n = 24)	Group 3 (n = 12)	Group 4 (n = 27)	
Genetics				
Ploidy				
3n	2	1	1	2v3 .99
2n/4n	14	9	15	2v4 .99
NA	8	2	11	3v4 .99
No. of numerical imbalances, median	2	1	0	2v3 .07 2v4 .03 3v4 < .001
No. of structural imbalances, median	6	4.5	3	2v3 .2 2v4 .02 3v4 < .001
Chr 3				
−3p	7	2	1	
−3	0	1	0	2v3 .2
NO	6	7	22	2v4 .001
NA	11	2	4	3v4 .2
Chr 4				
−4p	6	1	3	
−4	0	1	0	2v3 .09
NO	7	8	20	2v4 .046
NA	11	2	4	3v4 .99
Chr 9				
−9p	0	2	1	
−9	1	0	2	2v3 .2
NO	12	8	20	2v4 .99
NA	11	2	4	3v4 .2
Chr 11				
−11q	10	5	0	
−11	1	0	3	2v3 .4
NO	4	6	21	2v4 < .001
NA	9	1	3	3v4 .001
Chr 14				
−14q	2	1	2	
−14	3	1	1	2v3 .99
NO	8	8	20	2v4 .6
NA	11	2	4	3v4 .99
Chr 1				
+1q	4	3	2	2v3 .99
NO	9	7	21	2v4 .2
NA	11	2	4	3v4 .1
Chr 7				
+7q	3	2	0	
+7	3	0	1	2v3 .99
NO	7	8	22	2v4 .04
NA	11	2	4	3v4 .08
Histopathology				
Stroma				
Rich	2	1	0	2v3 .99
Poor	22	11	27	2v4 .2 3v4 .3
Diff, % cells				
0%	19	10	25	2v3 .6
< 5%	3	1	2	2v4 .3
≥ 5%	1	0	0	3v4 .8
NA	1	1	0	

Table 3 (Cont'd)

	No. of Patients			Statistical Comparison (P)*
	Group 2 (n = 24)	Group 3 (n = 12)	Group 4 (n = 27)	
Diff, INPC				
Diff	0	0	0	2v3 .99
Poorly	22	9	16	2v4 .001
Undiff	0	0	10	3v4 .03
NA	2	3	1	
MKI				
< 100	16	6	14	2v3 .9
100-200	4	1	2	2v4 .2
> 200	2	1	7	3v4 .6
NA	2	4	4	
Calcification				
Yes	9	5	3	2v3 .99
No	14	6	22	2v4 .046
NA	1	1	2	3v4 .04
CD44				
Yes	7	3	1	2v3 .4
No	0	1	9	2v4 < .001
NA	17	8	17	3v4 .04
Shimada original				
FH	5	3	6	2v3 .7
UH	18	6	17	2v4 .99
NA	1	3	4	3v4 .7
INPC				
FH	3	1	3	2v3 .99
UH	19	7	24	2v4 .99
NA	2	4	0	3v4 .99
Modified grade				
1	8	2	3	2v3 .6
2	13	6	13	2v4 .05
3	1	0	6	3v4 .3
NA	2	4	5	
Modified risk				
L	11	3	4	2v3 .7
H	12	5	18	2v4 .06
NA	1	4	5	3v4 .4
Clinical features				
Sex				
Male	13	7	17	2v3 .99
Female	11	5	10	2v4 .6
				3v4 .99
Age				
< 1 year	2	3	3	2v3 .3(.1)
≥ 1 year	22	9	24	2v4 .99(.002)
Median age, years	4.0	1.8	2.3	3v4 .3(.99)
Site				
Abdominal	17	9	24	2v3 .99
Other	7	3	3	2v4 .2
				3v4 .3
Stage, INSS				
1	2	0	0	
2	3	0	0	2v3 .6†
3	2	1	4	2v4 .5
4	17	10	22	3v4 .99
4s	0	1	1	

Abbreviations: diff, differentiating; undiff, undifferentiated; L, low; H, high; NO, normal; NA, not analyzed.
*Statistical comparisons made between groups.
†Stage 4 versus other.

Table 3: Association Of Groups 2,3, and 4 With Ploidy and Chromosomal Imbalances, Single Histopathologic Features and Histopathologic Risk Classifications, and Clinical Characteristics (N=63)

From the analyzed data above, there are three types of neuroblastoma. Type 1: numerical changes and a triploid number of chromosomes. Such tumors have been distinguished previously as type 1 by Brodeur et al57 and by Maris and Matthay. Then, it was found that this group is also significantly associated with losses of whole chromosomes 4, 14, and 3, gains of chromosomes 17 and 7, low MKI, calcification (present in >50% of cases), positive CD44 expression, absence of undifferentiated cells, and INPC favorable histopathology. Patients are mainly infants with low-stage disease and with excellent survival rates.

Type 2 (genetic groups 2 and 3; progressing) is distinguished from type 1 by having a large number of structural abnormalities, including frequent 11q deletion, INPC unfavorable histopathology, older age of patients, advanced stages of the disease, and poor prognosis.

Type 3 (genetic group 4; rapidly progressing) is characterized by an absence of 11q deletion, few other deletions, negative CD44 expression, and absence of calcification. In addition, only tumors of this type exhibited an undifferentiated morphology. Median age at diagnosis was lower (2.3 years) and median PFS shorter (9 months) than in type 2 tumors. Because this group is defined by the presence of *MYCN* amplification and there are no further genetic features specific to this group, MYCN amplification is the most obvious candidate for the observed alteration in tumor morphology. The three types are summarized in fig1[3].

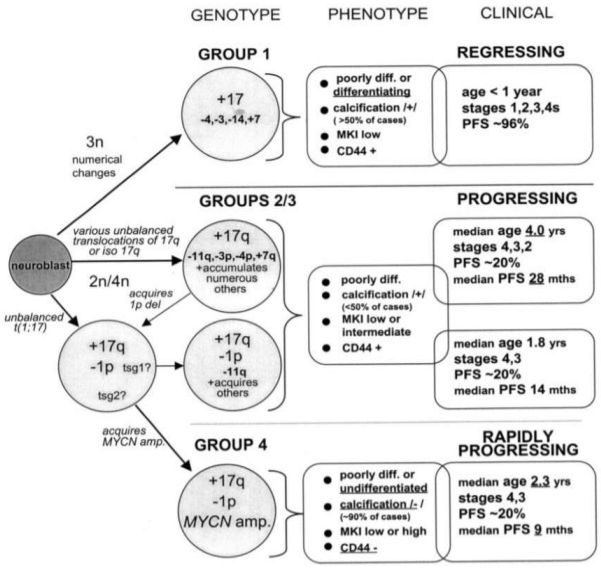

Figure 1: Neuroblastoma characteristics based on genetic, morphologic, and clinical features.

III. The Symptoms

40% of Neuroblastoma patients who present with clinical symptoms are under 1 year of age, less than 5% with clinical symptoms are over the age of 10 years, and the rest are between 1 and 10 years old.[4]

Neuroblastoma symptoms vary consistent with the tumor's location and the stage of the disease. Most of the time, cancer has spread to other parts of the body by the time signs appear.

Neuroblastoma within the abdomen, which is the commonest kind, may cause symptoms such as

abdominal pain, a mass under the skin that may not tender when touched, loss of appetite, and Changes in bowel habits, such as diarrhea or constipation.[5]

Neuroblastoma within the chest may cause symptoms such as wheezing, chest pain, trouble breathing (usually in young babies), and changes to the eyes, including drooping eyelids, unequal pupil size, and bulging eyes or dark circles below the eyes.[5]

Other common symptoms include a bump or lump in the neck, chest, pelvis, or abdomen (belly), or several lumps just under the skin that may appear blue or purple (in infants). Fatigue, cough, and fever. Pale skin (which is a sign of anemia). Painful, bloated belly. Weakness, movement problems, or paralysis in the legs and feet.[6]

Other symptoms of neuroblastoma may appear later as the disease progresses. They include high blood pressure and a fast heartbeat. Horner's syndrome, which causes droopy eyelids, small pupils, and sweating on only one side of the face. Pain in the bones, back, or legs. Problems with balance, and movement. Shortness of breath. Uncontrollable eye movements or eyes that move around quickly.[6]

IV. Diagnosis

The current criteria for diagnosis and staging of neuroblastoma are based upon INSS (The International Neuroblastoma Staging System), which was initially developed in 1986. The diagnosis of NB can be made by either characteristic histopathological evaluation of tumor tissue or by the presence of tumor cells in a bone marrow biopsy and elevated levels of urinary catecholamines (dopamine, vanillylmandelic acid, and homovanillic acid).[4]

Specific requirements for staging include bilateral bone marrow biopsies, computed tomography of the body (excluding the head if not indicated), bone scan, and metaiodobenzylguanidine (mIBG) scintigraphy. Initial diagnostic testing should include CT or MRI (magnetic resonance imaging) to evaluate primary tumor size and the regional extent and to assess for distant spread to the neck, thorax, abdomen, or pelvic sites. Brain imaging is recommended only if clinically indicated by examination or neurologic symptoms.[7]

V. The Causes

Neuroblastoma occurs when immature nerve tissues (neuroblasts) grow continuously without any control. The cells become abnormal and continue dividing, forming a tumor. A genetic mutation (a change in the neuroblast's genes) causes the cells to grow and divide uncontrollably. Scientists aren't sure till now what causes the genetic mutation.[6]

Children with a family history of neuroblastoma are more likely to develop this type of cancer. But in about 98% to 99% of the cases, neuroblastoma is not inherited. Children born with other birth defects may have a higher risk of developing neuroblastoma.[6]

Environmental factors are concerned with the development of neuroblastoma (eg, paternal exposure to electromagnetic fields or prenatal exposure to alcohol, pesticides, or phenobarbital). However, none of these environmental factors has been confirmed in independent studies.[6]

Neuroblastoma can also occur in patients affected with other neural crest disorders, such as Hirschsprung disease, neurofibromatosis type 1, and congenital central hypoventilation syndrome.[8] Genomic linkage studies have not found evidence of a link between Hirschprung disease and neuroblastoma development [8].

The co-occurrence of neuroblastoma and von Recklinghausen disease is of interest because both disorders are deviations of normal neural-crest cell development in the embryo [8].

It has been noticed the amplification of MYCN oncogene in approximately 20% of primary Neuroblastoma (NB) tumors, and its strong association with the presence of metastatic disease and poor prognosis [9]. These observations suggest that MYCN contributes to the clinically aggressive behavior of high-risk Neuroblastoma tumors, and

laboratory studies support this hypothesis.[7] The level of expression of MYCN has been shown to directly correlate with the growth of NB cells in vitro as well as in vivo. A role for MYCN in NB pathogenesis is supported by studies demonstrating NB tumor development in transgenic mice with targeted expression of MYCN.[7]

VI. The Treatment

The treatment therapy is divided into three stages, which are induction, consolidation, and post-consolidation (maintenance). The treatment process, as shown in figure 1, consists of chemotherapy, surgical resection, radiation therapy, immunotherapy, and isotretinoin [16]. Moreover, this process lasts for approximately 18 months.

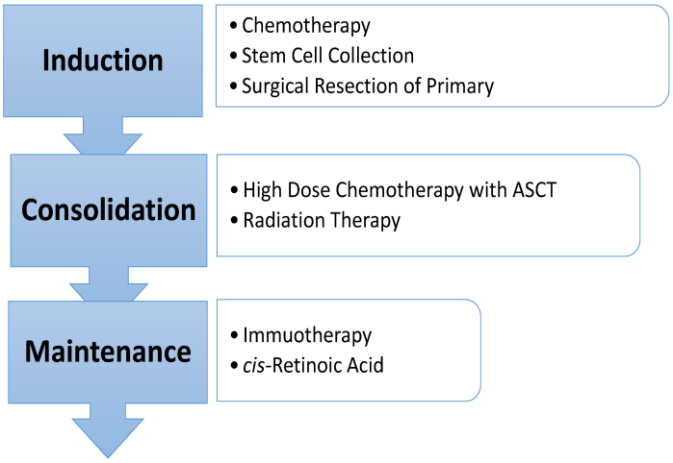

Figure 2: Stages of NB treatment

First, during the induction stage, a neuroblastoma patient will receive 5–8 cycles of intensive chemotherapy including platinum, alkylating, and topoisomerase agents. Second, also during Induction, patients undergo stem cell collection. Stem cells are collected either by periphery or bone marrow harvesting process. The harvesting process can be either post cycle 2 of induction as in COG protocols or as harvested at the end of the eight induction cycles in rapid COJEC stem cells. Unfortunately, it is common for patients to have residual bone marrow disease at the same time as collecting the stem cell. Therefore, the COG analyzed the after-effects of infusing autologous stem cells whether with or without purging. mOREOVER, surgery is another important component of the HRNBL therapy process, but it is typically conducted at or near the end of induction chemotherapy. This timing is decided to maximize tumor shrinkage in an effort to minimize surgical morbidity. Third, the consolidation phase comes after the induction with the goal to eliminate the remaining minimal disease. The consolidation process is divided into two parts which are: high dose chemotherapy followed by autologous stem cell transplant (ASCT) and radiation therapy [10].

Radiation therapy is only conducted once the patient has recovered from ASCT and is associated with a high rate of local control. The typical and standard amount of radiation administered is 21 Gy to the primary tumor, as well as radiation to end-induction sites of metastatic disease. High-risk neuroblastoma needs intensive multimodality treatment to achieve the current survival rate of slightly less than 50%. Continued understanding of the science of neuroblastoma will help to find factors that change the outcomes of patients within this group, in particular identifying high–risk neuroblastoma patients. Current research is focusing on further intensification of therapy to improve outcomes and evaluating the role of precision medicine in this patient population [10].

VII. Neuroblastoma & Brain Cancer

There can be some confusion between neuroblastoma and brain cancer. But as is shown above, the origin of neuroblastoma is extracranial. So, what about brain cancer?! Like any tumor, it is an uncontrolled division for abnormal or transformed cells. Brain tumors can be benign or malignant. Brain tumors can be classified into two main categories: primary and secondary. The primary brain tumor originates in the brain itself and its type depends on the class of the transformed cell. The secondary tumor category starts in other parts of the body and spreads to the brain so it is known as a metastatic brain tumor. The secondary tumor of the brain is a signal for another cancer in the body. Here, we can find a relation between neuroblastoma and brain tumors.

In an experiment, the clinical data of eligible patients with stage 4 neuroblastoma who were treated at the Department of Pediatric Oncology in SYSUCC between January 2004 and May 2013 were collected. The criteria for these cases was the clinical stage of the tumor is 4 and the age (less than 18 years old) without brain metastasis at the initial diagnosis, to achieve complete response (CR) or partial response (PR) or had stable disease (SD) at the primary sites after multidisciplinary treatment according to the International Neuroblastoma Response Criteria and finally, the first spread to the brain occurred after the achievement of CR, PR or SD.

Of the 106 children, 81 (76.4%) achieved CR, PR, or SD after multidisciplinary treatments. Twelve patients with CR received ASCT. After the completion of multidisciplinary treatment, all patients underwent maintenance therapy and were therefore followed up. The 5-year OS rate in patients who achieved the first CR or good PR was 45.9%. Of the 81 patients, 55 developed disease relapse and progression, including 11 patients who developed brain metastasis (Table 4).

Variable	**Patients with brain metastasis**	**Patients without brain metastasis**	***P*-value**
Total (cases)	11	44	
Age (years)			
Median	4	5	0.073
Range	2–10	1–10	
Sex (cases)			
Male	8	30	0.632
Female	3	14	
MYCN status (cases)[a]			
Positive	2	6	0.572
Negative	5	11	
Bone marrow involvement (cases)			
Yes	11	35	0.101
No	0	9	
Lactate dehydrogenase			
Median (U/L)	568	353	0.076
Range (U/L)	197–3,906	188–3,903	
0–500 U/L (cases)	6	23	0.533
501–1,000 U/L (cases)	4	10	
>1,000 U/L (cases)	1	9	
Tumor response (cases)			
CR	8	34	0.719
PR	1	6	
SD	2	4	

Table 4: Comparison of the clinical characteristics between patients with and without brain metastasis.

Of the 11 patients with CNS metastasis, 3 died at 1, 18, and 30 days, respectively, after giving up treatment; 8 received salvage therapy as shown in Table 4.

Of the 8 patients who were treated with salvage chemotherapy, 2 patients with MYCN amplification died: 1 died 3 months after the time of the detection of brain metastasis (The median interval from the initial diagnosis to the development of brain metastasis was 18 months (range 6–32 months).), and 1 died 10 months after the detection of brain metastasis; of the 5 patients without MYCN amplification, 3 were still alive at the last follow-up, and 2 died. One patient with unknown MYCN status died (Table 5).

Patient no.	Metastatic site	Surgery	Radiotherapy	Chemotherapy	Outcome
1	Bilateral cerebral hemisphere, right temporal lobe	No	32.4 Gy	IFO + VM26, 4 cycles	Died
2	Right frontal lobe	Partial resection	25.4 Gy	TMZ + CPT-11, 2 cycles; VIP, 5 cycles	Died
3	Bilateral frontal lobes	No	25.2 Gy	No	Died
4	Right temporal lobe	Complete resection	27.0 Gy whole brain cranial irradiation + 30.0 Gy localized irradiation	CPT-11 + TMZ, 6 cycles; CPT-11 + Bevacizumab, 1 cycle	Currently alive for 47 months
5	Right frontal lobe, left cerebellum, left frontal lobe, spinal cord	Partial resection of the right frontal lobe	30.0 Gy localized irradiation + 30.0 Gy spinal cord irradiation	CPT-11 + TMZ, 2 cycles; CPT-11 + Nedaplatin + VCR, 5 cycles	Currently alive for 29 months
6	Left cerebellum, medulla	No	30.0 Gy localized irradiation	CPT-11 + VCR + TMZ, 4 cycles; VIP, 1 cycle	Still alive for 30 months
7	Left frontal lobe	No	No	CPT-11 + TMZ, 1 cycle	Died

Table 5: Treatment strategies and outcomes of 8 patients with brain metastasis.

Patient 5 received radiotherapy 2 months after surgery. Patient 4 received radiotherapy 20 days after surgery. (Not mentioned in table)

After a median follow-up time of 24 months, 8 of the 11 patients died from tumor progression. The remaining 3 patients were alive for 29, 30, and 47 months, respectively, after the initiation of multidisciplinary therapy. The median OS was 25 months (range 9–47 months) for the 11 patients. The median interval from the initial diagnosis to the development of brain metastasis was 18 months (range 6–32 months). The median survival after the development of metastases in the CNS was 4 months (range 1 day to 29 months).

Of the 106 patients, 11 (10.4%) developed brain metastasis, accounting for 20.0% of 55 patients with relapse or progression. The cooperative clinical trials in advanced countries have shown that the overall incidence of CNS metastasis increased from 1.7% to 11.7% in patients who were treated with protocols from N4-N5 to N6-N7 and had prolonged survival.

From this data, it is concluded that brain metastasis for neuroblastoma patients isn't very common. But on its occurrence, it results in a poor prognosis [11].

VIII. Conclusion

Although humans have reached a high level of progress in neuroscience and other different biological sciences, till now they could not solve some mysteries in them such as Neuroblastoma.

We do know the disease, its symptoms, its stages, how to diagnose it, and even the most susceptible age group to it. But we do not know for sure what causes the gene mutation that leads to this disease or how to prevent being infected by it. Even the used treatment methods are just the traditional ones used for any other similar cancer diseases. And that means only one thing, what humans have achieved from progress in all fields of science is not enough, and there are always more and more things to reach and discover. So never give up on learning more, and applying what you have learned, so you could discover new things and reach a new status no one has reached before.

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