PROGRESS IN THE TREATMENT OF NEUROBLASTOMA

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ABSTRACT
The most common solid tumor of extra cranial in infancy, referred as neuroblastoma. Magnetic resonance imaging (MRI), ultra sound, computerized tomography scans, mIBG scan, biopsy and test for urine are used to diagnose neuroblastoma. Treatment at the younger age is beneficial because the spread of neuroblastoma cells is limited to particular part of the body. On the basis of stage of neuroblastoma before surgical removal, the tumor is shrinked chemotherapeutically. Radiotherapy is followed in certain cases for killing the left off cancer cells. About 50% of neuroblastoma is aggressive in nature and the cancer may return back despite of treating it intensively, in such cases further treatment is required. 2005-2010- The current randomization includes Metaiodobenzylguanidine therapy (mIBG). The main factor for the determination of risk group is the stage of neuroblastoma. Age, histology and biology of tumor are considered as secondary factors for risk group determination. Metaiodobenzylguanidine (mIBG) does not completely cure neuroblastoma but is able to gain control to provide possible disease stabilization. A more highly radioactive MIBG is also used for treating advanced neuroblastoma in some children’s along with various other treatments. This therapy is also used for the treatment of refractory/ relapsed neuroblastoma. Studies were conducted and it was observed that 30-40% patients with relapsed neuroblastoma gave a positive response to mIBG therapy. I-131-MIBG acts as an active agent in treating neuroblastoma patients. No serious side effect is been noticed. Combination of MIBG along with other radio labeled agents as a component of clinical trials, such as chemotherapy to find out if these further combinations can improve cure rates.

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INTRODUCTION
Neuroblastoma

The most common solid tumor of extra cranial in infancy, referred as neuroblastoma. It is the malignant growth of sympathetic nervous system in embryonic stage arising from the neuroblasts.[1]

Diagnosis of Neuroblastoma
Following tests are used to diagnose neuroblastoma:
- Test for urine: Urine has been tested for the production of certain chemicals, excreted by the neuroblastoma cells.
- Magnetic resonance imaging (MRI), ultra sound, computerized tomography scans: Used to identify the cancer affected parts in the body.
- mIBG scan: It involves injecting of a substance into the body, which is been taken up anywhere in the body by the neuroblastoma cells.
- Biopsy: In this a tissue sample is removed from the body under general anesthetic conditions by a special needle, cancer is identified on microscopic examination.[2] The cancerous tissue is observed under microscope and one of the following biopsy is carried on.
  a. The entire lymph node is removed (Excisional Biopsy).
  b. A part of lymph node is removed (Incisional Biopsy).
  c. By means of wide needle, the tissue is removed from the lymph node (Core Biopsy).
  d. By means of thin needle, the fluid or the tissue is removed from the lymph node (Fine Needle Aspiration Biopsy- FNA). [3]

Stages of Neuroblastoma
On the basis of spread of cancer, definition of neuroblastoma is given in the following stages.
- Stage 1 (L1)- At this stage the cancer has not yet spread and is confined to a limited area.
- Stage 2 (L1)- It is similar to stage 1 with no spread of cancer.
- Stage 3 (L2)- The cancer doesn’t spread to distant parts but is localized in the body.
- Stage 4 (M)- At this stage distant parts (organs) are affected by cancer.
- Stage 4s (Ms)- It is been diagnosed in babies of <1 yr, it is the special stage of tumor diagnosis. Even though it spreads to various parts of body, it can be cured better.[2]

PROGRESS IN THE NEUROBLASTOMA TREATMENT
Treatment at the younger age is beneficial because the spread of neuroblastoma cells is limited to particular part of the body.
Babies of <1 yr need no treatment because at stage 4s the cancer is cured on its own. On the basis of stage of neuroblastoma before surgical removal, the tumor is shrunk chemotherapeutically. Radiotherapy is followed in certain cases for killing the left off cancer cells. About 50% of neuroblastoma is aggressive in nature and the cancer may return back despite of treating it intensively, in such cases further treatment is required.[2]

1982-1985
In 1982-1985, European Neuroblastoma Study Group (ENSG1) treated with certain specific drugs and evaluated 167 children at different stages of neuroblastoma. The randomized value was derived in a multi centre trial for melphalan myeloablative (megatherapy). After the surgical removal of carcinoma, 69% of the children who attained a partial or a complete response were randomized further either for high dose melphalan autologous bone marrow sustain or no further treatment. 65 patients were considered for each transplant and no transplant poles and the report revealed that the stage 4 revealed 5 year better survival over 1 year old (13% : 17%) respectively.[4]

1990-1999
European study (EU-20592 or CCLGNB-1990-11) at same dose randomized 262 children at high risk for rapid sequence induction, revealing high survival rate over 1 year at standard induction. Free survival for 10 years was 27% with respect to no radiotherapy, surgical approach and melphalan versus 18% reported for stem cell transplant or bone marrow therapies.[5]

1991-1996
Children's Cancer Group (CCG-3891) carried out phase III trial demonstrating improvements in survival conducted by randomizing 379 high-risk patients in a sequence for four arms of studies consisting of 50 patients in each, when subjected to 13-cis-retinoic acid and myeloablative therapy.[6] [7]
In 1996-2003, 295 high-risk patients were randomized by the German (GPOH) study NB97 and the outcomes for stem cell transplant were compared with that of consolidation therapy. Transplants resulted in increased survival.[8]

The need for stem cell transplant of carboplatin, etoposide, melphalan, with local irradiation (CEM-LI)[9] was questioned in a recent study benefiting 486 patients. No improvement in survival was noted by Purging stem cells.[10] The 2010 randomization includes Metaiodobenzylguanidine therapy (mIBG). After transplant cis-retinoic acid is given for six months then three-month break followed by retinoic acid given for three months.[11]

Improved survival was determined by an antibody ch14.18 given with interleukin 2 and a combination of GPOH NB90 and NB 97 without cytokines at lower dose.[12] Phase III study started on Dec 2009 to benefit 105 patients to collect efficacy and safety information for FDA approval.[13]

Unituxin (dinutuximab) has currently been approved by the FDA for treating neuroblastoma in childrens.[14].

For various cancers, planning for the treatment is based on the stage of cancer the patient is affected with, but in case of neuroblastoma the risk group is considered for its treatment. The main factor for the determination of risk group is the stage of neuroblastoma. Age, histology and biology of tumor are considered as secondary factor for risk group determination.
Risk groups are categorized as low, intermediate and high risk groups
- Chances of curing are more for the low and intermediate risk groups.
- Chances of curing are difficult for high risk group.

Recurrent neuroblastoma- The recurrence of neuroblastoma again after its treatment in the similar or other body parts is referred to as recurrent neuroblastoma.

Treatment for the low-risk neuroblastoma includes-
- After the observation, surgery is done.
- For some patients chemotherapy is done (along with surgery or no surgery).
- Infants possessing neuroblastoma symptoms or signs are taken under observation. For the standard treatment further studying of patient is required.
- Clinical trials are carried out to know certain changes or responses in tumor treatment.

Treatment for intermediate-risk neuroblastoma is similar in some aspects to low-risk neuroblastoma. Few different ways are given below-
- Tumors which do not respond to surgery/chemotherapy leading to serious problems are treated by radiation therapy.
- Radiation therapy is also done if cancer cells do not respond towards various other treatments.

Its treatment includes-
- Combination of certain methods in regimen (like chemotherapy followed by surgery, stem cell rescue and so on ending up with the isotretino).n
- Clinical trial including chemotherapy in combination with mIBG following surgery, chemotherapy and so on.
- Clinical trial of combination of chemotherapy with the stem cell rescue proceeding with isotretino (monoclonal antibody, biological therapy may or may not take place).[3]
Metaiodobenzylguanidine (MIBG) does not completely cure neuroblastoma but is able to gain control over disease (as in case of relapsed neuroblastoma) for a prolonged period to provide possible disease stabilization.[15] A more highly radioactive MIBG is also used for treating advanced neuroblastoma in some children’s along with various other treatments.[16]

Metaiodobenzylguanidine (MIBG) for targeted radiation therapy is delivered in combination with radioactive labeled iodine (I-131). High-risk neuroblastoma can be treated with I-131 MIBG therapy. MIBG is done in a short span with no severe pain and providing effective treatment to patients. Certain nerve tissues like cells of neuroblastoma are capable to absorb MIBG compound. Intravenous administration of I-131 MIBG is done in children’s. I-131 MIBG is absorbed by neuroblastoma cells which are further killed by I-131 radioactive radiations. In this therapy the cancer cell is destroyed and normal, healthy tissue is refrained. This therapy is also used for the treatment of refractory/relapsed neuroblastoma. Studies were conducted and it was observed that 30-40% patients with relapsed neuroblastoma gave a positive response to MIBG therapy.[15] I-131-MIBG acts as an active agent in treating neuroblastoma patients.[17]

Possible side effects of MIBG radiotherapy

No serious side effect is been noticed as the MIBG radiations to which the child is exposed is mainly limited to area affected by neuroblastoma. Sometimes it may lead to mild nausea with urge to vomit making the children inactive and feeling tired. In some children’s, their cheeks get swollen because the salivary glands get affected by MIBG radiations. Blood pressure is raised in rare cases for a short span of time. [16]

FOOD AND DRUG ADMINISTRATION (FDA) APPROVAL OF UNITUXIN (DINUTUXIMAB) FOR TREATING NEUROBLASTOMA IN CHILDREN-

Unituxin (dinutuximab) has been approved as the component of first-line therapy by the U.S. Food and Drug Administration –FDA for treating high-risk neuroblastoma pediatric patients. Dinutuximab goes and binds with the neuroblastoma cell surface, leading to approval for the usage in surgery, radiation therapy and chemotherapy as a component of multimodality regimen specifically for the patients who responded partially to first-line multimodality or multiagent therapy.

650 new cases are estimated every year for neuroblastoma in U.S. 40-50% opportunity for the long-term survival is observed for the high-risk neuroblastoma patients with aggressive therapy.

Richard Pazdur (director at FDA’s center for the drug research and evaluation) said: Unituxin marks for treatment of high-risk neuroblastoma patients as a first approval for a specifically aimed therapy.

Possible side effects of unituxin (dinutuximab)

Clinical trials were conducted and the following side effects were observed in the patients with the administration of dinutuximab combined with colony-stimulating factor-granulocyte-macrophage and interleukin-2, thus enhancing the activity of dinutuximab.

- severe pain,
- fever,
- low blood pressure,
- decrease in platelet count,
- infusion reaction,
- low levels of blood pressure,
- Loss of water from body,
- Expelling of in taken food
- low potassium levels of potassium in the blood,
- elevated liver enzymes,
- capillary leak syndrome,
- low blood calcium levels,
- lymphopenia, and
- neutropenia hives.[14]

FUTURE SCOPE

Dr. Armstrong in the future along with his team are working ahead to combine MIBG along with other radio labeled agents as a component of clinical trials, such as chemotherapy to find out if these further combinations can improve cure rates.[18] Unituxin approved by the FDA fulfills an essential need by prolonging survival in high-risk neuroblastoma children as a treatment option.[14]
CONCLUSION
Various advancements have been taken since 1982-2015 in the diagnosis and treatment of neuroblastoma.
- Metaiodobenzylguanidine (mIBG) may not completely cure neuroblastoma but is able to gain control over disease as in case of relapsed neuroblastoma for prolong period to provide possible disease stabilization.
- A more highly radioactive MIBG is also used for treating advanced neuroblastoma in some children’s along with various other treatments.
- For many years, it has been used diagnostically to determine where cancerous activity is occurring within the body.
- In this therapy the cancer cell is destroyed and normal, healthy tissue is refrained. This therapy is also used for the treatment of refractory/relapsed (recurrence of neuroblastoma again after its treatment) neuroblastoma.
- Studies were conducted and it was observed that 30-40% patients with relapsed neuroblastoma gave a positive response to mIBG therapy.
- I-131-MIBG acts as an active agent in treating neuroblastoma patients. mIBG can radiate metastatic tumors throughout the body in one treatment, which is much more difficult with traditional radiation therapy. Hence among the various methods for treatment, mIBG therapy can be considered as an effective therapy in treating neuroblastoma with fewer side effects.
- Combination of MIBG along with other radio labeled agents as a component of clinical trials, such as chemotherapy to find out possibility to improve cure rates of neuroblastoma.
- Unituxin has been marked for the treatment of high-risk neuroblastoma patients as a first approval for a specifically aimed therapy
- Unituxin approved by the FDA in 2015 fulfills an essential need in high-risk neuroblastoma children as a treatment option for improving the better or prolonging survival.

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