Primary CNS Lymphoma (PCNSL)

Is an aggressive malignancy arising exclusively in the CNS

- **brain parenchyma**
- **spinal cord**
- **eyes**
- **cranial nerves and/or**
- **meninges**

PCNSL

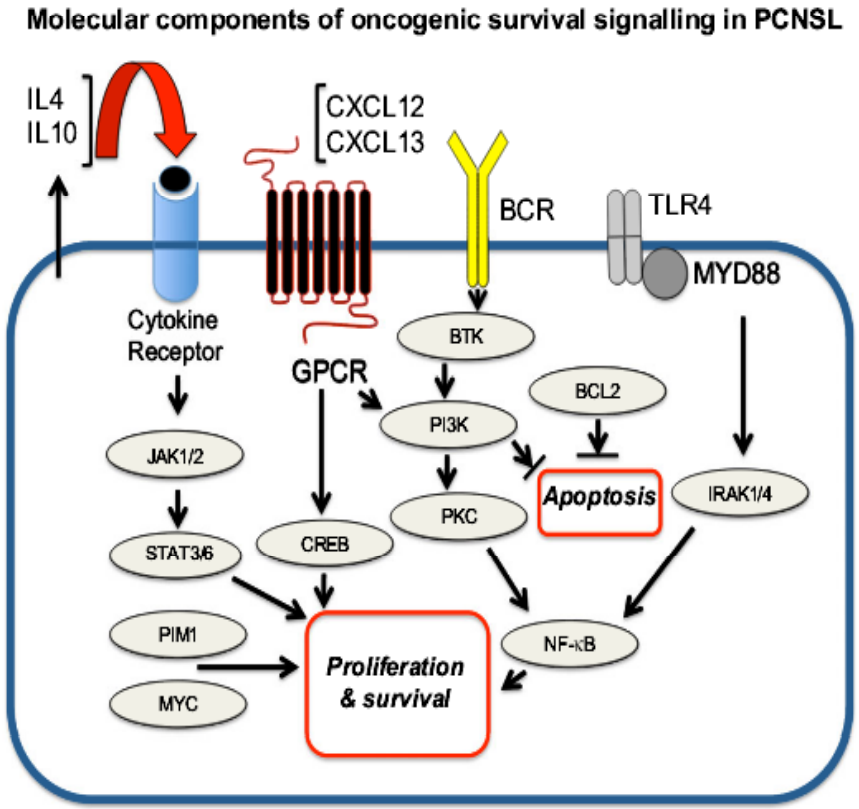


Fig 1. Molecular components of oncogenic survival signalling in primary central nervous system lymphoma. Notably, activation of the TLR/MYD88 pathway may directly contribute to pro-survival signalling via NFκB as well as via enhanced secretion of IL10, which probably promotes pro-survival signals via the JAK/STAT pathway. GPCR, G protein-coupled receptor.

British Journal of Haematology, 2014, **166,** 311–325

PCNSL

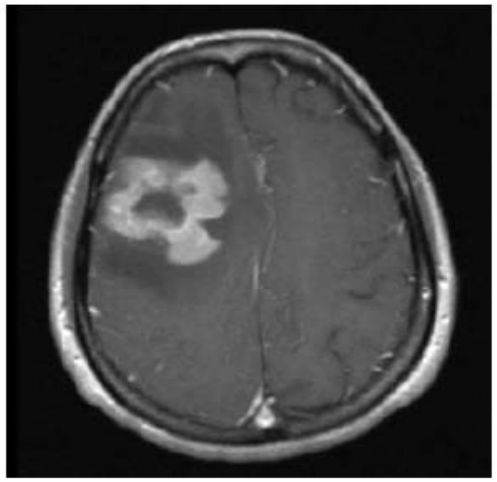
Epidemiology:

- 0,5 / 100 000 / year
- 1 - 2 % of all extranodal NHL
- 4 to 7 % of newly diagnosed primary CNS tumors
- increasing incidence - more than ten-fold over the past three decades
- Median age: 61 ys.

PCNSL

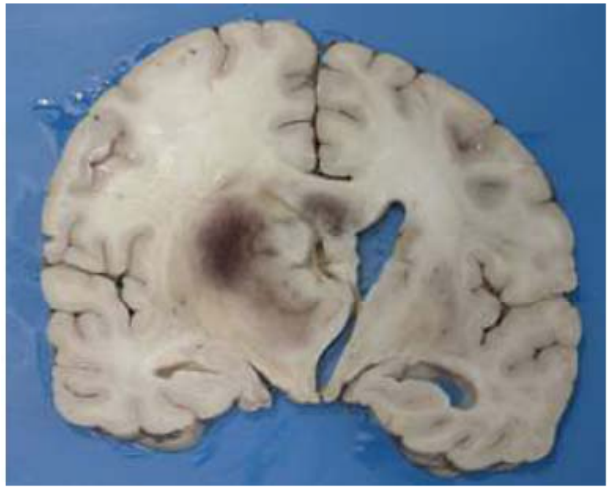
Clinical Presentation:

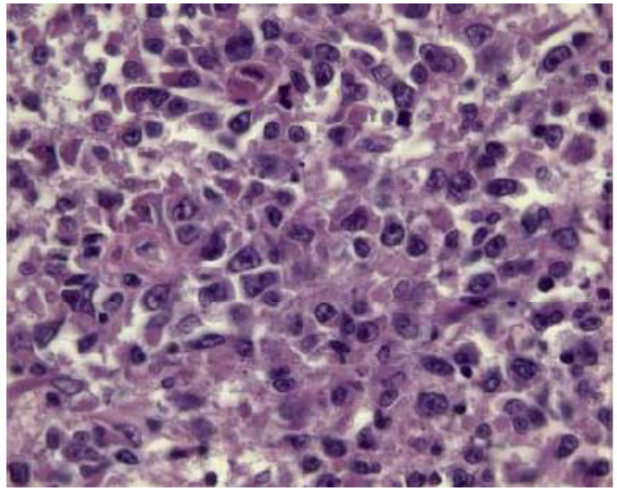
- History of 3 - 7 months
- Personality changes
- neurocognitive impairment (dementia…)
- focal neurologic deficits
- intracranial pressure, headache, nausea…



PCNSL

> 90% DLBCL; T-NHL, low grade B-NHL < 5%

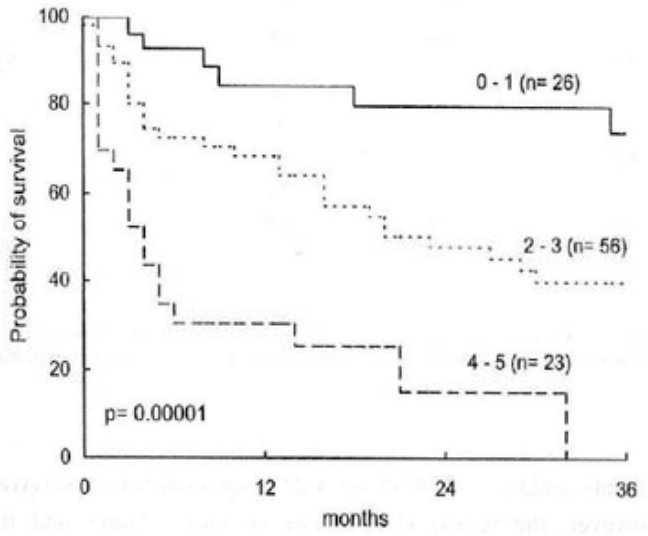




PCNSL

Risk Factors I

- Age > 60
- ECOG > 0
- LDH > n
- CSF-protein > n
- deep brain lesions
- N = 105



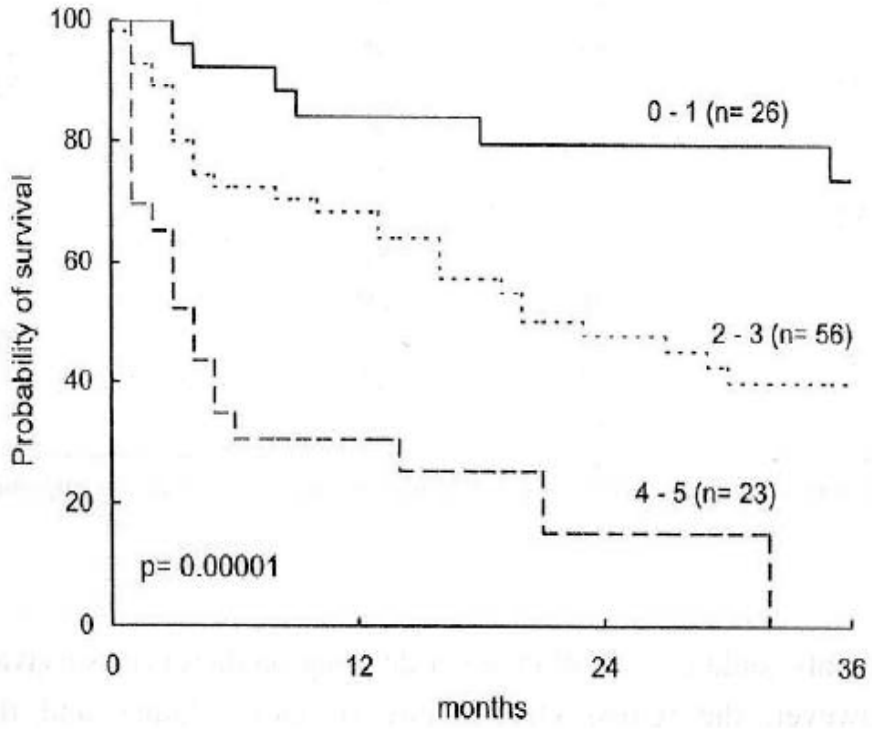
(Ferreri et al., Journal of Clin Onc 2003)

Cooperative Study Group CNS-Lymphoma

Klinikum Stuttgart

Risk Factors I

- Age > 60
- ECOG > 0
- LDH > n
- CSF-protein > n
- deep brain lesions
- N = 105



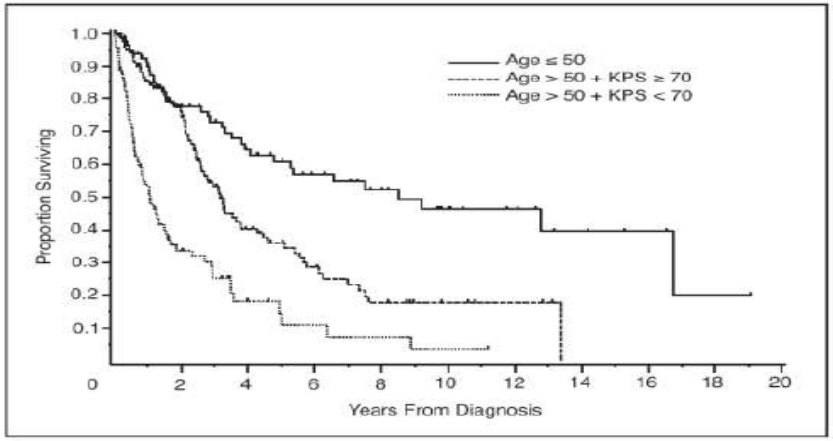
(Ferreri et al., Journal of Clin Onc 2003)

PCNSL

Risk Factors II

- Age > 50 years
- KPS < 70 and age >50

- N=338



(Abrey et al., Journal of Clin Onc 2006)

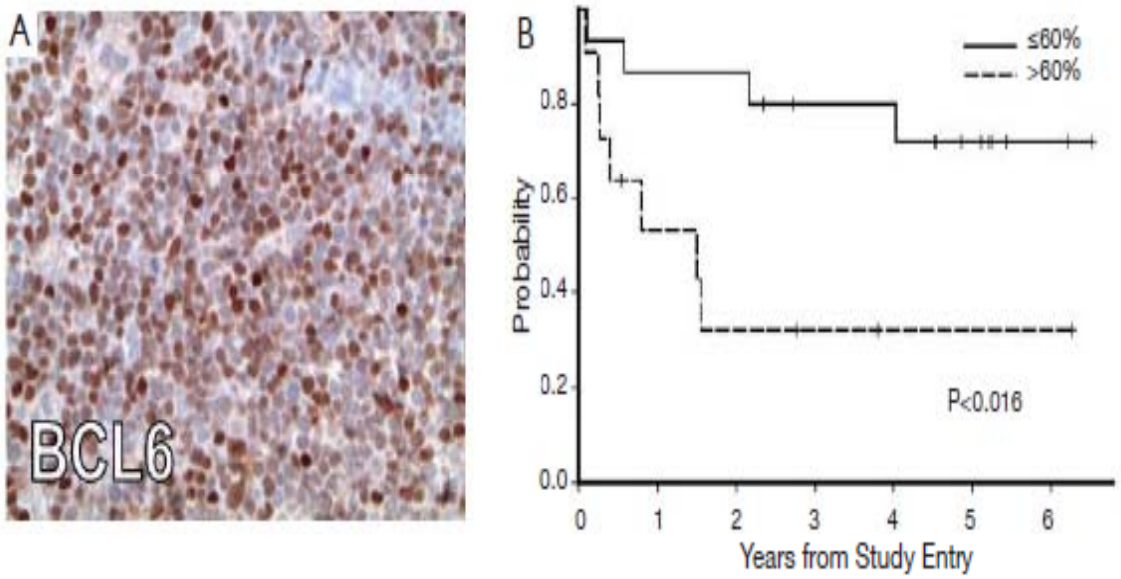


Figure 1 BCL6 expression is associated with shorter progression-free and overall survival in PCNSL patients treated in the CALGB 50202 study. (A) Strong nuclear BCL6 expression in a PCNSL case from patient treated on study (40× magnification); (B) high BCL6 expression (60% of lymphoma nuclei) was associated with shorter progression-free survival ($P<0.016$). High BCL6 was also associated with shorter overall survival ($P<0.009$).

PCNSL-DIAGNOSIS

» CSF examination

Lymphomas cells(50% sensitivity)

II

Biopsy – Gold Standard

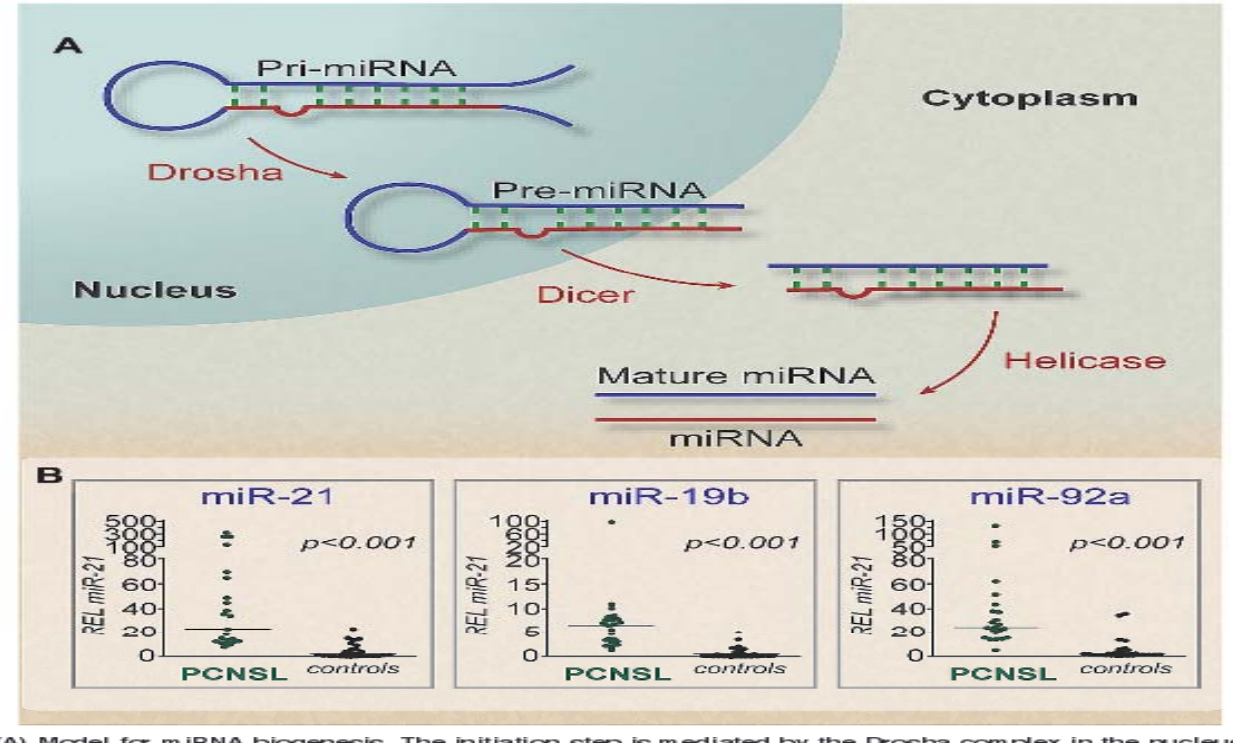
PCNSL-delayed diagnosis

Neurological sciences 2016

Diagnostic delay and prognosis in primary central nervous system lymphoma compared with glioblastoma multiforme

R. Cerqua, S. Balestrini , C. Perozzi, V. Cameriere, S. Renzi, G. Lagalla, G. Mancini, M. Montanari, P. Leoni and 5 more

PCNSL-biomarker better than biopsy?



PCNSL-biomarker

- miR-21
- miR-19 sensitivity 96% specificity 97%
- miR-92a

Have diagnostic value in distinguishing PCNSL from inflammatory CNS diseases and other neurologic disorders

PCNSL

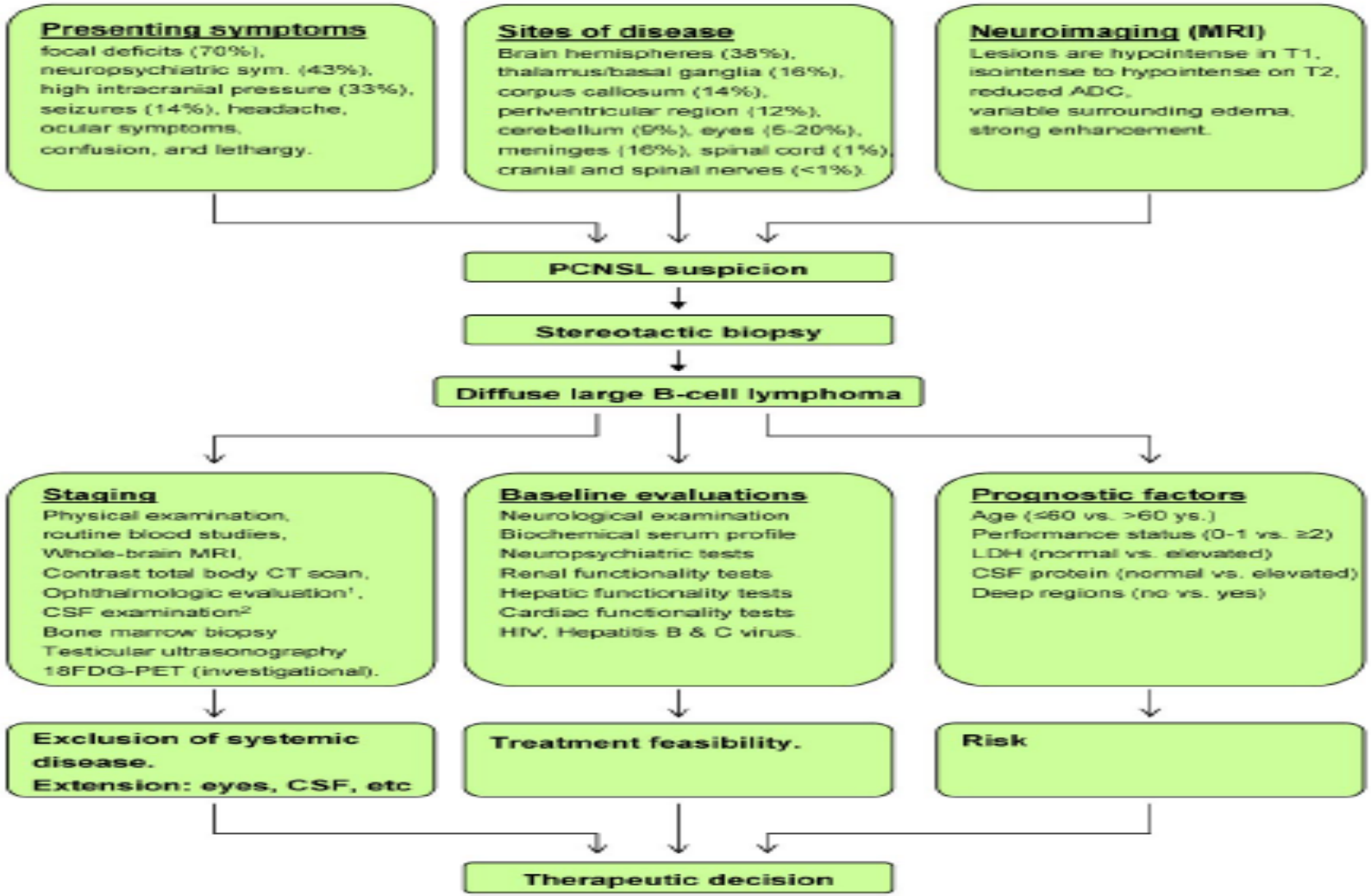


Figure 1. Flow chart of management of PCNSL from presentation to therapeutic decision in ordinary clinical practice. MRI indicates magnetic resonance imaging; CT, computerized tomography; CSF, cerebrospinal fluid; LDH, lactate dehydrogenase serum level; and ADC, average diffusion coefficient. Deep regions refers to basal ganglia, corpus callosum, periventricular areas, brain stem, and/or cerebellum. (1) Ocular examination should include slit-lamp examination, indirect ophthalmoscopy,and ophthalmic ultrasonography. (2) Cerebrospinal fluid evaluation should include cell counts, protein and glucose levels, cytology, flow cytometry, and IgH-IV gene rearrangement studies.

PCNSL

Special issues in PCNSL:

- aggressive lymphoma entity with a unique localisation
- the surrounding brain tissue is highly vulnerable
  → risk of leukencephalopathy (from disease / from therapy)
- aggressive lymphoma is a systemic disease
  → need for systemic therapy
- effective regimens for systemic lymphoma (i.e. CHOP) do not work in PCNSL

PCNSL

Special issues in PCNSL II:

- Local therapy without (long-term) benefit
- Whole brain radiotherapy – highly effectice, med OS appr. 18mo
- MTX alone effective - but most patients relapse
- Polychemotherapy more effective - more toxic

  → not always more effective

PCNSL

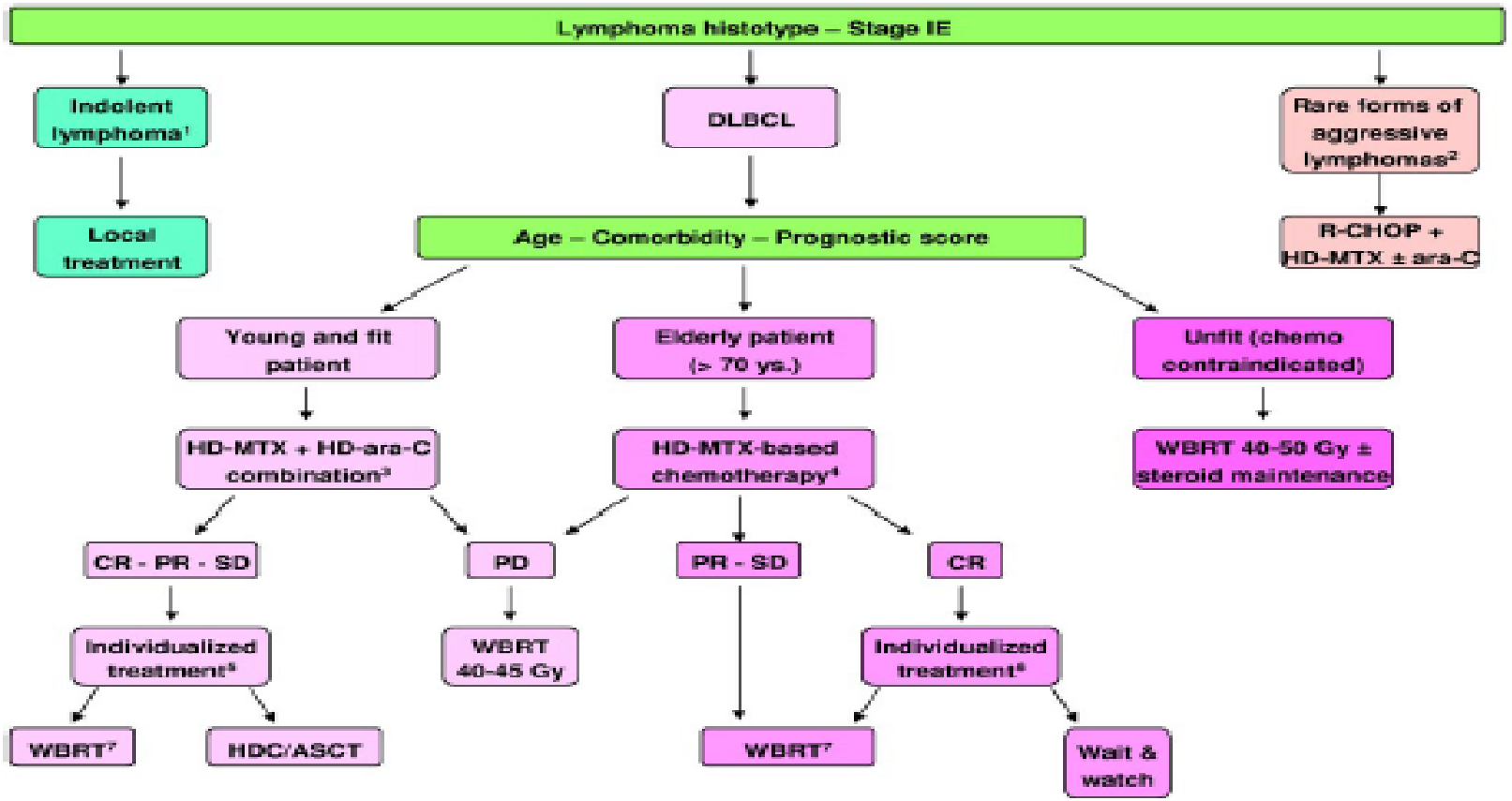


Figure 4. Flow chart of therapeutic management of PCNSL in everyday practice. (1) Mostly marginal zone B-cell lymphoma, small lymphocytic lymphoma, and lymphoplasmacytic lymphoma. (2) Mostly intravascular large B-cell lymphoma and neurolymphomatosis. (3) Conclusion from the IELSG no. 20 trial.[45] (4) Several regimens are available (Table 3). (5) A higher amount of available evidence suggests WBRT. The discussion with selected patients about the pros and cons of the use of consolidation WBRT or HDC/ASCT is recommended. (6) Available literature suggesting that some elderly patients in CR after primary chemotherapy could be watchful waited without OS impairment is constituted by a few small retrospective series. However, to delay WBRT until relapse is an acceptable strategy considering the increased risk of disabling neurotoxicity in these patients. (7) Radiation field and dose should be chosen on the bases of response to primary chemotherapy. WBRT dose reduction to 23-30 Gy in patients in CR after chemotherapy is recommended. DLBCL indicates diffuse large B-cell lymphoma; HD-MTX, high-dose methotrexate; ara-C, cytarabine; WBRT, whole-brain radiotherapy; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; and HDC/ASCT, high-dose chemotherapy supported by autologous stem cell transplantation.

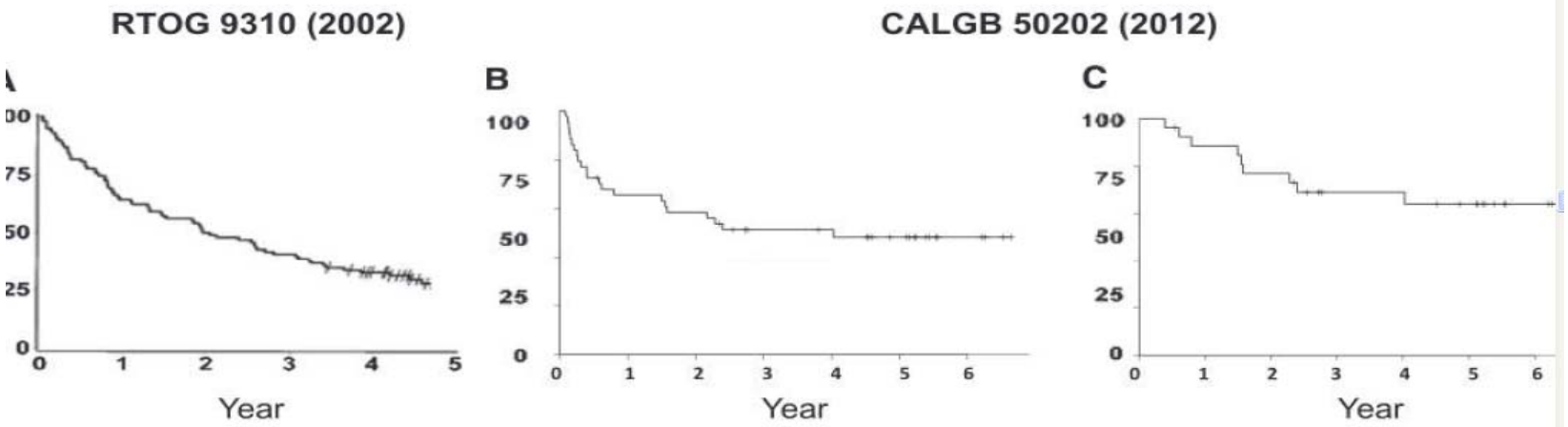
CNS-NHL THERAPY

Table 1 Trials in PCNSL that resulted in progression-free survival ≥2 years

Regimen	Reference	No. Pts	Median PFS	Median OS
MTX 2.5 g/m^2, PCB, Vinc, IT-MTX, WBRT	DeAngelis *et al*. (77)	98	24	37
MTX 8 g/m^2, TMZ, Ritux, Etop, Ara-C	Wieduwilt *et al*. (10)	31	24	66
MTX 8 g/m^2, TMZ, Ritux, Etop, Ara-C	Rubenstein *et al*. (12)	44	48	NR
MTX 3.5 g/m^2, Ritux, PCB, Ara-C, rd-WBRT	Morris *et al*. (68)	52	39	79

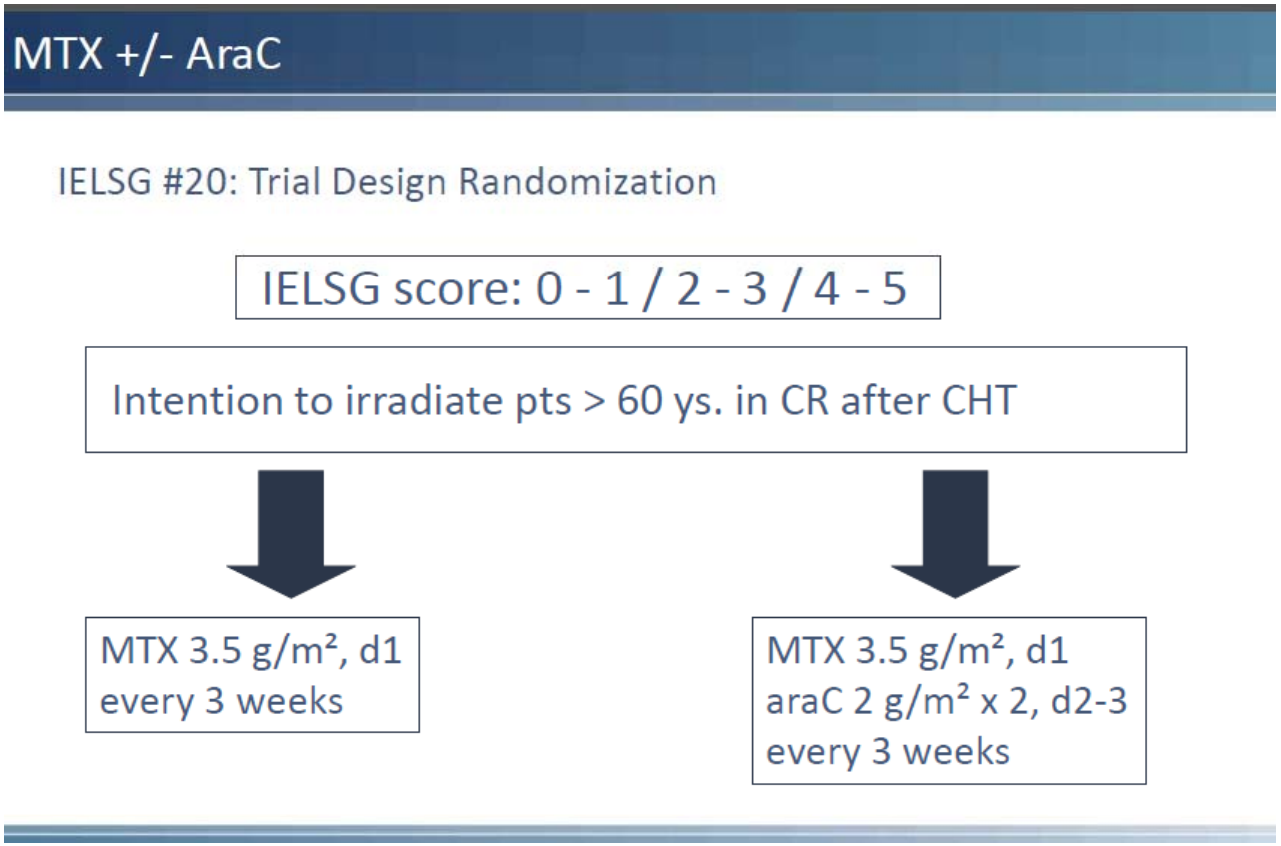
MTX, methotrexate; Pcb, procarbazine; Vinc, vincristine; IT-MTX, intrathecal methotrexate; WBRT, whole brain radiotherapy; temozolomide; ritux, rituximab; Etop, etoposide; Ara-C, cytarabine; rd-WBRT, reduced dose whole brain radiotherapy; NF reached.

CNS NHL



gure 5. Progress in the treatment of PCNSL. Comparison of outcomes for newly diagnosed PCNSL in 2 multicenter cooperative group clinical trials. (A) Comb odality therapy with whole-brain radiotherapy in RTOG-9310 resulted in median progression-free survival of 2 years, with a significant rate of disease progression beyo ars. (B) Immunochemotherapy with rituximab plus intensive consolidation—CALGB (Alliance) 50202—resulted in a median progression-free survival of 4 years vidence for a stable plateau in the survival curve. (C) Progression-free survival was particularly encouraging for the 65% of patients who received both induction nsolidation treatment modules of CALGB (Alliance) 50202.

PCNSL TREATMENT



PCNSL TREATMENT

MTX +/- AraC

Tolerability	Methotrexate (n=40)	Methotrexate+cytarabine (n=39)	p value
Toxic deaths	1 (3%)	3 (8%)	0·35
Neutropenia	6 (15%)	35 (90%)	0·00001
Thrombocytopenia	3 (8%)	36 (92%)	0·00001
Anaemia	4 (10%)	18 (46%)	0·00001
Infective complications	1 (3%)	9 (23%)	0·0002
Hepatotoxicity	1 (3%)	4 (10%)	0·05
Nephrotoxicity	2 (5%)	1 (3%)	0·31
GI/mucositis	2 (5%)	1 (3%)	0·31
Cardiotoxicity	1 (3%)	1 (3%)	0·87
Neurotoxicity	0	1 (3%)	0·29
Coagulation/DVT	4 (10%)	1 (3%)	0·002

The worst toxicity per organ, per patient was considered for analyses. GI=gastrointestinal. DVT=deep venous thrombosis.

Table 2: **Grade 3–4 toxic effects per treatment group**

Ferreri et al. Lancet 2009

PCNSL TREATMENT

MTX +/- AraC

Activity

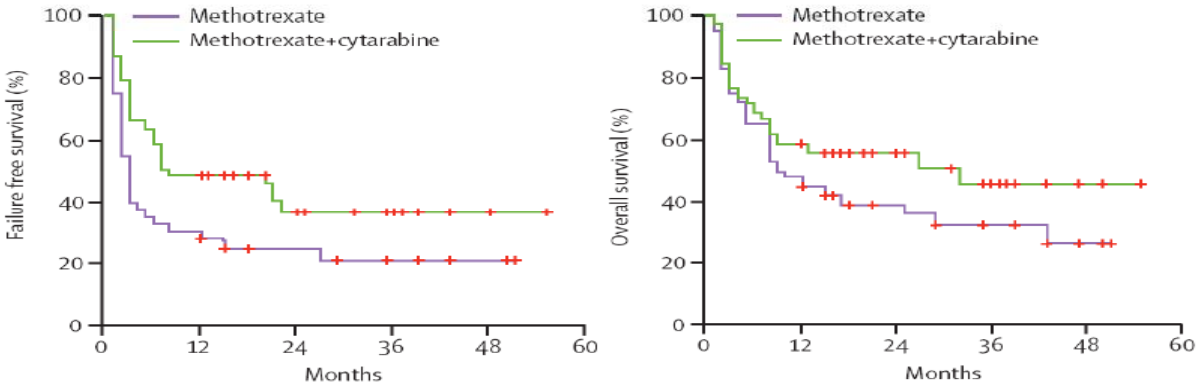
	Methotrexate (n=40)	Methotrexate+cytarabine (n=39)	p value
Complete remission	7 (18%)	18 (46%)	0·006
Partial response	9 (23%)	9 (23%)	..
Overall response	16 (40%)	27 (69%)	0·009
Stable disease	1 (3%)	2 (5%)	..
Progressive disease	22 (55%)	7 (18%)	..
Toxic deaths	1 (3%)	3 (8%)	0·35

Ferreri et al. Lancet 2009

PCNSL TREATMENT

MTX +/- AraC

IELSG #20: Survival Curves

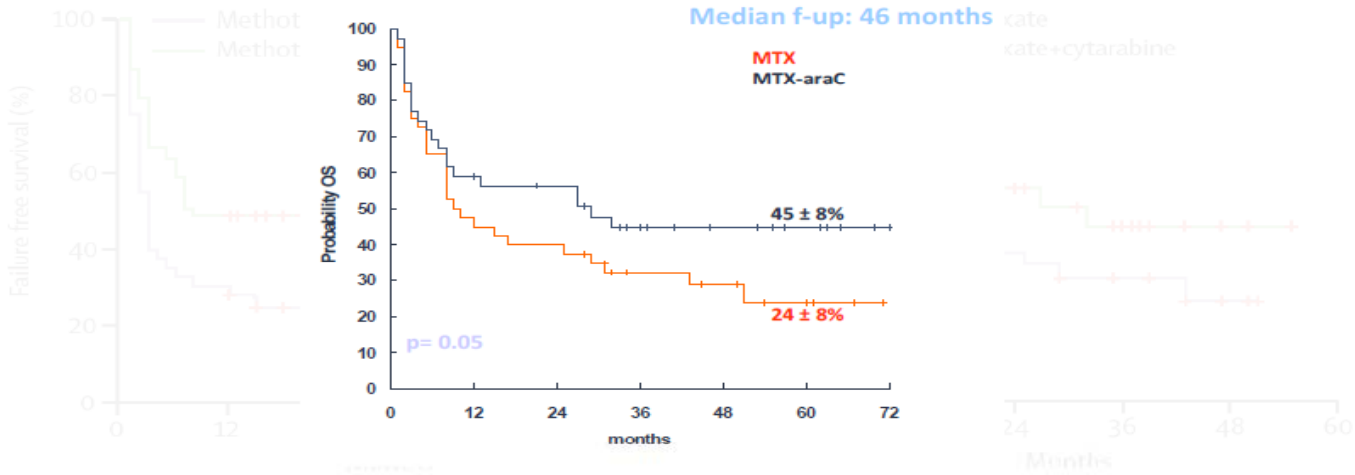


Ferreri et al. Lancet 2009

PCNSL TREATMENT

MTX +/- AraC

IELSG #20: Survival Curves



PCNSL

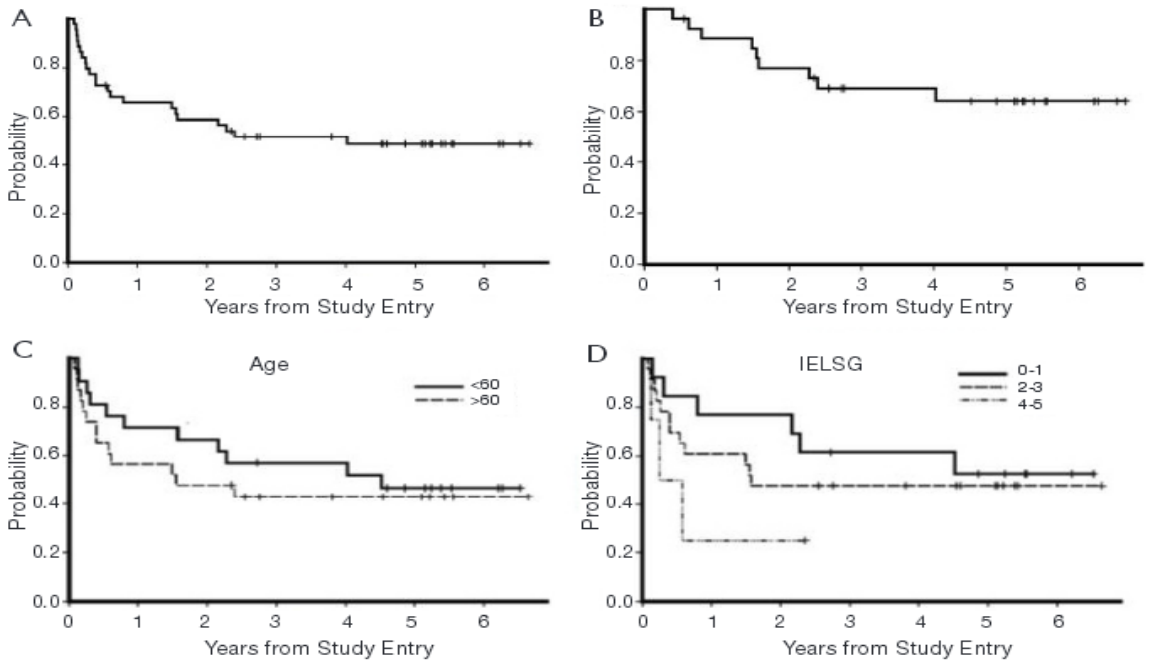


Figure 3 Outcomes with intensive chemotherapy and immunotherapy in newly-diagnosed PCNSL, without WBRT: CALGB (Alliance) 50202. (A) Outcome for all 50,202 patients; y-axis refers to probability of event, PFS for all patients, the 2-year PFS was 59%; (B) PFS for patients who attained a complete response with MT-R induction and received EA consolidation (n=27); (C) PFS was similar for patients age >60 (n=23) and for younger patients (n=21; P=0.48); (D) there was a trend between shorter PFS and higher IELSG risk score of 4–5 (P=0.16)

PCNSL

Treatment Strategies

High-Dose Chemotherapy in PCNSL

PCNSL TREATMENT

High-Dose Chemotherapy in PCNSL

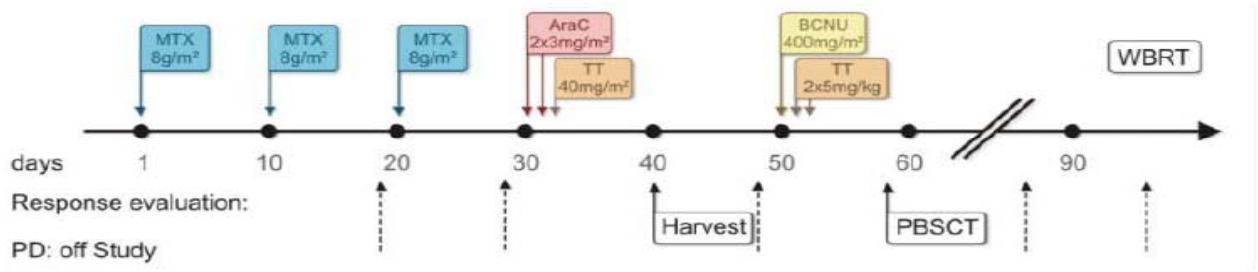
Background

- High-dose-MTX (>3g / ≤4h) + AraC +/- WBRT old / new **"gold-standard" for PCNSL** → long-term survival appr. 40-50%
- Intensive chemotherapy (BCNU / thiotepa / busulfan / melphalan….) is expected to deliver **adequate cytotoxic levels** CSF / brain
- **Objective: to eradicate residual lymphoma cells** systemically and behind the BBB → HDT as **CONSOLIDSATION**

PCNSL TREATMENT

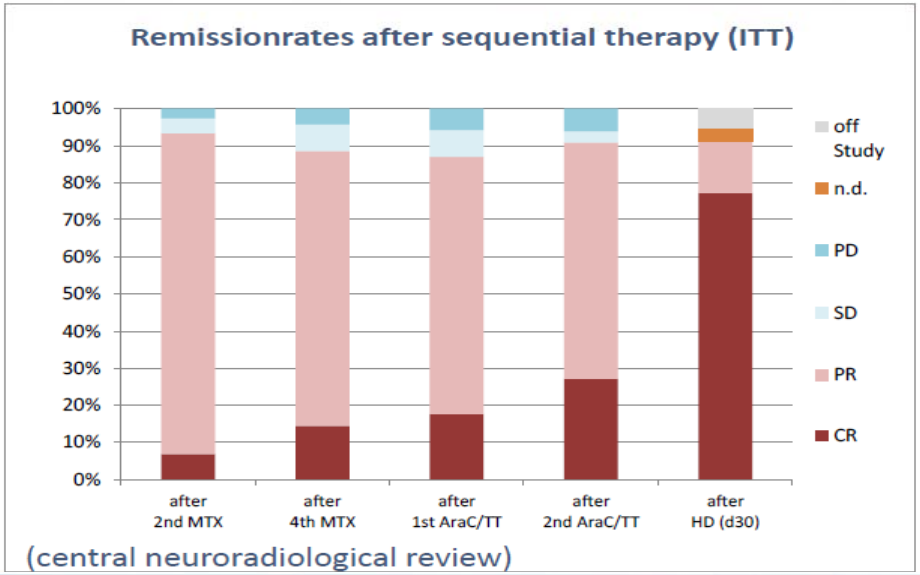
High-Dose Chemotherapy in PCNSL

HDT and ASCT - "Freiburg I" (1998-2003)



PCNSL TREATMENT

High-Dose Chemotherapy in PCNSL



PCNSL TREATMENT

High-Dose Chemotherapy in PCNSL

What did we learn from this pilot trial (Freiburg II)?

- High-Dose Chemotherapy in PCNSL is feasible and safe

Open questions:

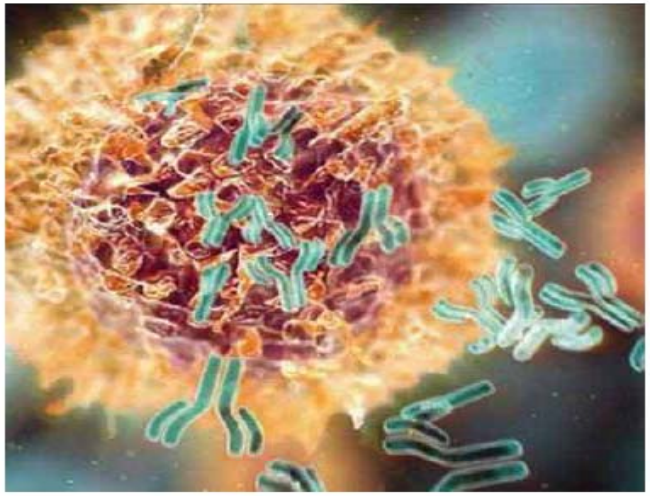
- Is WBRT restrictable to pts not in CR after HDT?
- Can we improve the inducion treatment?
- Is there a role for Rituximab?

PCNSL TREATMENT

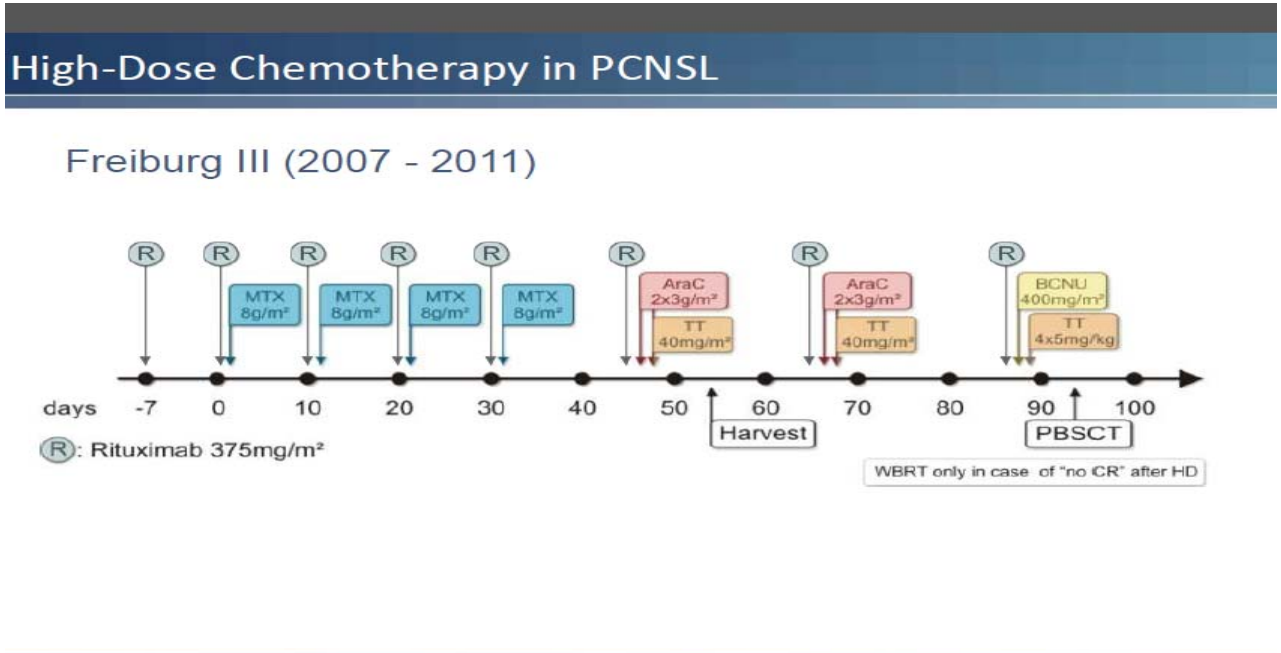
Antibodies

Rituximab - open questions:

- passage through BBB?
- how much is necessary in the CNS compartement?
- efficacy as single drug in PCNSL!



PCNSL TREATMENT



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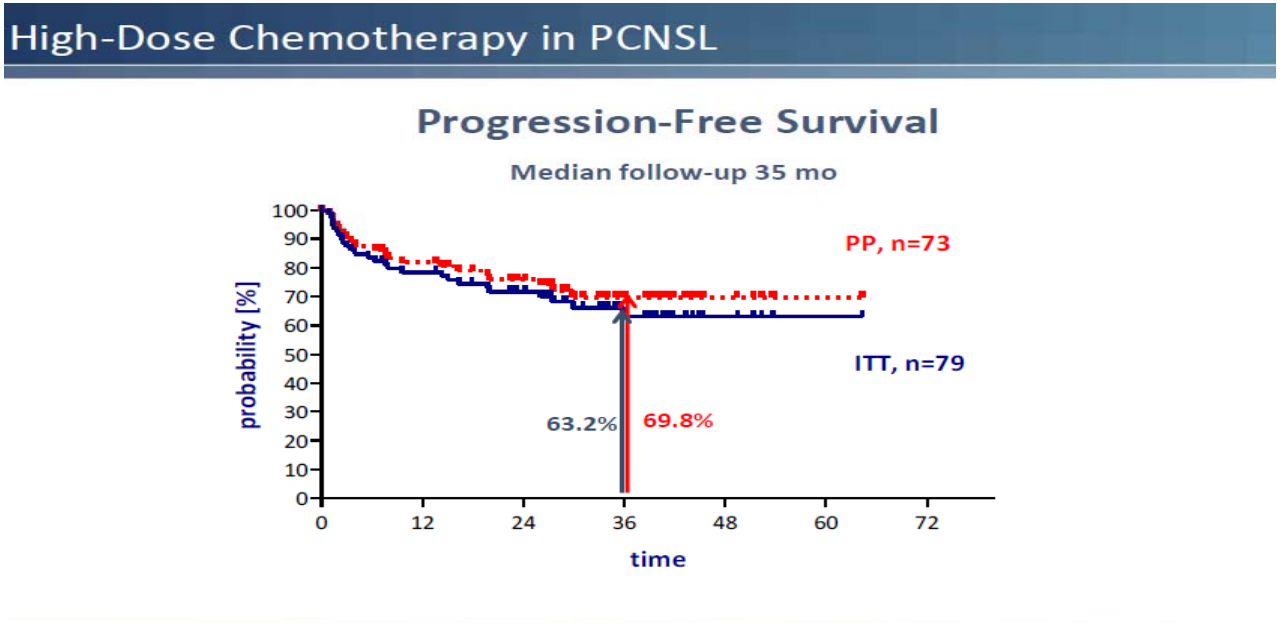
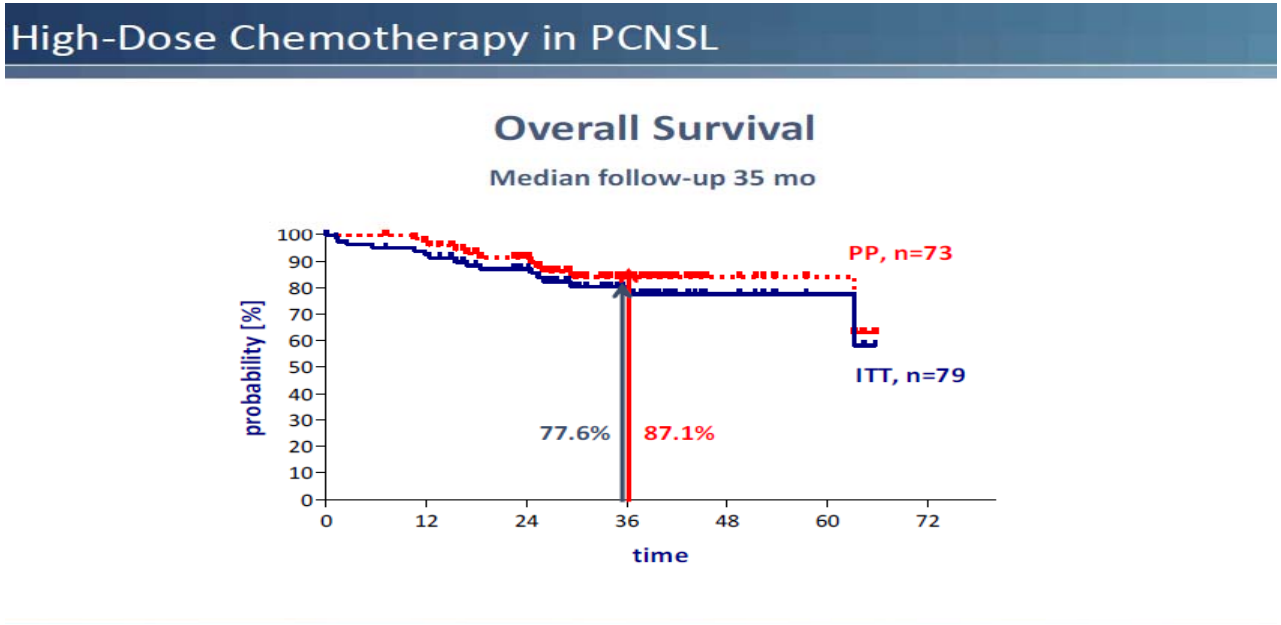


PCNSL TREATMENT



PCNSL

Conclusion

- Thiotepa based high-dose chemotherapy for PCNSL is highly effective (98% ORR, 3y OS 87%)
- Manageable toxicity
- WBRT may not be needed in 1st line treatment
- The role of consolidating WBRT vs. HDT and PBSCT has to be determined → IELSG32-Trial
- Inducion treatment could be more effective

PCNSL

PCNSL must be treated „as hard as possible“

- Early intensive inducion with MTX / AraC + R?
- Consolidation with Thiotepa based Condtioning

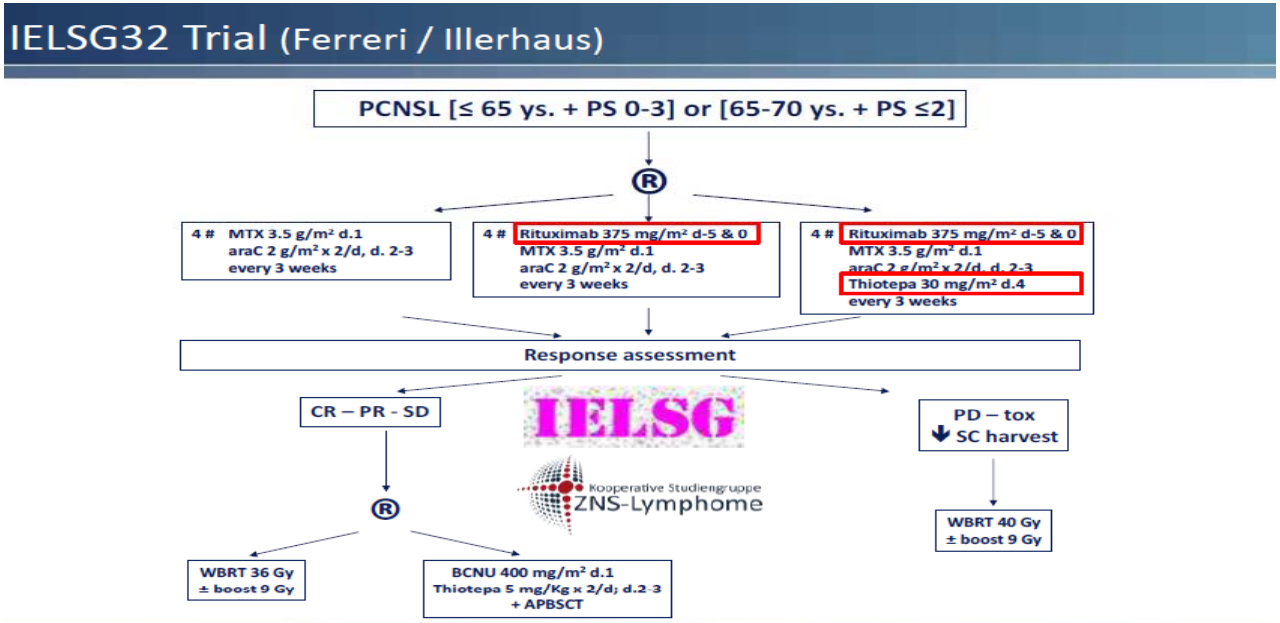
→ may produce long term survival in most patients

Current and future trials try to answer the role of

HDT vs. WBRT

HDT vs. conventional consolidation

PCNSL-Treatment



PCNSL

Table 3 Recent and active randomized controlled trials for PCNSL

Trial	Regimen	Status
G-PCNSL-SG1	HD-MTX-based induction +/– WBRT consolidation	Thiel *et al.* (81)
IELSG-20	HD-MTX +/– HD-Ara-C- > WBRT consolidation	Ferreri *et al.* (80)
IELSG-32	Myeloablative *vs.* WBRT consolidation	Accrual complete
Alliance 51101	Intensive *vs.* myeloablative consolidation	Active
PRECIS	Myeloablative *vs.* WBRT consolidation	Active
Matrix/IELSG43	Intensive *vs.* myeloablative consolidation	Active

CALGB (Alliance) 51101 compares dose-intensive consolidation with infusional etoposide plus high-dose cytarabine (EA) with high-dose chemotherapy (BCNU plus thiotepa), supported by autologous stem cell transplant (7). The MATRIX/IELSG43 evaluates high-dose chemotherapy, BCNU plus thiotepa supported by autologous stem cell transplant in comparison to a dose-intensive consolidation regimen consisting of dexamethasone, etoposide, carboplatin and ifosfamide). HD-MTX, high-dose methotrexate; WBRT, whole brain radiotherapy; Ara-C, cytarabine.

CNS NHL THERAPY

able 3. Therapeutic approaches for intraocular lymphoma

herapy	Efficacy	Toxicity	Reference
cular XRT (30-40Gy) Wash U Protocol − 35 Gy	Rare local recurrence 60-95% RR; no impact on OS	Cataracts, dry eyes, retinopathy (mild)	Berenbom et al, 200
D-MTX	; 50% sustained response, poor vitreous penetration	Mild	Batchelor et al, 200
D-MTX + Binocular XRT (± overlap)	100% CR	Cataracts, dry eyes, retinopathy	Stefanovic et al, 201
tensive chemo (EA) + ASCT (TBC)	>50% patients respond to EA; 6/10 CR	Neurologic toxicity, hemorrhage, VOD	Soussain et al, 2001
travitreal rituximab (1 mg) or MTX (200 mcg) in 0.1 mL	Requires >6 injections to achieve CR; investigational	Conjunctival keratopathy, cataracts, optic atrophy, endophthalmitis	Itty and Pulido, 200 Kim et al, 2006[11]

TBC, thiotepa, busulfan, cyclophosphamide; VOD, venoocclusive disease.