Neuroblastoma (NB)

Multidisciplinary ttt
Prognostic factors
Treatment outcome
(↑ control, ↓ morbidity)

- 8-10% of childhood malignancies (Median age 2yrs <50%)
- Unique feature (differentiation & spontaneous regression 10% [stage 4s liver, skin, BM])
- 40%, 25%, 15%, 5% (abdomen, spinal ganglion, thoracic, pelvis)
- Tumor markers(↑urine or serum VMA, HVA --- 65% / high level w/ advanced)

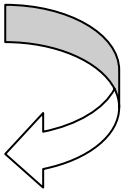
Stage at diagnosis:

68% > 1 yr (diss. Disease)	25% < 1 yr disseminated ?? (15% 4s)
32% > 1 yr (localized)	60 % < 1 yr localized

STAGING INSS 1, 2[a-b], 3, 4 (4s)
POG A, B, C
Evans/Dangio I , II

Prognostic Factors: 17 prognostic factor

1. Age <1yr.
2. Stage
3. Biological markers (N-myc amplification / Trk A / DNA ploidy/ histology grade*)



- N-myc amplification: (25% of 1ry tumors = advanced , poor clinical outcome, tumor progression, independent of age/stage)

- Trk A : 1-proto-oncogene of nerve growth factor receptor – a significant prognostic factor in N-myc –ve pts.
  2-High Trk A is associated with favourable stage (I,II,IV s) < 1 yr., no N- myc amplification
  3- High Trk A = Favorable outcome - strong correlation w/survival – 5-yr survival of 84% vs 14% ($p<0.001$)

- DNA ploidy: Prognostic factor in pts. < 1 year - Diploid tumors > in disseminated disease – hyperdiploid ones show more CR to CTh.

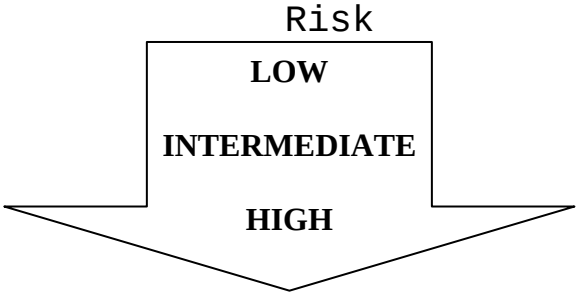
Favourable

*Histological grade: Shimada histological classification

1. Stroma rich / poor unfavorable
2. extent of differentiation
3. mitotic karyorrexic index

Treatment depends on Risk stratification:

Age
Stage
N-myc
ploidy
Histology



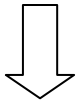
Low – Intermediate – high

INSS I, • any myc, age 0-21 yr., any shimada, any DNA ploidy	INSS ?2b/ 3 • < 1yr, -ve myc, any (shimada, Ploidy)	• >1 yr w/ stage 4
INSS 2 a/b • age <1y , all (myc – shimada- ploidy) • 1-21y, -ve myc, favorable shimada	• > 1 yr., –ve myc, favorable shimada	• > 1 yr stage 2a/b w/ +ve myc & UH
INSS 4s	Favorable (DI>1) Unfavorable (DI=1)	> 1 yr stage 3 w/ +ve myc or UH
- SURGERY - EFS 89-94% 206 patients S only ------ Cth* / Rth** for salvage – 3-y EFS 81% & OS 97% • INSS 4s ---- Cth* only w/PFS 95% -ve myc, 5-y survival 90% * Carbo/VP16 Carbo/Cycl/Doxo	SURGERY +/- Cth* 3y survival 75-98% *stage 2b, 3 S –Cth CDDP/VP alt. Cyclo/ Doxo—2nd look S & Cth (Rth for residual) PFS 92% vs. 58% for shimada favorable *stage 4 with-ve myc/ +ve myc has 3 yr DFS of	Cth <20% response & RTh** * stage 4 ----- ABMT w/ or w/o TBI --- PFS 27-63% at 2-6 yrs. **NBL is radio-responsive but w/ ?? survival advantage total dose is 24 Gy post SCT volume + 2 cm margin

** 1.5 Gyx14 Fx (21Gy) (4s 1.5x3 Fx)	95% & 75% respectively *Cth Cisplatin/ Doxo/ VP16/ Cyclo	

Points to remember:

1. All myc +ve pts w/ stage 3,4,4s are ttt as high risk
2. stage 4 > 1 yr. high risk (any shimada, any myc) should:
   - receive Cth w/ or w/o Rth



1- Clinical progression despite of Cth +/- S

2- Persistant viable disease w/ UH & 2nd look S

3- PR after S for local rec. > 3 m after initial ttt

4- PR after 8 cycles of Cth & S w/ UH

RTh dose 24 Gy in 1.5 Gy fraction size

4s (4.5 Gy in 3 Fx [liver])

Volume: 2cm margin around any viable gross or microresidual for UH

Biological treatment:

Cis-retinoic acid (cis-RA) induces differentiation & growth arrest of NBL cells in vitro

A randomized trial of Cis-RA following Transplant

Significant survival improvement was also observed in 380 pts. with induction Cth followed by ABMT (vs. non myeloablative Cth) + cis-RA (vs. none) with 3 year EFS 34% vs. 22%.

Conclusion was:

- regardless of previous ttt Cis-RA improved survival
- most effective in Minimal Residual Disease

?? to improve treatment outcome in High Risk NBL pts.

1. Double ABMT (ASCT)
2. MIBG treatment
3. Immunomodulation w/ anti-GD2 ab. w/ IL2/GMCSF
4. Cis-RA post treatment for all pts.

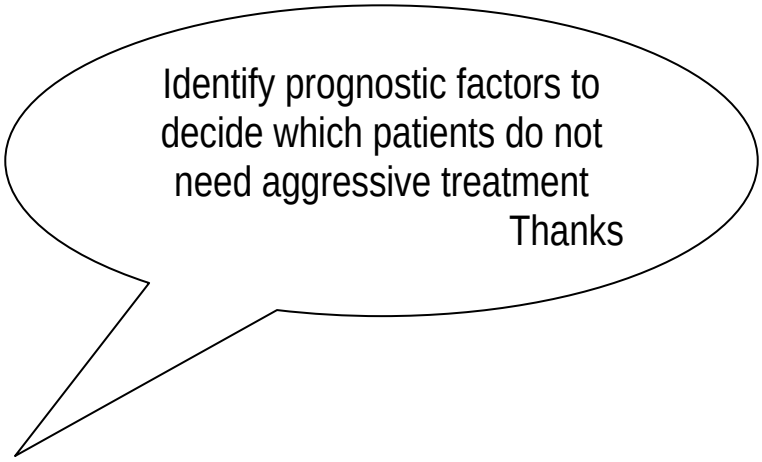
MIBG:

I ^{131} meta iodobenzyl guanidine bound at cell membrane; actively transported into cells by majority of NBL cells

1. Therapeutic use I ^{131} MIBG has been used as an up-front setting for ttt of pts w/ unresectable tumors resulting in CR or in primary tumors becoming 95% resected
2. Trials combining I ^{131} Cth, S, and RTh are in progress.
3. Dose escalation trial in relapsed pts. of 3-18 mci/kg of I ^{131} stem cells given for > 12 mci/kg. RR of 37% (1CR, 10 PR, 3 mixed,10 SD, 6 PD)

Late effects of treatment:

1. Disturbance in growth
2. neuropsychological sequalae
3. Infertility (Ctoxan, RT)
4. Endocrinopathy
5. Pulmonary & Cardiac effects
6. 2nd malignancy



Prognostic factors

1. Pathology: FH > UH
2. Age < 2 y better than > 2 y
3. NSE (1-100ng/ml) Abnormal > 100
4. Ferritin level (0-150ng/ml) Abnormal > 150
5. VMA/HVA ratio High if > 1
6. Stage I,II, or IVs > III > IVn > IV
7. Site of primary: neck / Med./ pelvis >> abdomen
8. Gallium uptake
9. *n-myc* gene amplification: 1 *n-myc* gene copy >> greater than 1 copy ↓
10. DNA flow cytometry: favorable outcome – aneuploid, % of G2, S, M phases.
11. B.M. mets detection:
12. P-glycoprotien expression
13. Neural growth factor receptor (TRK) gene expression = favorable outcome
14. LDH level : < 1500
15. Neuropeptide – Y: detect early relapse
16. ↓ H-ras p21 expression = aggressive tumor, ↑ = high DFS

17. BCL-2 oncogene expression = poor prognosis

18. Chromosome Ip deletion = poor survival

Remember:

Low risk group:

- INSS I:: S alone – DFS 90% -- Cth for rec. – Cth 5 cycles
- INSS 2 A,B < 1y, or 3 < 1y S & Cth – 2y DFS 85%

Intermediate risk group:

- INSS > 1y stage 2B – Induction CTh + RTh 24-30 Gy --- 2nd look S --- maintenance CTh CR 75% /// EFS 60%
- > 1 y & INSS stage 3 --- S – CTh (induction & maintenance) – 2nd look S --- Local RTh 14-36Gy – 3rd look S //// EFS 70%
- < 1y INSS stage 4 -- S –CTh MADDOC q 3 w (9-12m) /// EFS 75%

High risk group:

- > 1y INSS 4 –Initial ttt Cth (PVAC) – preconditioning transplant regimen ---ABMT --- overall 3y relapse 49% overall progression free survival is 44%

Dumbbell & spinal cord compression NB:

Decompression CTh + steroids --- response ??80-85% ----Surgery w/ complete neurologic recovery of 30-40% ---- RTh no longer indicated