Recent Advances In Management Of Retinoblastoma

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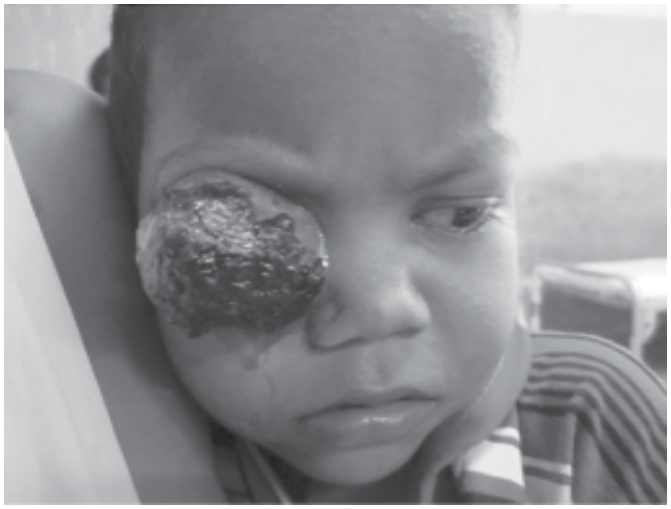
Very frequently we come across a child with a fungating mass protruding from one of the orbits in the lap of a mother.We can wonder how the poor child might be suffering.This is retinoblastoma -a common childhood cancer.Delayed diagnosis and treatment with ignorance among rural population leads to this common problem turn so large at presentation.

Retinoblastoma,one of the life threatening cancer,in children is presented to an ophthalmologist as leucocoria(commonest presentation),squint,secondary glaucoma,pseudohypopyon and endophthalmitis and at a later stage proptosis with a protruding fungating mass from the orbit.A timely diagnosis could save the progression to this extent and save the child.Modern methods of diagnosis



and treatment can help the child lead a normal life.

Retinoblastoma is the most common primary intraocular malignancy of childhood and infancy with a cumulative life time incidence of 1 in 3,300 to 1 in 20,000 live births worldwide.Indian studies have shown the incidence of the tumour in India as 1:15,000 live births.Retinoblastoma arises from accumulation of proliferating embryonic retinal cells.

Proper management is the key to patient survival. Management of retinoblastoma has undergone a lot of changes in recent years.There has been a dramatic shift in the goal of retinoblastoma therapy now,not only to save the life but also preserve the eyeball and vision

Diagnosis: Unless the child presents with stage III or stage IV disease,an indirect ophthalmoscopic examination with scleral depressor,under sedation of the child is the mainstay.

USG is an useful adjunct showing the high reflective spikes in areas of calcification but is limited by inability to show the optic nerve/extrascleral extension.It is useful in followup after conservative treatment and provides an objective measurement of tumour regression.

CT scan dileneates extraocular extension and detects the presence of an associated pinealoblastoma.

MRI is specifically indicated if optic nerve invasion or intracranial extension is suspected.It can distinguish between active tumour and haemorrhage and exudation.

Fluorescin angiography of small intracranial tumours show minimally dilated feeding vessels in the arterial phase ,mild hypervascularity in the venous phase and late staining of the mass.

Although aspiration biopsy is not routinely used due to the friability of the tumour and fear of spread of malignancy, FNAC has to be resorted to if the diagnosis can't be made with any of other modes.Alternatively Frozen section biopsy can be carried out.Once diagnosis is confirmed,it has to be followed up with enucleation in the same sitting because delaying enucleation after FNAC/ biopsy increase the chances of metastasis.The route of FNAC/biopsy is through the peripheral cornea (not the pars plana) and then through the iris,zonules and in to the tumour.This offers multiple barriers to prevent tumour spread out of the eye.

Retcam is an electronic contact camera that can be used to view ,document,email the fundus picture of the fellow eye as well as the same eye for follow up.

Genetic diagnosis could be resorted to.Lecocytes

carry the 13q14 deletion in heritable cases.Chromosomal analysis can pick up this defect in 6-8% of heritable retinoblastoma pts.DNA analysis will pick up a genetic anomaly in 80-85%pts.Linkage markers -Esterase D enzyme is also located in 13q14 location of the gene.Serum levels of this enzyme are decreased in 13q14 deletion.

Complete systemic metastatic evaluation like routine haemogram,bone marrow biopsy,CSF tap,radionucleide bone scan,liver scan,CT scan are necessary.

STAGING : Is essential for management

International Staging Schema For Patients With Retinoblastoma

- Stage 0: Intraocular tumour only
- Stage I : Tumour completely removed by enucleation
- Stage II: Residual orbital tumour
- Stage III:Overt regional disease
  1. Overt orbital extension
  2. Preauricular or cervical lymph node extension
- Stage IV: Metastatic disease

1. Haematogenous metastasis without CNS disease
   a. Single lesion
   2. CNS disease
   a. Prechiasmatic lesion
   b. CNS mass
   c. Leptomeningeal disease

Management : radiation and Enucleation were the treatment modalities in the past.but currently newer therapies like chemoreduction, Transpupillary Thermotherapy,laser photocoagulation,Cryotherapy have drastically affected management .

Thermotherapy : Transpupillary Thermotherapy is a non-photocoagulating low intensity long duration laser application.An Infrared laser beam[wavelength 810 nm] is directed at the tumour using an operating microscope or ophthalmoscopic delivery system.Large spots of 2-3 mm diameter with long duration->60 sec are given.The temperature rises 6-10?c more thannormal body temp.This causes cytolysis and mitochondrial damage.Thermotherapy can reach upto 3.5 mm depth of the tumour which is the major difference from photocoagulation.Complications are same as any laser photocoagulation.

Laser photocoagulation:Argon green laser used to produce chorioretinal atrophy of tumour with spot size 1-2 mm and 1 sec exposure per spot.

Both TTT and laser photocoagulation can be used to treat small intraretinal extramacular and extrapapillary tumours in eyes with clear optic media.

Thermochemotherapy : Is the modified chemotherapy to give Intravenous Carboplatin and then treat the tumour with continuous diode laser for 10-20 mins.Tumours upto 5 mm depth can be treated due to synergistic effect of both modalities.

Cryotherapy : Application of Trans-scleral cryotherapy by double freeze thaw/triple freeze thaw technique is used to treat small to medium size retinal tumours with minimal or no intravitreal or subretinal seeds or associated retinal detachment when tumours are in equatorial or pre-equatorial region of fundus.It is currently used to break blood retinal barrier to facilitate entry of chemotherapeutic agents into the vitreous.

External Beam Radiation Therapy:Is now reserved for advanced tumours but can be used for small tumours if they are located close to disc and fovea where laser photocoagulation can't be used.Total 40-50 Gy of radiation are given in multiple fractions of 150-200 cGy over 4-5 wks.Besides the uncommon and delayed development of posterior subcapsular cataract,radiation retinopathy and neovascular glaucoma,EBRT is chiefly limited by development of extraorbital neoplasms and orbital bone growth arrestwhen applied to children< 1 year.A child with heritable retinoblastoma has 6% risk of developing non-ocular malignancies .It increases 6 fold if EBRT is used.

Chemoreduction:is currently the first line of treatmentin most cases in which conservative management is preferred.It is also the primary therapeutic option in bilateral retinoblastoma. Carboplatin-Etoposide-Vincristine are used. Cyclosporine is added to prevent multidrug resistance.Given every 3-4 wks for 6-9 cycles,intravenously.Partially regressed tumours viable after the second course of chemotherapy and any new tumours developing during the course of chemotherapy must be treated by obliterative local therapies such as cryotherapy,laser therapy and episcleral plaque radiation therapy.Periocular and subconjunctival chemotherapy is being evaluated,though complications like orbital reaction and optic nerve damage prevent its wide use.

Chemoreduction is especially useful in Stage III to

V of Reese Ellsworth classification.Radiation may still be necessary in some patients with advanced diseases or those who do not respond to chemoreduction.

Enucleation : has to be done in cases where there is no visual potential like anterior segment tumours, rubeosis iridis, neovascular glaucoma, vitreos haemorrhage, optic nerve and choroidal involvement, persistent tumours despite treatment, large multifocal tumours, vitreous/subretinal haemorrhage>2 quadrants, or pthisical eyes. During enucleation an attempt should be made to cut 10-15 mm of the optic nerve.

Orbital implants are always used unless there is strong likelihood of residual tumour in the orbit.Orbital recurrence and metastatic disease are better managed with high dose chemotherapy and radiation therapy. Genetic counselling is advised to all pts. with heritable tumours with examination of parents.

Retinoblastoma pts. need a very close follow up once in a three months for first year then six monthly for second year and then yearly thereafter if tumour is controlled.Patients with sporadic tumours are followed upto 5 years after treatment and hereditary tumours for life.

Children's Oncology Group Trials(Non-Randomized, response based single armed trials)

Murphree stage :	**COG Protocol**
Group A : Small	Local treatment usually curative. Systemic chemo not used.
Group B : Medium	-2 agent chemo (Vincristine, Low dose Carboplatin) for 6 Cycles. Local therapy (cryo, Green laser photoablation Diode hyperthermia, brachy Therapy-30-35 GyI125 /Ru 106) From cycle-2-6
Group C : Confined Medium	-3 agent chemo(CEV-high Dose carboplatin) -Local chemo=Subtenon Car boplatin day 0 of course 2-4 of CEV[no cryo with Subtenon] -Local therapies
Group D:Diffuse Large	-Identical to group C protoc -ol
Group E : Enucleation advanced	-3 agent chemo(CEV [C low dose]) 6 cycles initiated within 35 days of enucleation. -Enucleation required for cure -At risk for extraocular Spread -Unilateral Rb pts.with ON invasion beyond Lamina cribrosa/choroid invasion
Group F:Failure to contain Extraocular	-Induction(cycle-1,2-cycl ophosmamide, topotec
Class I:distant metastasis but no CNS involvement	an;cycle-3,4-CEV,cyclo phosphamide
Class II:Metastatic CNS involvem ent/Trilateral Rb.	-Consolidation class I,II High dose carboplatin,
Class III:Isolated orbital disease/ Regional L.N. metastasis.	thiotepa,etoposide Autologous Stem cell No distant metastasis rescue -EBRT-to bulk of disease 4000 cGy to bone.1950 cGy to liver

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