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► **To cite this version:**

Antonin Levy, Cécile Le Péchoux, Hitesh Mistry, Isabelle Martel-Lafay, Andrea Bezjak, et al.. Prophylactic Cranial Irradiation for Limited-Stage Small-Cell Lung Cancer Patients: Secondary Findings From the Prospective Randomized Phase 3 CONVERT Trial. *Journal of Thoracic Oncology*, 2019, 14 (2), pp.294-297. 10.1016/j.jtho.2018.09.019 . hal-04508663

HAL Id: hal-04508663

<https://hal.science/hal-04508663v1>

Submitted on 29 Nov 2024

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Brief report

Prophylactic cranial irradiation for limited-stage small-cell lung cancer patients: secondary findings from the prospective randomized phase 3 CONVERT trial.

Short title: PCI results from the CONVERT trial

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This study was presented at WCLC Sept 2018, Toronto, Canada.

Disclosures

Dr Le Péchoux has participated in Astra Zeneca national boards in France

Abstract

Introduction: The impact of the dose and fractionation of thoracic radiotherapy on the risk of developing brain metastasis (BM) has not been evaluated prospectively in LS-SCLC patients receiving prophylactic cerebral irradiation (PCI).

Methods: Data in patients treated with PCI from the CONVERT trial was analysed.

Results: 449/547 (82%) received PCI after completion of chemoradiotherapy. Baseline brain imaging consisted of CT-scan in 356/449 patients (79%) and MRI in 83/449 (18%) patients. PCI was delivered to 220/273 participants (81%) in the twice-daily (BD) group and 229/270 in the once-daily (OD) group (85%; $p=0.49$). Total median PCI dose was 25Gy in both BD and OD groups ($p=0.74$). In patients who received PCI, 75 (17%) developed BM (35 [8%] in OD and 40 [9%] in BD) and 173 (39%) other extracranial progression. In the univariate analysis, GTV was associated with an increased risk of BM ($p=0.007$) or other radiological progression events ($p=0.006$), whereas in a multivariate analysis both thoracic GTV (tGTV) and PS were associated with either progression type. The median OS of patients treated with PCI was 29 months. In the univariate analysis of OS, PCI timing from end of chemotherapy, weight loss $>10\%$, and tGTV were prognostic factors associated with OS. In the multivariate analysis, only tGTV was associated with OS. Delay between end of chemotherapy and PCI was not associated with OS.

Conclusion: Patients receiving OD or BD thoracic RT have the same risk of developing BM. Larger tumours are associated with a higher risk of BM.

Keywords: Cranial irradiation, lung cancer, phase III trial.

Introduction

Small-cell lung cancer (SCLC) is characterised by a rapid doubling time and brain metastases (BM) are frequent in its natural history. Prophylactic cranial irradiation (PCI) in limited-stage (LS) SCLC patients has been shown to reduce the incidence of BM. Furthermore in good performance status LS-SCLC patients who respond to standard platinum-based chemoradiotherapy (CTRTR), two meta-analyses demonstrated that PCI led to an absolute overall survival (OS) benefit.^{1,2} PCI is therefore considered to be part of the standard management in this setting.^{3,4}

However there are a number of unresolved issues regarding PCI. Firstly, the meta-analyses included studies that were performed before brain magnetic resonance imaging (MRI) became a standard investigation for SCLC.^{3,4} Therefore the role of PCI in patients screened with brain MRI is uncertain. Secondly, the optimal timing of PCI delivery after CTRTR is undefined, even if a trend in favour of early PCI is suggested. Finally, the impact of the dose and fractionation of thoracic radiotherapy (RT) on the risk of developing BM has not been evaluated prospectively. Accelerated hyperfractionated RT can theoretically reduce the risk of tumour cell repopulation during treatment by shortening the overall treatment time.⁵

Patients and Methods

We report here on PCI delivery and timing relating to CTRTR, survival and impact of thoracic dose fractionation on risk of brain relapse in patients treated as part of the CONVERT trial (NCT00433563).⁶ CONVERT is a multi-centre phase III trial that randomly assigned (1:1 using minimization method) patients with Eastern Cooperative Oncology Group performance score (PS) 0-2 with LS-SCLC to receive either twice-daily (BD; 45 Gy in 30

fractions) or once-daily (OD; 66 Gy in 33 fractions) RT starting with cycle 2 of chemotherapy. Chemotherapy consisted of 4-6 cycles of cisplatin and etoposide. A CT or MR of the brain was mandated and performed within 4 weeks prior to randomisation. In this trial, patients without evidence of progressive disease after chemotherapy and with no clinical evidence of BM were offered PCI. The dose and fractionation of PCI was left to the discretion of each principal investigator to allow for variation in local practice. The protocol specified that PCI should start no later than 6 weeks after the last cycle of CT.

In this analysis, data on PCI status from CONVERT participants was evaluated. Descriptive statistics for the patients included in this analysis were reported. Brain relapse times and OS, for assessment of predictors, were calculated from PCI initiation to time of first relapse or death respectively. Patients who did not experience an event were right censored. Predictors for brain relapse rates were assessed using the competing risk regression model developed by Fine and Gray,⁷ whereas predictors for OS were assessed using the Cox proportional hazards model. The proportionality assumption was assessed using Schoenfeld residual plots. All analyses were conducted using R v3.4.

Results

Between April 2008 and Nov 2013, 547 patients from 73 centres across 8 countries were recruited. 274 patients were randomly assigned to receive BD CTRT and 273 to receive OD CTRT. The modified intention-to-treat survival analysis included 543 patients (273 in the BD group and 270 in the OD group); four patients were lost to follow-up. Baseline imaging of the brain consisted of CT-scan for 356/449 patients (79%) and MRI for 83/449 (18%) patients. Out of 543 patients, 449 (83%) received PCI after completion of CTRT. PCI was delivered to 220 (81%) of 273 participants in the BD group and 229 (85%) of 270 in the OD

group ($p=0.49$). **Table S1** shows the patients characteristics according to PCI delivery. Both groups were comparable at baseline, except that no-PCI patients were older ($p=0.01$), and the proportion of Asian patients ($p=0.01$) and baseline LDH levels were higher ($p=0.04$). The UICC/AJCC stages of patients who received PCI were I, II, and III for 4 (1%), 74 (16%), 346 (77%) respectively and was unknown in 25 patients.

The total median PCI dose was 25 Gy in both BD (range, 12.5-37.5 Gy) and OD (range, 2.5-30 Gy) groups ($p=0.74$; **Table 1**). PCI was delivered later after the last chemotherapy cycle in the OD (median days post chemotherapy of 37 days [range, 25-209 days]) compared with the BD group (median days post chemotherapy of 35 days [range, 9-174 days]; $p=0.04$). However there was no difference between the 2 groups in PCI delivery timing when calculating from the start of chemotherapy (median days from start of chemotherapy of 107 days for OD [range, 44-272 days] vs. 101 days [range, 56-205 days] for BD ($p=0.8$)).

In patients who received PCI, at a median follow-up of 45 months, 75 (17%) developed BM (35 out of 220 [16%] in the OD group and 40 out of 229 [17%] in the BD group) and 173 (39%) other extracranial progression. In the univariate analysis, only the thoracic gross tumour volume (tGTV; HR: 1.37 [95% CI 1.09-1.73]; $p=0.007$) was associated with the occurrence of BM (HR: 1.37 [95% CI 1.09-1.73]; $p=0.007$) and of other extracranial sites of progression (HR: 1.43 [95% CI 1.11-1.85]; $p=0.006$). The thoracic fractionation type, PCI timing, PCI dose, and type of baseline brain imaging (MRI vs. CT-scan) were not associated with the occurrence of BM. In the multivariate analysis, tGTV and $PS \geq 1$ were associated with both occurrence of BM and of other extracranial sites of progression (**Table 2**).

The median OS in the PCI group was 29 months (95% CI 25.8-35.7 months). Median OS was 28 months in the BD (95% CI 22-35) and 31 months in the OD group (95% CI 27-52);

p=0.1. In patients receiving PCI, the 3-year OS rates were 45% (95%CI 40-50) 42% (95%CI 36-49), and 48% (95%CI 41-55), for the whole population, OD group, and BD group, respectively. In the univariate analysis of OS, PCI timing from end of CT, weight loss > 10%, and tGTV were prognostic factors. In the multivariate analysis, only tGTV was associated with OS. PCI timing from end of chemotherapy did not remain significantly associated with OS (p=0.2; **Table 2**). The median OS in the non-PCI group was 11.8 (95% CI: 8.7-17.6) months. Excluding patients with poor prognosis who had either unknown or progressive disease after CTRT, the median OS in the non-PCI group was 13.9 months (95% CI 9.5-24.8 months, p<0.001 vs. PCI group).

Discussion

The role of PCI in the management of LS-SCLC has been controversial due to the potential risk of neuropsychological toxicity.^{1,8} The recently published Japanese trial comparing active brain MRI surveillance to PCI in extensive-stage SCLC, has challenged the standard of care established by the European Organisation for Research and Treatment of Cancer (EORTC) trial in 2007.^{9,10} In the Japanese trial, PCI did not result in longer OS compared with observation (median 11.6 vs. 13.7 months; p=0.09). The latter trial has been scrutinised given that some cofactors might have attenuated the benefits of PCI (e.g. important rates of salvage brain RT with probable salvage radiosurgery in both groups).^{11,12} Consequently there is a clear need for new PCI trials performed in the MR imaging era. In LS-SCLC, a recent US survey of practice showed that most (n=309) radiation oncologists recommend PCI (98%) and brain-MRI prior to treatment (96%).¹³ There is also a need to develop decision support systems to guide doctors and patients. In the CONVERT trial we showed that larger tumours, but not the thoracic fractionation type,¹⁴ are associated with a

higher risk of BM, but also higher risk of extra cranial recurrences. Predictive models need to be refined to achieve a more personalised management.

Acknowledgements

The authors thank Sally Falk for her editorial assistance

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Table 1: PCI delivery according to twice-daily vs. once-daily radiotherapy groups

	Twice-daily (n=229)	Once-daily (n=220)	p-value
Total Dose (Gy); Median (Range)	25 (12.5-37.5)	25 (2.5-30)	0.741**
Total Dose (Gy)			
25	187 (82%)	167 (76%)	0.278*
>25	25 (11%)	32 (15%)	
<25	15 (7%)	20 (9%)	
Days post chemotherapy ; Median (Range)	35 (9-174)	37 (25-209)	0.043**

* Chi-sq test; ** Wilcoxon Rank Sum test

Table 2: Univariate and multivariate competing risks sub-distribution hazard ratios for brain progression and overall survival hazard ratios for patients with PCI treatment only

	Patients	Brain Progression from PCI initiation				Survival from PCI initiation			
	N/BP/Death	Univariate		Multivariate		Univariate		Multivariate	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
log(tGTV)	430/70/246	1.37 (1.09-1.73)	0.007	1.43 (1.11-1.85)	0.006	1.37 (1.19-1.56)	<0.001	1.33 (1.16-1.54)	<0.001
OD v BD (BD is referent)	449/75/263	0.95 (0.60-1.50)	0.830	0.93 (0.57-1.53)	0.770	1.21 (0.95-1.54)	0.121	1.16 (0.89-1.51)	0.275
Brain CT v MRI (MRI is referent)	438/73/255	1.17 (0.67-2.07)	0.580	1.28 (0.67-2.46)	0.450	1.30 (0.94-1.81)	0.113	1.41 (0.99-2.00)	0.151
Weight loss >10% (yes vs. no) (no is referent)	418/70/248	1.57 (0.59-4.18)	0.360	1.83 (0.69-4.89)	0.230	2.31 (1.34-3.97)	0.002	1.98 (1.14-3.43)	0.015
ECOG PS 1 or 2 vs. 0 (0 is referent)	449/75/263	0.64 (0.40-1.02)	0.059	0.54 (0.32-0.90)	0.018	1.28 (1.00-1.63)	0.049	1.12 (0.86-1.46)	0.348
log(PCI) Timing from randomisation	449/75/263	2.84 (0.82-9.82)	0.100	1.82 (0.04-8.62)	0.760	1.07 (0.59-1.93)	0.820	0.66 (0.11-4.14)	0.659
log(PCI) Timing from end of CTRT	446/74/262	1.10 (0.63-1.89)	0.750	0.83 (0.48-1.45)	0.520	1.48 (1.12-1.96)	0.007	1.32 (0.93-1.87)	0.189
log(PCI Timing from beginning of CT)	446/74/262	3.28 (0.91-11.9)	0.070	1.68 (0.03-10.67)	0.810	1.16 (0.63-2.14)	0.640	1.07 (0.15-7.84)	0.945
PCI Dose >25 vs. ≤25 Gy (≤25 is referent)	449/75/263	0.70 (0.37-1.33)	0.280	0.67 (0.34-1.28)	0.220	0.86 (0.61-1.22)	0.394	0.93 (0.65-1.34)	0.776

N: total number of patients; BP: number of patients with brain progression; OP: number of patients with other radiological progressions; tGTV: thoracic Gross Tumour Volume; OD: once-daily; BD: twice-daily; HR: Hazard Ratio; CI: confidence interval; CT: chemotherapy; CTRT: chemoradiotherapy. (p-values calculated using the Wald-test)