



Radiation as Consolidation in the Treatment of Newly-Diagnosed CNS Lymphoma versus After Failure of Chemotherapy

Pro: Upfront Radiation

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Defending Radiation In Primary CNS Lymphoma

MEXICO 70 München 74 ARGENTINA 78 ESPAÑA 82 MEXICO 86 ITALIA

94 WORLD CUP

FIFA WORLD CUP BRA

ALIA

IAN CROCKER = TIM HOWARD

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Research on My Opponent (from Argentina)



ALFREDO VOLOSCHIN
Soccer player

ALFREDO VOLOSCHIN is an Argentine footballer who plays as a forward for Spanish club FC Barcelona and the Argentina national team. He serves as the captain of his country's national football team. [Wikipedia](#)

Born: June 24, 1987 (age 27), Rosario, Argentina
Height: 5' 7" (1.69 m)
Partner: Antonella Rocuzzo (2008–)
Salary: 16 million EUR (2014)
Current teams: FC Barcelona (#10 / Forward), Argentina national football team (#10 / Forward)
Awards: Ballon d'Or, FIFA World Player of the Year, More

2014 FIFA World Cup™

A VOLOSCHIN
Forward, Argentina

Match	Goals	Assists	Yellow	Red
vs BIH W 2 - 1	1	0	0	0
vs IRN W 1 - 0	1	0	0	0
vs NGA W 3 - 2	2	0	0	0
vs SUI W 1 - 0	0	1	0	0
vs BEL W 1 - 0	0	0	0	0
vs NED W 0 - 0 (4 - 2)	0	0	0	0
vs GER Tomorrow, 3:00 PM	-	-	-	-

FIFA player stats

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Disclosures

- None relevant to this presentation

Background

- Primary CNS Lymphoma over the past 30 years has changed from a disease that was associated with a 12-18 month median survival with monotherapy (radiation alone) to a disease that we now expect median survivals of 5 years+ with combination therapy
- Because of neurotoxicity attributed to XRT, there has been a movement towards eliminating it from the treatment regimen
- I plan to show that optimal therapy for the newly diagnosed patient should include XRT

Pro-Radiation Outline

1. Radiation is one of the most (if not the most effective agent) in the treatment of CNS Lymphoma
2. Given the age and poor KPS/health of newly diagnosed patients, radiation is often a part of up –front management of these patients
3. Chemotherapy alone studies are associated with early progressions and poor progression free survival, which translates into poor outcomes for these patients treated with salvage therapies including XRT

Pro-Radiation Outline

4. Modern series of multi-agent chemotherapy combined with radiation in unselected patients are associated with outstanding PFS and OS in unselected patients virtually no neurotoxicity

Effectiveness of Radiation-RTOG 8315

Eligibility:

- Age >18 or older
- KPS >40
- No AIDS patients

Treatment:

- 40 Gy to whole brain
- 20 Gy Boost to contrast enhancing lesions
- No chemotherapy until disease progression
(7/41 received chemotherapy)

RTOG 8315

Result:

- MST was 12.2 months from diagnosis; 5 year survival of 5%
- KPS >70 had MST of 21.1 months
- Age <60 had MST of 23.1 months
- CR rate of 62%; near CR of 19% on CT Scan done 4 months post tx

Conclusions:

- In unselected patients high but not durable responses

SEER Data

- Patients >65 diagnosed with PCNSL between 1994-2002
- 579 cases identified; only 464 (80%) received any treatment
- XRT alone delivered to 46% of patients; CMT to 33% and Chemo alone to 22%
- The use of chemo decreased with age ($p < 0.0001$)
- MST was 7 months

Results of Salvage Whole Brain Radiotherapy

- **48 patients received salvage WBRT for PCNSL progression or recurrence**
- **58% achieved a CR; 21% a PR**
- **MST was 10 months; 31% had no recurrence after XRT**
- **Treatment related neurotoxicity was observed in 22% of patients**
- **Patients >60 years and disease free interval of <6 months was associated with increased risk of neurotoxicity**



Salvage whole brain radiotherapy for recurrent or refractory primary CNS lymphoma. Hottinger A et al. Neurology 69: 1178-82, 2007

Chemotherapy Alone NABTT 96-07

Eligibility:

- **Age > 18**
- **KPS \geq 60**
- **Negative HIV serology**

Treatment:

- **Induction MTX 8 g/m² q 14 days until CR or 8 cycles; if CR two additional cycles**
- **Maintenance MTX 8 g/m² q 28 days X 11 cycles**



Treatment of Primary CNS Lymphoma with MTX and Deferred Radiotherapy: A Report of NABTT 96-07. Bathelot T et al. J Clin Oncol 21: 1044-1049, 2003

NABTT 96-07

Result:

- 25 treated; 23 evaluable for response
- 52% CR and 22% PR; 22% progressed during MTX treatment
- Median PFS of 12.8 months
- 2 patients died of leukoencephalopathy

Conclusions:

- Poorer overall response rate than RTOG 8315 despite a healthier patient population
- Chemo alone does not eliminate neurotoxicity

Benefits of Multi-agent Chemotherapy (IELSG Study)

Eligibility:

- Age 18-75
- ECOG \leq 3
- HIV negative

Treatment:

- 4 courses of MTX on Day 1 or four course of MTS on Day 1 combined with Cytarabine twice/day on days 2 & 3; cycles repeated every 3 weeks
- If CR or PR after two courses; received 2 additional courses followed by XRT

IELSG Study

Result:

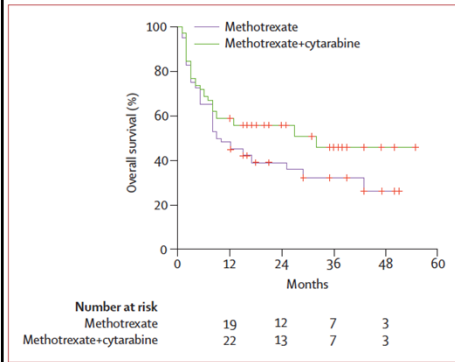


Figure 3: Overall survival curves

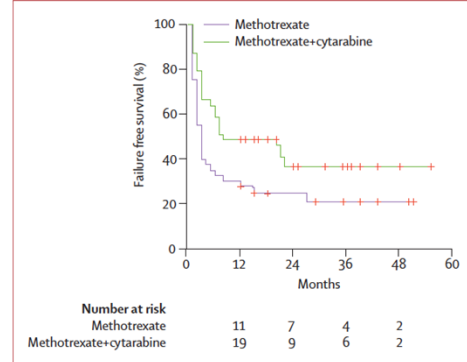


Figure 2: Failure-free survival curves

IELSG Study

Results:

- CR with MTX was 18%; 46% with MTX + Cytarabine
- Overall response rate with MTX was 40%; 69% with MTX + Cytarabine
- 55% receiving MTX and 18% receiving MTX/Cytarabine progressed during therapy

Conclusions:

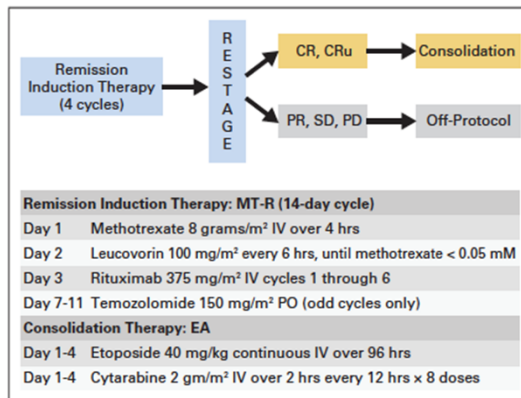
- Improved outcomes with combination therapy. Still frequent non-responders and progressors even during treatment

Effectiveness of Multi-agent Chemotherapy Alone (CALGB 50202)

Eligibility:

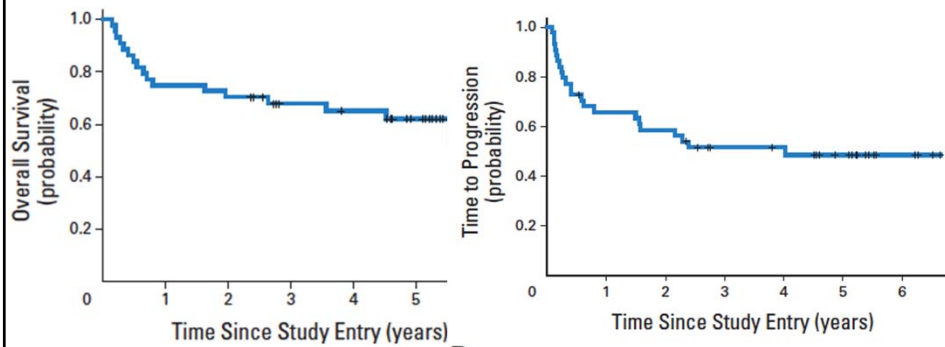
- No lower age limit
- ECOG ≤ 2
- HIV negative

Treatment Schema



Intensive Chemotherapy and Immunotherapy in Patients with Newly Diagnosed Primary CNS Lymphoma: CALGB 50202. Rubenstein J et al. J Clin Oncol 31: 3061-3068, 2013

CALGB 50202



CALBG 50202

Results:

- After MT-R induction, 20% experienced progressive disease, 1 had stable disease 5 (11%) had a PR and 29 (66%) had a CR
- 1 death due to sepsis
- 2 year PFS was 59%

Conclusions:

- Despite aggressive multi-agent induction and consolidation, still frequent early progressors
- No formal neurocognitive testing

Chemo +/- WBRT (G-PCNSL-SG-1)

Study Background:

- Non-inferiority study to determine if chemo alone could be shown to be non-inferior to chemo-XRT
- Overall plan was to enroll 151 patients/group which resulted in a 60% power to prove non-inferiority of omitting chemo with an HR of 1.2

Eligibility:

- Standard eligibility
- 551 patients enrolled of whom 318 received treatment per protocol

G-PCNSL-SG-1

Treatment

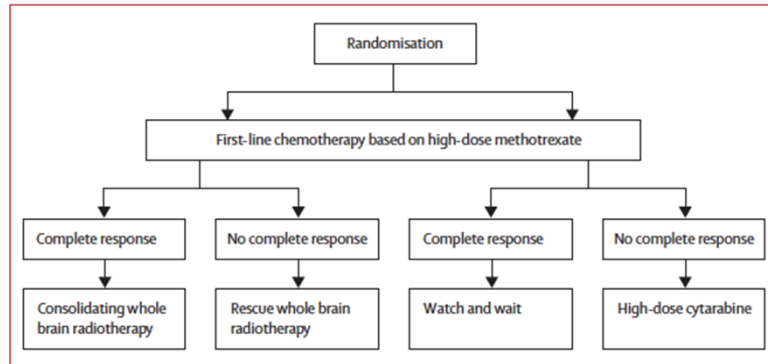


Figure 1: Trial design

– XRT was 45 Gy in 30 fractions

G-PCNSL-SG-1

	First-line chemotherapy with whole brain radiotherapy			First-line chemotherapy without whole brain radiotherapy		
	Patients	Events	Median time (months; 95% CI)	Patients	Events	Median time (months; 95% CI)
All patients						
Progression-free survival	154	113	18.3 (11.6-25.0)	164	124	11.9 (7.3-16.5)
Overall survival	154	97	32.4 (25.8-39.0)	164	96	37.1 (27.5-46.7)
Patients with complete response						
Progression-free survival	56	33	36.3 (19.3-53.3)	96	62	21.5 (12.5-30.5)
Overall survival	56	32	38.8 (23.2-54.4)	96	46	39.4 (20.7-58.0)
Patients without complete response						
Progression-free survival	98	80	5.6 (1.6-9.5)	68	62	3.0 (2.7-3.3)
Overall survival	98	65	24.3 (12.2-36.3)	68	50	18.6 (8.3-29.0)

Table 3: Progression-free and overall survival (per-protocol population)

G-PCNSL-SG-1

	Univariate analysis (simple Cox regression model)		Multivariate analysis (multiple Cox regression model without variable selection)	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Progression-free survival				
Age*	1.22 (0.95-1.59)	0.13	1.11 (0.84-1.49)	0.46
Karnofsky performance score†	1.09 (1.01-1.18)	0.02	1.11 (1.02-1.20)	0.012
Sex‡	0.84 (0.65-1.09)	0.19	0.73 (0.55-0.98)	0.037
Study group§	0.82 (0.64-1.07)	0.14	0.82 (0.62-1.09)	0.18
Drug treatment¶	0.94 (0.66-1.34)	0.74	0.82 (0.55-1.22)	0.33
Overall survival				
Age*	1.69 (1.26-2.26)	0.0004	1.54 (1.12-2.12)	0.008
Karnofsky performance score†	1.16 (1.07-1.26)	0.0005	1.16 (1.07-1.27)	0.001
Sex‡	0.82 (0.61-1.09)	0.17	0.70 (0.51-0.97)	0.031
Study group§	1.06 (0.80-1.40)	0.71	1.05 (0.77-1.44)	0.74
Drug treatment¶	1.05 (0.66-1.65)	0.84	1.11 (0.68-1.81)	0.69

*Age of 60 years or older versus younger than 60 years. †10% decrease in Karnofsky performance score. ‡Female sex versus male sex. §First-line chemotherapy with whole brain radiotherapy versus first-line chemotherapy without whole brain radiotherapy. ¶High-dose methotrexate plus ifosfamide versus high-dose methotrexate alone.

Table 4: Univariate and multivariate analyses for progression-free survival and overall survival (per-protocol population)

G-PCNSL-SG-1

Conclusions:

- Study is generally discounted due to the high numbers of patients unaccounted for and the large number of patients who didn't receive treatment per protocol
- However, the study did not meet its primary end-point of non-inferiority of chemotherapy alone (which seems to be frequently overlooked in referencing this paper)

Effectiveness of Combined Chemotherapy-RT RTOG 9310

Eligibility:

- Standard eligibility criteria with minimum KPS of 40

Treatment:

- 5 initial cycles of chemotherapy
- Each cycle consisted of MTX 2.5 g/m², VCR 1.4 mg/m² on Day 1; Procarbazine 100 mg/m²/d x 7 days on cycles 1, 3 and 5
- Followed by WBRT to 45 Gy/25 fractions
- Study modified to allow 15 patients who had a CR to receive 36 Gy in 1.2 Gy fractions delivered twice daily
- At completion of XRT, two course of high dose Ara-C



Combined Chemotherapy and radiotherapy for PCNSL: RTOG Study 9310. DeAngelis L et al. J Clin Oncol 20: 4643-4648, 2002

RTOG 9310

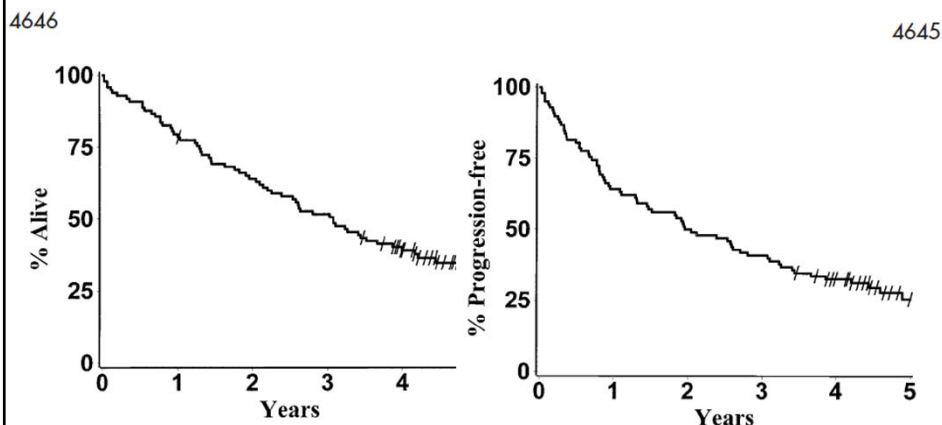


Fig 2. Overall survival for all patients.

Fig 1. Progression-free survival for all patients.



RTOG 9310

Results:

- 58 % CR; 36% PR for ORR of 94% to neoadjuvant chemotherapy
- Median PFS was 24 months; OS 36.9 months
- 12 patients (15%) experienced severe delayed neurologic toxicity of whom 8 died
- PFS and OS no different in HFX and Conventional RT groups
- **2/16 HF patients (13%) and 6/66 (9%) RT patients developed grade 5 neurotoxicity. At 2 years 5% of RT patients vs 0% of HFX patients had developed leukoencephalopathy suggesting a delayed effect with HFX treatment



**Secondary analysis of RTOG 9310 Fisher B et al. J of Neuro-Oncol. 74: 201-205, 2005

RTOG 9310

Conclusions:

- First multicenter study to show conclusively in unselected patients the benefits of combined chemotherapy and radiation treatment over radiation therapy alone
- Late severe neurotoxicity a major concern which did not appear to be adequately addressed by accelerated hyperfractionated XRT
- Need for more intensive chemotherapy allowing for further reduction in doses of XRT



Effectiveness of Combined Chemotherapy- Radiotherapy

Background

- MSKCC has published a series of papers describing sequential modifications of standard chemotherapy-radiation for patients with CNS lymphoma incorporating additional agents and de-escalating doses of RT
- I will describe their latest paper and then the recent RTOG trials based on that treatment paradigm

Effectiveness of Combined Chemotherapy- Radiotherapy-MSKCC

Eligibility:

- Multi-center trial
- Age >18
- HIV –ve
- No lower limit to KPS

Treatment:

- Five 14 day cycles of induction chemotherapy
- Day 1-Rituximab 500 mg/m²; Day 2-MTX 3.5 gm/m² + VCR 1.4 mg/m²; days 1-7 Procarbazine 100mg/m² (odd cycles only)
- If CR- WBRT to 23.5 Gy in 13 fractions; otherwise 45 Gy in 25 fractions
- Then 2 cycles of Ara-C (3 gm/m² on Days 1 and 2)
- If PR -2 additional cycles of induction chemotherapy; then XRT as above

Effectiveness of Combined Chemotherapy- Radiotherapy-MSKCC

Additional Outcome Measures

- Prospective Neuropsychological evaluation were offered to patients treated at MSKCC
- Executive, Verbal Memory and Motor Speed were assessed with standard measures
- QOL was examined using the FACT-Brain Cancer test
- Mood was assessed with the Beck Depression Inventory
- White matter changes on sequential MRI scans were graded using the Fazekas scale

Effectiveness of Combined Chemotherapy- Radiotherapy-MSKCC

Results:

- 79% of patients achieved a CR after induction chemotherapy; 16% a PR
- 5 year OS was 80%; PFS at 2 years was 77% (best results reported in literature)
- No deaths from neurotoxicity
- For patients who received rdWBRT
 - On neuropsych testing cognitive impairment was present in several domains at baseline and improved after induction chemotherapy

Effectiveness of Combined Chemotherapy- Radiotherapy-MSKCC

RESULTS:

- NO EVIDENCE OF SIGNIFICANT COGNITIVE DECLINE WAS OBSERVED DURING THE FOLLOW-UP PERIOD FROM XRT
- THERE WAS SOME PROGRESSION OF WHITE MATTER CHANGES ON MRI BUT NO PATIENT DEVELOPED SEVERE (FAZEKAS 4/5) CHANGES
- THERE WAS ALSO NO EVIDENCE OF DEPRESSED MOOD AND SELF REPORTED QOL REMAINED STABLE

Effectiveness of Combined Chemotherapy- Radiotherapy-MSKCC

Conclusions:

- Combined chemo-immunotherapy with low dose RT is associated with the highest rate of overall survival and progression free survival reported in the literature
- Even with careful neurocognitive assessments, there was no deleterious effect of XRT on neurocognitive outcomes

RTOG 1114

- Whether WBRT can be eliminated in Primary CNS Lymphoma using modern chemo-immunotherapy is being addressed by this study
- Treatment arms will be r-MPV vs rMPRV + low dose XRT (23.4 Gy/13 fractions for induction CR)
- The study will test the following hypotheses
 - Addition of low dose WBRT will improve PFS
 - Low dose WBRT will result in improved long term cognitive function by decreasing cognitive deterioration from early disease recurrence and salvage therapy

Conclusions

- No study of chemotherapy or chemo-immunotherapy alone in unselected patients has convincingly demonstrated that one can achieve results similar to combined Chemo-RT
- Until we see the results of RTOG 1114, Chemo-immunotherapy combined with low dose XRT should be the standard of care for patients with primary CNS lymphoma

Conclusions

