Atipik teratoid/Rhabdoid tumor Kemoterapi

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The 2007 WHO Classification of Tumours of the Central Nervous System

	I	II	III	IV
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour of the fourth ventricle	•			
Pineal tumours				
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Embryonal tumours				
Medulloblastoma				•
CNS primitive neuroectodermal tumour (PNET)				•
Atypical teratoid / rhabdoid tumour				•

- 1987'de ayrı bir antite olarak tanımlandı
- Beyin tumorlerinin %3'ü

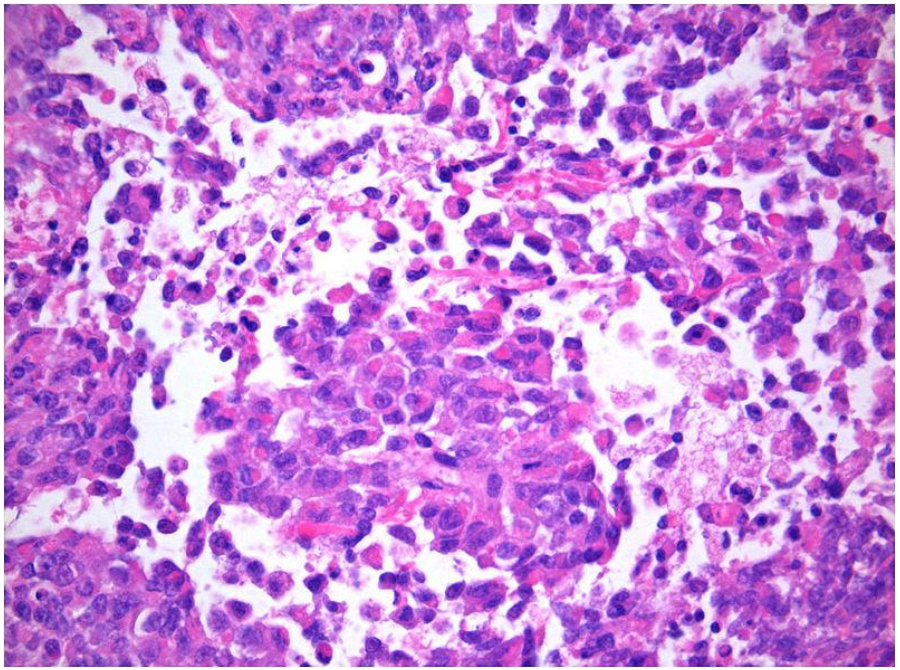
ATRT/PNET-MBL =

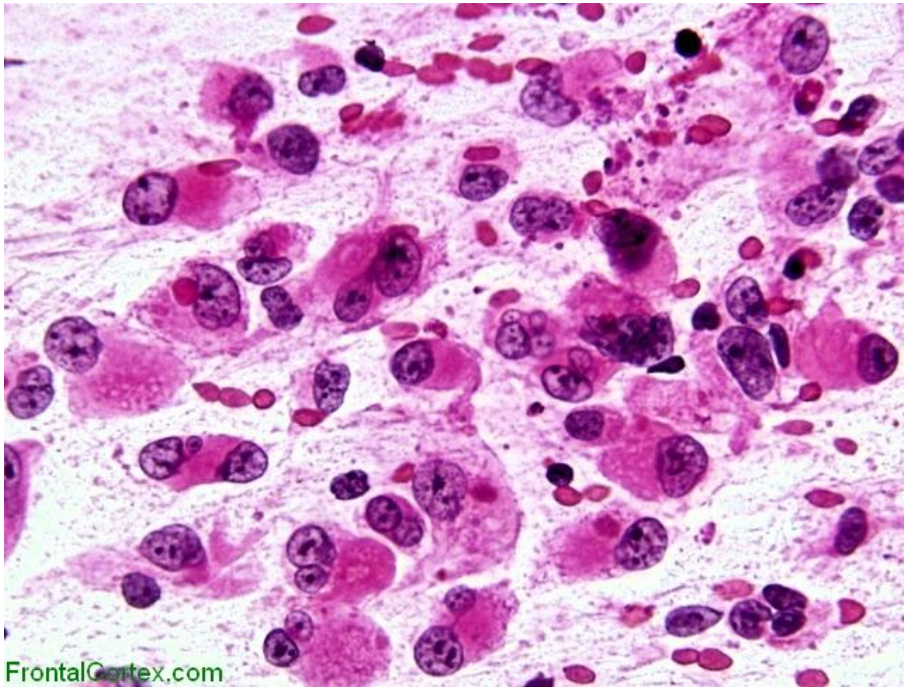
- Çocuk ⟶ 1/12.2
- <1 yaş ⟶ 1/1.5

- Çok maliyn
- Küçük çocuk (<3 yaş)
- Agresif tedavi gerekir
- Diğer embriyoner tmden ayırmak önemli

Tanı

- **Histopatoloji:** Rhabdoid tumor hücreleri ve değişik alanlarda primitiv nöroektodermal, epitelial ve mezenkimal diferansiyasyon

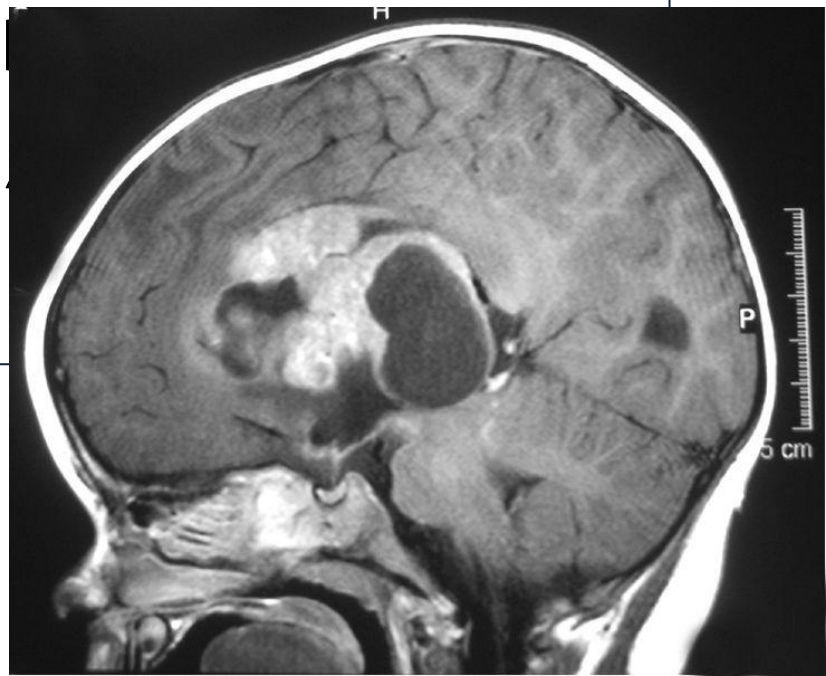




Tanı

- **Radyoloji:** Non-spesifik
- % 50 posterior fossa, % 20 **dissemine**
- 52% posterior fossa, 39% sPNET, 5%pineal, 2%spinal, ve 2% multi-fokal
- **Buyuk tumor,** kanamaya meğilli, kalsifikasyon ve nekroz olabilir
- T2: heterojen -hiperintens kistik
  T1: hiperintens (kanamaya bağlı), heterojen ve nodular kontrast tutulum

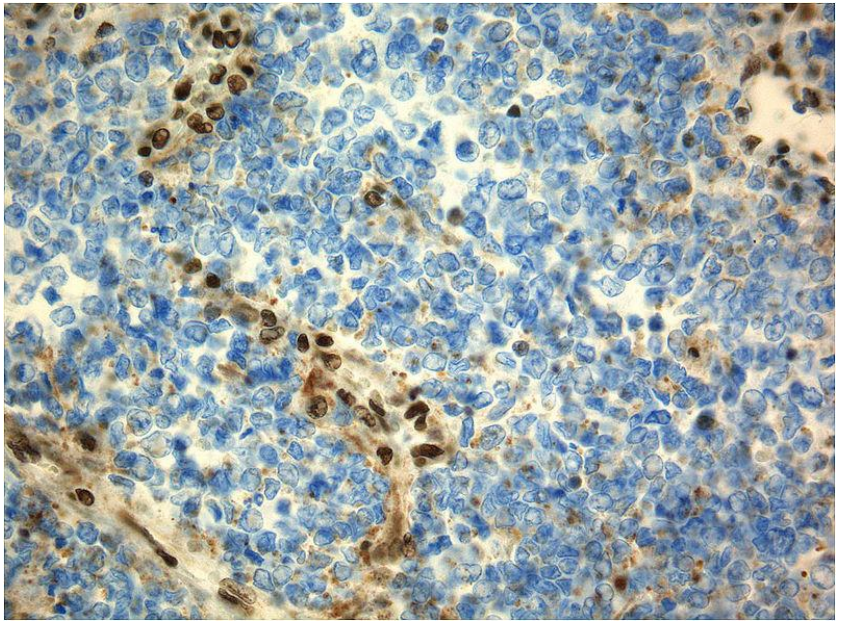
küçük çocuk + radyoloji



Loss of SMARCB1 protein (INI1) ekspresyonu

- IHK: Rhabdoid hücre olmasa da (küçük biyopsi) gösterilmesi kötü prognoz
- IHK + FISH + genomic sequencing genetik değişiklik %75 olguda gösteriliyor. ⟶

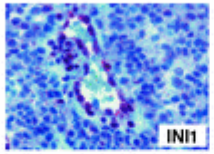
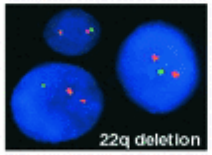
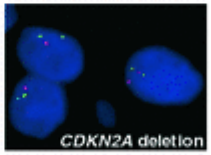
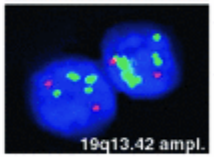
Immunhistokimya :for INI1, the product of the SMARCB1 gene typically defective in ATRT. Note loss of brown staining in the nuclei of tumor cells with defective SMARCB1 as compared to retained staining of nuclei of vascular cells (internal positive control)



Genetik

- 22q21 ⟶ *SMARCB1/INI1*
- Tümör supresor gen
- Malign rhabdoid tumorlerde de var
- Diğer beyin tm. de de var (CNS PNET, medulloblastoma, veya choroid plexus carcinoma) ⟶ ATRT
- Monozomi, delesyon, LOH, mutasyon ⟶ inaktivasyon
- de-novo *SMARCB1/INI1* konstitüsyonel mutasyonu ⟶ "rhabdoid tumor predisposition syndrome"

AT/RT and CNS PNET

Histology	AT/RT	CNS neuroblastoma	Embryonal tumor with multilayered rosettes
Expression characteristics	Loss of INI1 expression 		
Genetic characteristics	-22q *SMARCB1* mutation/ deletion 	- 9p21.3 *CDKN2A* deletion 	+19 *19q13.42* ampl. 
Clinical characteristics	Rarely metastatic, 50% infratentorial, supratentorial, pineal gland	Rarely metastatic, cerebral hemispheres	Rarely metastatic, mostly supratentorial
Age groups	infants	all age groups	infants
Prognosis	Poor	Poor	Poor

Tedavi

- Yoğun
- Multimodel (agresif cerrahi + KT + RT)
- Küçük yaş dezavantaj (RT)
- **Standart multiajan KT** ile sonuçlar kötü, hızlı progresyon ve sık dissemine hastalık (med survival 8.5 ay)
- < 3 yaş çok kötü

Standart multiajan KT

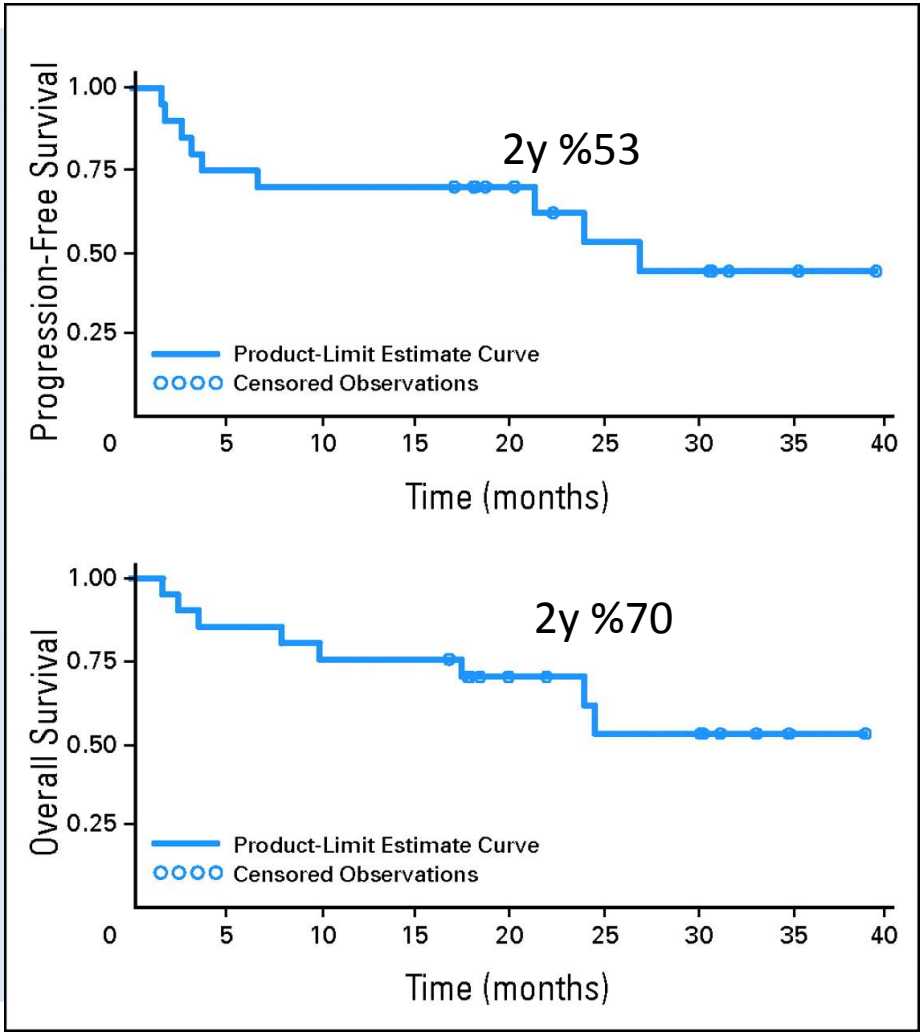
- COG : < 3 yaş 28 hasta ⟶ 2 y. EFS %14
- German HIT trial center ⟶ 1988-2004
  - 56 hasta
  - 3 y. OS %22, EFS %13, 8 hasta yaşamış
  - Küçük yaş, tanıda metastatik hastalık kötü

•Geyer JR,et al.Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group. J Clin Oncol 23 (30): 7621-31, 2005.

•Frequency, risk-factors and survival of children with atypical teratoid rhabdoid tumors (AT/RT) of the CNS diagnosed between 1988 and 2004, and registered to the German HIT database Pediatr Blood Cancer ,2011 Dec 1;57(6):978-85.

Sarkom tipi tedavi (+IT tedavi)

- Dana-Farber Cancer Inst
- Prospektif çalışma
- 25 ATRT
- IRS-III tipi tedavi
- **IT tedavi (**MTX/ARAC/hidrokortizon) sistemik multiajan KT (VCR/CYC/CPPD/DOX/ETO)
- RT/temozolamid



Chi S N et al. JCO 2009;27:385-389

JOURNAL OF CLINICAL ONCOLOGY

Sarkom tipi tedavi (+IT tedavi)

- RHABDOID 2007 - 5 YEAR FOLLOW-UP OF A CONSENSUS TREATMENT REGIMEN IN 29 GERMAN CHILDREN WITH AT/RT
- 2007-2009
- Germline mutasyon %14
- 9 kür VCD ve ICE alterne tedavi + IT MTX
- 5 y. EFS %41, OS %48

EURHAB ⟶ European phase II study in AT/RT and other rhabdoid tumors (2009)

Neuro Oncol (2012) 14 (suppl) 15th International Symposium on Pediatric Neuro-Oncology, June 24-27 2012 Toronto, Ontario, Canada

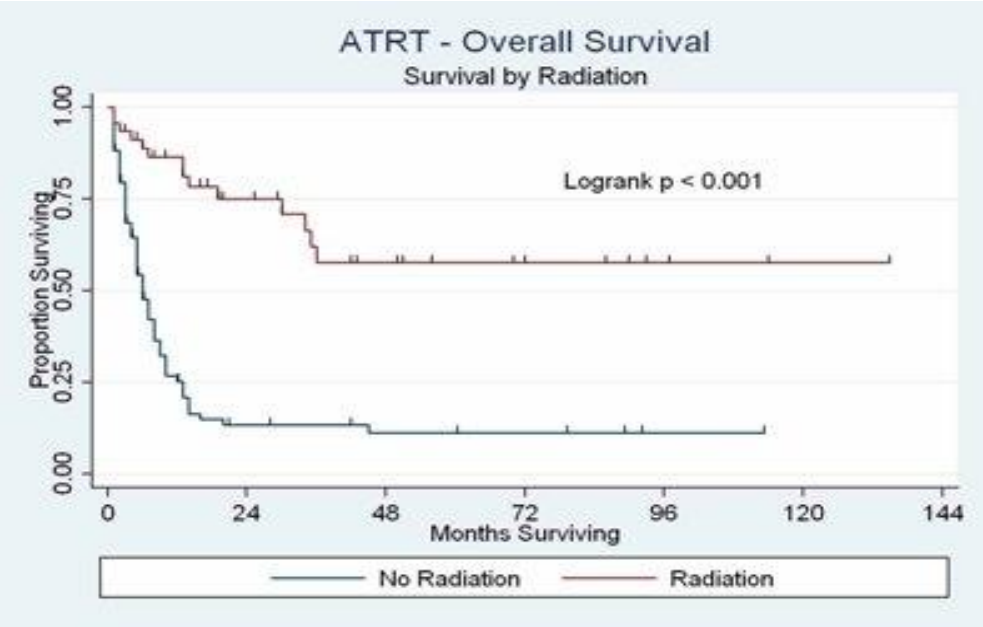
Yüksek doz Kemoterapi (YDKT)

- Yoğun KT içeren tedavi ile uzun yaşayan olgular var (1998-Hidden et al.)
- YDKT işe yarar mı ??

AMAÇ :

- Kan-beyin bariyerini aşmak
- Tümör yükünü azaltıp RT etkisini artırmak

Yoğun alkilleyici KT + RT



- 3 yaş üstü
- Yüksek doz alkilleyici içeren KT
- RT

•Tekautz TM, et al.: Atypical teratoid/rhabdoid tumors (ATRT): improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy. J Clin Oncol 23 (7): 1491-9, 2005**. St. Jude Hospital**

Alkilleyici-YDKT

- **COG 99703**

  Klasik KT +3 kür Carbo + TT ⟶ 5/10 yaşıyor

- **AIEOP**

- 1995-2003 ⟶ 29 hasta, 11 klasik vs 13 YDKT

  ⟶ 5 y. PFS %18 vs %15

- Roma(Fidani et al)⟶ CECAT (cyc/eto/carbo/tt) vs ICE +YDKT ⟶ 3 / 4 vs 2/8 progrese oldu

- Son protokol 2004 -…. ⟶ ICE + YDKT (TT ± Melp)+ RT

• *Garrè ML. Atypical teratoid/rhabdoid tumour of the central nervous system (CNS): Final results of the first Italian Cooperative Study for the very young children. Haematol Rep2006; 2: 6.*

• *Fidani P, A multimodal strategy based on surgery, radiotherapy, ICE regimen and high dose chemotherapy in atypical teratoid/rhabdoid tumours: A single institution experience. J Neurooncol2009; 92: 177–183.*

2010'a kadar özet

Multiajan KT ± YDKT+ "second look cerrahi"+RT

- IT tedavi yok
- Daha yoğun tedaviler ile sonuçlar daha iyi gibi
- Olgu sayıları çok az,
- Tedaviler standart değil, izlem süreleri kısa
- YDKT'nin etkisi bilinmiyor (ek tedaviler de heterojen)
- En etkili ilaçlar?
- Multiajan ve alkilleyici içeren KT !!!!

Garrè, M. L. and Tekautz, T. (2010), Role of high-dose chemotherapy (HDCT) in treatment of atypical teratoid/rhabdoid tumors (AT/RTs). Pediatr. Blood Cancer, 54: 647–648.

Güncel tedaviler

- Multiajan yoğun KT (ICE)
- Second-look cerrahi
- Yüksek doz alkilleyici (TT, CARBO, Melp, temozolamid)
- IT tedavi
- YDKT
- Kraniospinal RT
- >3 yaş çocuklarda işe yarayabiliyor

•Nicolaides T, Tihan T, Horn B, et al.: High-dose chemotherapy and autologous stem cell rescue for atypical teratoid/rhabdoid tumor of the central nervous system. J Neurooncol 98 (1): 117-23, 2010

•Finkelstein-Shechter T, Gassas A, Mabbott D, et al.: Atypical teratoid or rhabdoid tumors: improved outcome with high-dose chemotherapy. J Pediatr Hematol Oncol 32 (5): e182-6, 2010.

•Gardner SL,et al.: Intensive induction chemotherapy followed by high dose chemotherapy with autologous hematopoietic progenitor cell rescue in young children newly diagnosed with central nervous system atypical teratoid rhabdoid tumors. Pediatr Blood Cancer 51 (2): 235-40, 2008.

EUROPEAN RHABDOID REGISTRY

EU-RHAB

EUROPEAN Rhabdoid Registry

Kasım 2010

PART I:

CONSENSUS THERAPY RECOMMENDATIONS

FOR PATIENTS WITH RHABDOID TUMORS OF THE CNS

(AT/RT – atypical teratoid / rhabdoid tumors)

EU-RHAB

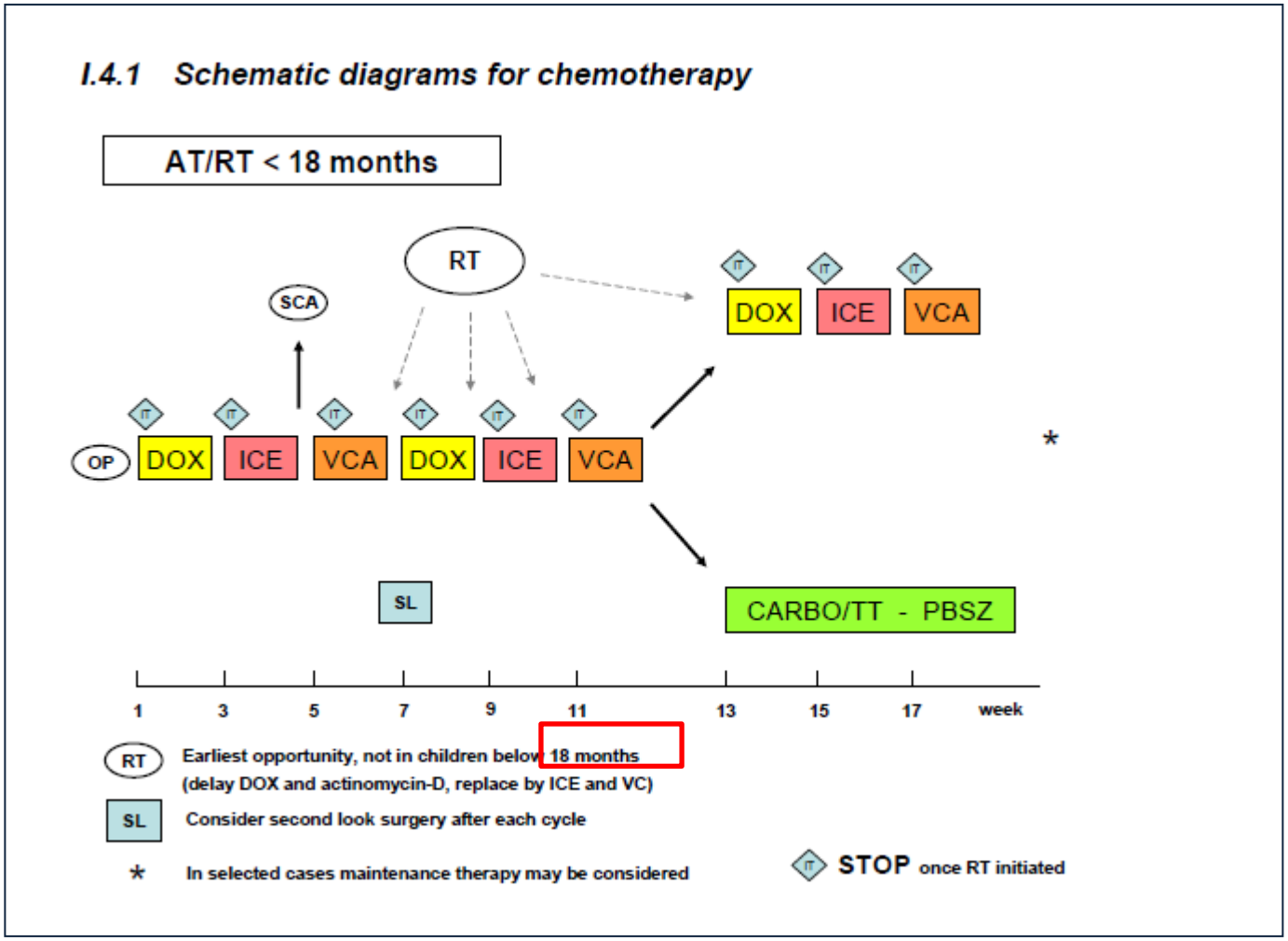
Geniş tarama PET-CT, tüm vücut MR

Initial Staging

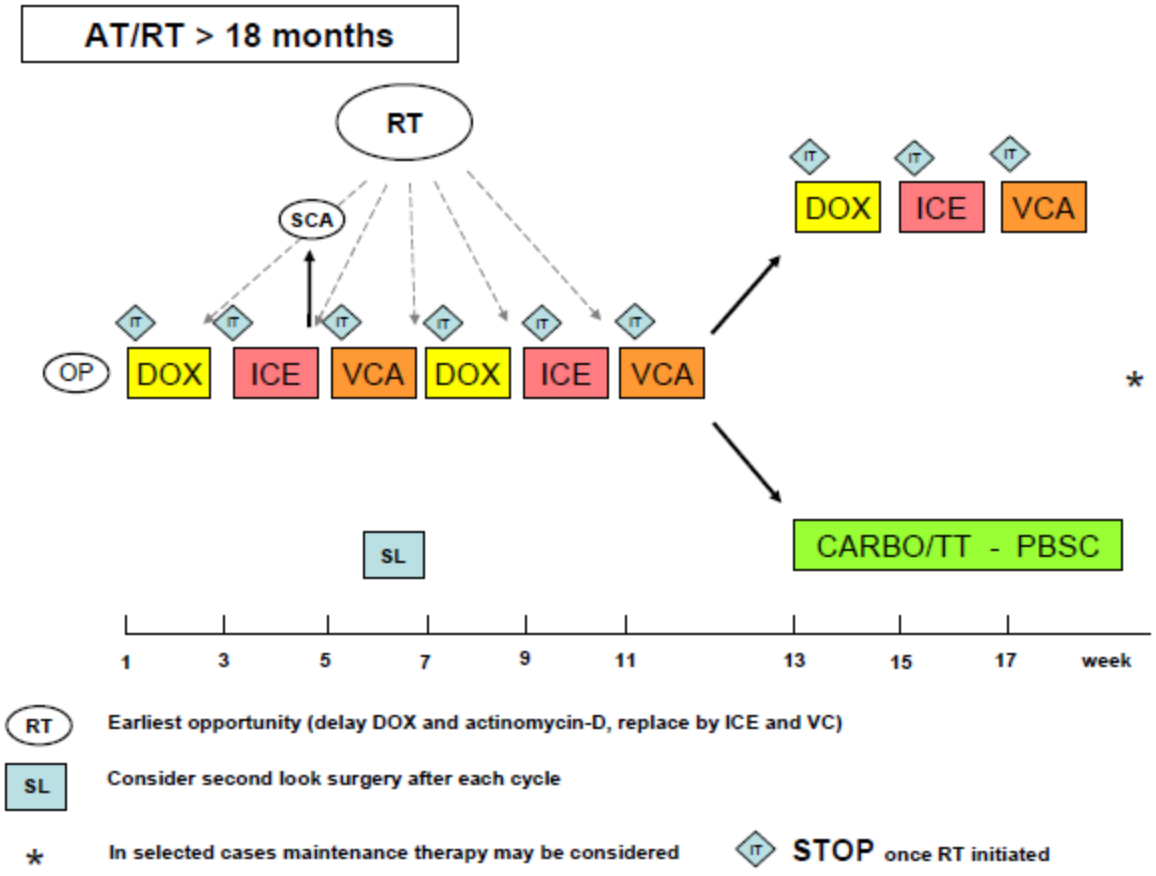
- Imaging of the primary tumor: ultrasound and MRI scan with measurement of tumor volume (for details see chapter I.2)
- Skeletal system: if available PET-CT, alternatively Tc bone scan, MRI of sites suspicious on bone scan (details see chapter I.2)
- Whole body MRI (see below)
- Cerebro-Spinal-Fluid: local pathology and reference evaluation (competence centre)

It is recommended that imaging is performed fewer than 28 days prior to the start of treatment. Documentation of the dimensions of the tumour is obtained. Data will be reviewed centrally (see below). Detailed guidelines for imaging, especially neuroradiologic imaging, are given below. Early postoperative imaging (24 – 48 hours after neurosurgery) will help delineate postoperative residual tumor from non-specific tissue changes associated with the operative procedure.

EU-RHAB

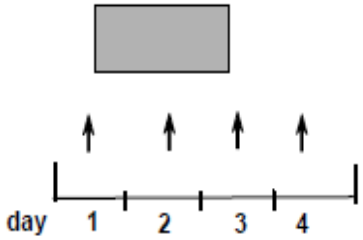

I.4.1 Schematic diagrams for chemotherapy
AT/RT < 18 months
RT
SCA
DOX
ICE
VCA
OP
DOX
ICE
VCA
DOX
ICE
VCA
*
SL
CARBO/TT - PBSZ
1
3
5
7
9
11
13
15
17
week
RT
Earliest opportunity, not in children below 18 months
(delay DOX and actinomycin-D, replace by ICE and VC)
SL
Consider second look surgery after each cycle
*
In selected cases maintenance therapy may be considered
STOP once RT initiated

EU-RHAB


AT/RT > 18 months
RT
SCA
OP
DOX
ICE
VCA
DOX
ICE
VCA
IT
DOX
ICE
VCA
*
SL
CARBO/TT - PBSC
1
3
5
7
9
11
13
15
17
week
RT
Earliest opportunity (delay DOX and actinomycin-D, replace by ICE and VC)
SL
Consider second look surgery after each cycle
*
In selected cases maintenance therapy may be considered
IT
STOP once RT initiated

EU-RHAB

DOX



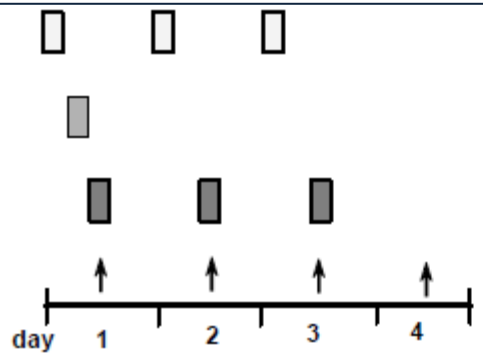
Doxorubicin (24h) 37,5 mg/m² x 2 = |__|__|__| mg

MTX i.ventr. = |__|__| mg

Dose : <2Y 2-3Y >3Y

MTX 0,5 1 2 mg
(CSF levels)

ICE



Ifosfamide p.i. (1h) 2000mg/m² x 3 = |__|__|__|__| mg/D
with MESNA:
2.000mg/m² with hydration 3.000ml/m2/d

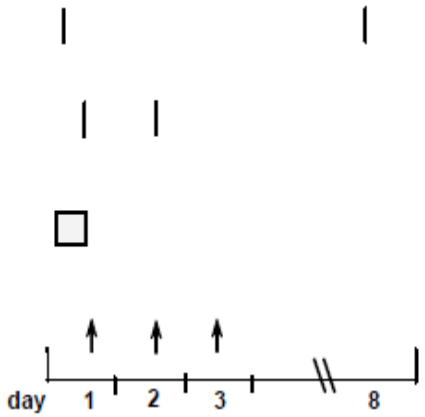
Carboplatinum (1h) 500mg/m² = |__|__|__| mg

Etoposide (1h) 100mg/m² x 3 = |__|__|__| mg/D

MTX i.ventr. = |__|__| mg

Dose : <2Y 2-3Y >3Y

VCA



VCR i.v. (max. 2mg) 1,5mg/m² x 2 = |__| , |__|__| mg

Act-D i.v. 25 µg/kg x 2 = |__| , |__|__| mg
Not during RT!

CPM p.i. (1h) 1500mg/m² = |__|__|__|__| mg
with MESNA:
day 1: 500 mg/m² bolus
day 1+2: 1500 mg/m² 24-h-Infusion

MTX i.ventr. = |__|__| mg

Dose : <2y 2-3y >3y

EU-RHAB

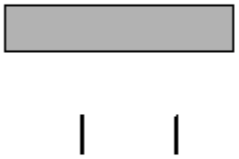
Weight	= _____	kg
Height	= _____	cm
BSA	= _____	m ²

AT/RT
High-dose: Carbo / Thio

Hospital:

Name: _____

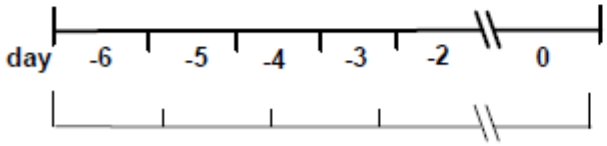
dob: _____



Carboplatinum 500mg/m²/d = |__|__|__| mg/d
day -6 to -4

Thiotepa 300 mg/m²/d 1 h = |__|__|__| mg/d
day -6 to -4

X **ASCT**



Please report CTC toxicity !!!

G-CSF: 150 µg/m²/d or 5 µg/kg/d s.c. day +5 until ANC > 1000/µl for 3 days

_____

HIGH-DOSE CHEMOTHERAPY (HDCT) WITH AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (APBSCT) IN CHILDREN WITH ATYPICAL TERATOID/RHABDOID TUMORS (AT/RT): A REPORT FROM THE EUROPEAN RHABDOID REGISTRY (EU-RHAB)

- 13 hasta (5 metastatik)
- Med follow-up 15 ay, 11 hasta da (85%) progresyon, 3 hasta yaşıyor
- 2 y. PFS %15, OS %38.
- Median progresyon süresi 11.3 ay.

Neuro Oncol (2012) 14 (suppl) 15th International Symposium on Pediatric Neuro-Oncology, June 24-27 2012 Toronto, Ontario, Canada

Güncel Tedavi ABD (NCI)

- **COG-ACNS0333**
- Combination Chemotherapy, Radiation Therapy, and an Autologous Peripheral Blood Stem Cell Transplant in Treating Young Patients With AT/RT of the CNS: phase III study for patients aged 0 to 21 years with AT/RT.

COG-ACNS0333

- < 36 ay - histoloji tipik
- <36 ay - tanı sadece INI1 mutasyonu ile (histoloji tipik değil)
- ≥ 36 ay –histoloji tipik
- ≥ 36 ay - tanı sadece INI1 mutasyonu ile (histoloji tipik değil)

COG-ACNS0333

Induksiyon tedavisi:

- VCR/ YD-MTX/ etoposide / cyclophosp /cisplatin (+G-CSF)
- 21 gün ara ile 2 kür
- Her kür sonrası periferik kök hücre topla

Değerlendirme

- Rezidu tm ⟶ sekond-look cerrahi

Konsolidasyon tedavisi ve kök hücre desteği (TANDEM):

- YDKT- carboplatin + thiotepa
- 28 günde bir 3 kür

RT

Hedeflenmiş tedavi

- INI1 ⟶ hücresel fonksiyonlar (proliferasyon-differans-migrasyon-invazyon)

Hedeflenmiş tedavi

Cyclin D1 ve CDK inhibitorleri (fenretinide, flavoperidol)

- Cyclin D1 ⟶ Rhabdoid hücre proliferasyonu
- INI1 ⟶ CD1 inaktivasyonu

  INI1 inaktivasyonu ⟶ CD1 aktivasyonu
- Flavopiridol invitro rhabdoid tm hücrelerine sitotoksik

  cyclin D1'de down-regulation ve p21'de up-regulation yapıyor

Flavopiridol rhabdoid tumor tedavisinde potansiyel ilaç

Smith ME, l. Rhabdoid tumor growth is inhibited by flavoperidol. Clin Cancer Res2008; 14: 523–532.

Hedeflenmiş tedavi

ErbB2-EGFR yolak inhibitorleri (small molecule lapatinib)

- Lapatinib ⟶ hücre migrasyonunu azaltıyor ve apopitosisi uyarıyor
- Xenograft çalışmaları ⟶ in vivo antitumor aktivite

Singh A. Profiling pathway-specific novel therapeutics in preclinical assessment for central nervous system atypical teratoid rhabdoid tumors (CNS ATRT): Favorable activity of targeting EGFR- ErbB2 signaling with lapatinib. Mol Oncol. 2013 Jan 11. doi:pii: S1574-7891.

Hedeflenmiş tedavi

Histone deacetylase inhibitorleri

Atipik teratoid/rhabdoid tumor hücrelerinin

- proliferasyonunu azaltıyor
- ionize radyasyonun etkisini artırıyor

Neuro Oncol. 2012 Feb;14(2):175-83.

Özet

- İnfantlarda sık ve çok maliyn
- Tanımak önemli, daha agresif tedavi gerekir (INI bakılmalı)
- Multi-model agresif tedavi (Cerrahi+KT+RT)
- multi-ajan kemoterapi -Sarkom tipi tedavi (ICE, alkilleyiciler)
- Intratekal – intraventrikuler (omaya ile)tedavi
- Yüksek doz KT + Kök hücre desteği !!!! (daha çalışılmalı- Sadece KT'nin agresifliği yeterli değil)
- Hedeflenmiş tedavi (hedef var-umut vadediyor)
- Güncel tedavi ile bile prognoz kötü, sekel çok

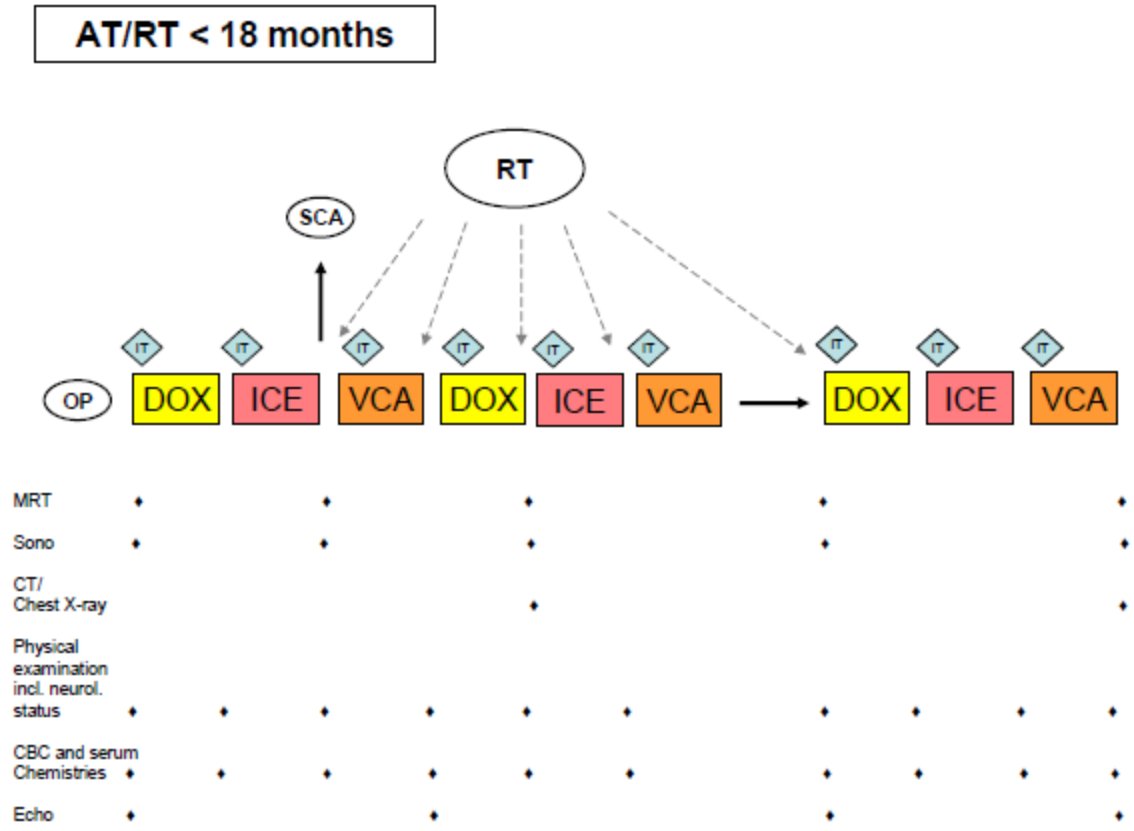


Figure I.1: AT/RT < 18 months, conventional therapy

AT/RT < 18 months

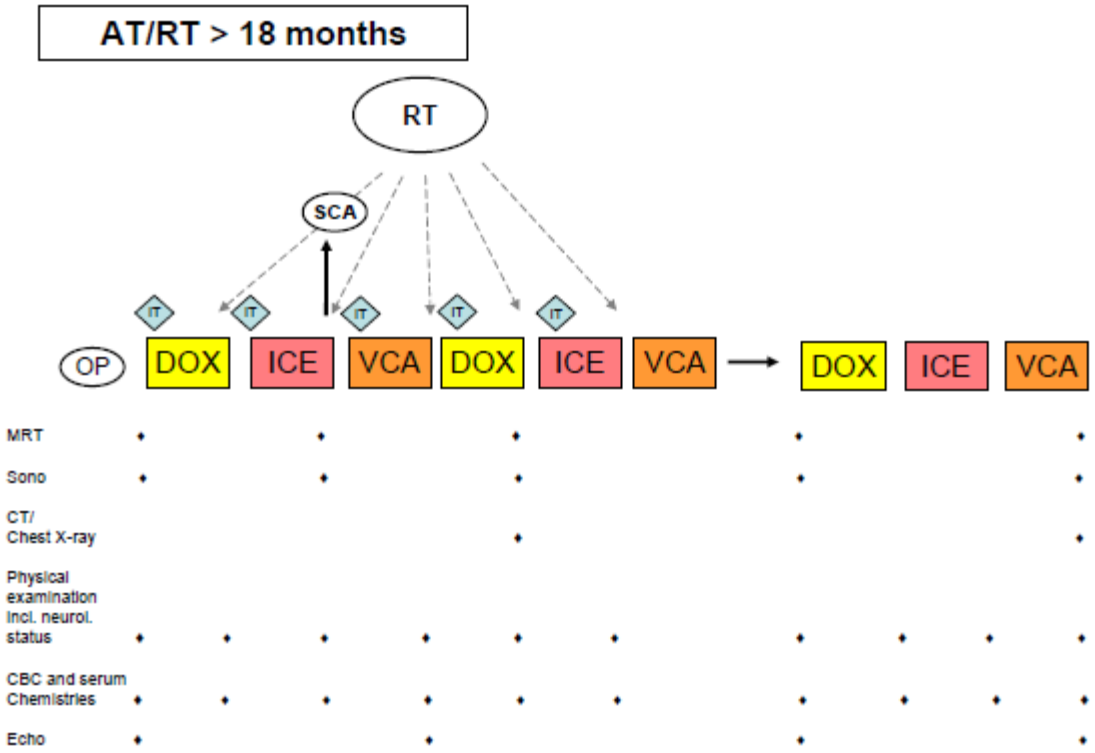
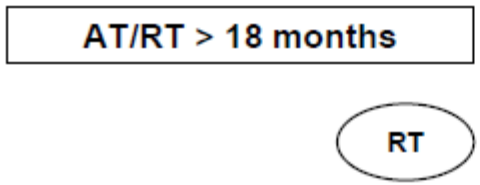


Figure I.3: AT/RT > 18 months, conventional therapy



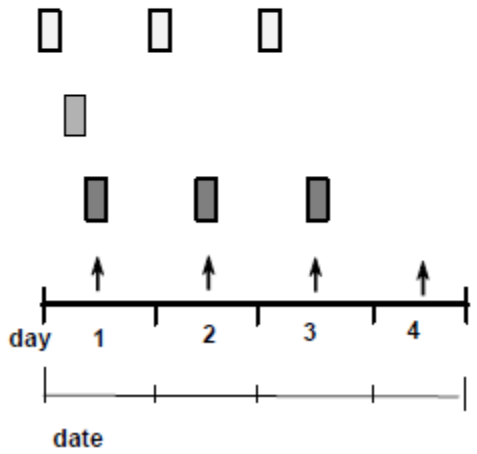
Weight = _____ kg
Height = _____ cm
BSA = _____ m^2

ICE (AT/RT)

Hospital:

Name: _____

dob: _____



Ifosfamide p.i. (1h) 2000mg/m^2 x 3 = |__|__|__|__| mg/D
with MESNA:
2.000mg/m^2 with hydration 3.000ml/m2/d

Carboplatinum (1h) 500mg/m^2 = |__|__|__| mg

Etoposide (1h) 100mg/m^2 x 3 = |__|__|__| mg/D

MTX i.ventr. = |__|__| mg

Dose :	<2Y	2-3Y	>3Y
MTX (CSF levels)	0,5	1	2 mg

VCA (AT/RT)

Weight	= _____	kg
Height	= _____	cm
BSA	= _____	m ²

Hospital:

Name: _____

dob: _____

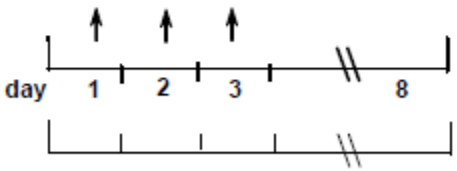
VCR i.v. (max. 2mg) 1,5mg/m² x 2 = |__| , |__|__| mg

Act-D i.v. 25 µg/kg x 2 = |__| , |__|__| mg
Not during RT!

CPM p.i. (1h) 1500mg/m² = |__|__|__|__| mg
with MESNA:
day 1: 500 mg/m² bolus
day 1+2: 1500 mg/m² 24-h-infusion

MTX i.ventr. = |__|__| mg

Dose :	<2y	2-3y	>3y
MTX (CSF levels)	0,5	1	2 mg



date

Dose reduction in children < 6 months or < 10 kg!
Dose in mg/kg: (Dose/m² divided by 30 x kg BW)

Please report CTC toxicity !!!

_____

signature

Send copy to local study centre or