Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Is prophylactic cranial irradiation (PCI) needed in patients with extensive-stage small cell lung cancer showing complete response to first-line chemotherapy?

Kaname Nosaki [a], Takashi Seto [a,*], Mototsugu Shimokawa [b], Toshiaki Takahashi [c], Nobuyuki Yamamoto [d]

[a] Department of Thoracic Oncology; [b] Cancer Biostatistics Laboratory, Clinical Research Institute, National Kyushu Cancer Center; [c] Division of Thoracic Oncology, Shizuoka Cancer Center; and [d] Third Department of Internal Medicine, Wakayama Medical University, Japan

ARTICLE INFO

Article history:
Received 27 February 2018
Received in revised form 6 April 2018
Accepted 6 April 2018
Available online xxxx

Keywords:
Small cell lung cancer
Prophylactic cranial irradiation
Cognitive impairment

ABSTRACT

Throughout the entire world, prophylactic cranial irradiation (PCI) is the standard care for patients with small cell lung cancer (SCLC) in whom a favorable therapeutic effect is achieved after front-line treatment, regardless of whether the disease is in the limited stage or extensive stage. In the EORTC study, PCI was shown to confer a survival benefit for patients with extensive-stage small cell lung cancer (ES-SCLC) who experienced any positive response after initial chemotherapy. However, the Japan study failed to confirm a survival benefit. As a result, the guidelines in Japan recommend that PCI should not be carried out in cases of ES-SCLC. Complete response (CR) subset analysis in the Japan study suggested that PCI did not provide a survival benefit for patients with ES-SCLC.

PCI with a risk of adverse events has poor significance, even if the patients show CR to chemotherapy.
 Radiotherapy and Oncology xxx (2018) xxx–xxx

Small cell lung cancer (SCLC) is classified as either limited disease (LS-SCLC) or extensive disease (ES-SCLC). The standard therapy for LS-SCLC is concurrent chemoradiotherapy. Prophylactic cranial irradiation (PCI) is strongly recommended for those who achieve complete response (CR) or good partial response (PR) with initial therapy. On the other hand, the standard therapy for ES-SCLC is chemotherapy only. After PCI was shown to confer a survival benefit for patients with ES-SCLC who experienced any positive response after initial chemotherapy in the EORTC study, PCI became the standard care throughout the world for patients with SCLC in whom a favorable therapeutic effect is achieved after first-line chemotherapy, regardless of whether the disease is in the limited stage or extensive stage. However, the Japan study failed to confirm a survival benefit. This review article compares two studies conducted on patients with ES-SCLC, and particularly examines the significance of PCI in ES-SCLC cases that showed CR to first-line chemotherapy.

History of PCI

PCI has been carried out since the 1970s to prevent brain and central nervous system metastases, which are less likely to be effectively cured by systemic chemotherapy alone because of the presence of the blood–brain barrier [1]. Seven randomized controlled trials that examined the efficacy of PCI were conducted between 1977 and 1995 [2–6]. Auperin et al. carried out a meta-analysis using the individual data of 987 patients who showed CR to chemotherapy in these trials [7]. Carrying out PCI allowed for a significant decrease in the cumulative incidence of brain metastasis with a hazard ratio of 0.46 (95% confidence interval: 0.38–0.57, $p < 0.001$), as well as a decrease in the cumulative incidence of brain metastasis at 3 years after allocation, namely from 58.6% (non-PCI group) to 33.3% (PCI group). In addition, the overall survival (OS) in the PCI group also showed a hazard ratio of 0.84 (95% confidence interval: 0.73–0.97, $p = 0.01$) and significantly improved in comparison to that found in the non-PCI group—the three-year survival rate reportedly increased from 15.3% (non-PCI group) to 20.7% (PCI group). Findings from subgroup analyses have reportedly shown that regardless of age, general physical condition, disease stage before treatment, or type of treatment, the survival rate was better in the PCI group; however, patients with ES-SCLC accounted for only 14% (140 cases) with a hazard ratio of 0.77 (95% confidence interval: 0.54–1.11); thus, the findings lacked power to demonstrate the usefulness of PCI. In addition, the definition of CR was sometimes based on evaluations using chest radiographs only or evaluations using chest CT/head CT. This differs from the present routine medical care in which head MRI and PET are currently performed. On the basis of the

* Corresponding author at: Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan.
E-mail address: tseto@nk-cc.go.jp (T. Seto).

https://doi.org/10.1016/j.radonc.2018.04.010
0167-8140/

background described above, PCI was indicated not only in patients with CR but also in those with good partial response (PR).

Meert et al. also reported the results of a systematic review of 12 randomized controlled trials conducted between 1997 and 1998 that examined the outcomes in cases of use or non-use of PCI. Five of these studies allowed for examining the usefulness of PCI in patients who showed CR after chemotherapy [2,3,5,6,8,9]; the hazard ratio for developing a brain tumor was 0.49 (95% confidence interval: 0.39–0.62) and the hazard ratio of OS was 0.82 (95% confidence interval: 0.71–0.96). Therefore, similarly to Auperin et al., they concluded that in cases with LS-SCLC as well as at all stages of SCLC, PCI reduced the development of metastatic brain tumors and prolonged the OS in patients showing CR to first-line therapy. However, among these studies, only two excluded metastatic brain tumors on the basis of brain CT performed before PCI, and none of the studies used brain MRI findings as a criterion for exclusion of metastatic brain tumors.

Later, the use of PCI in patients with ES-SCLC was examined, and reports have shown that in patients who showed positive responses (CR, PR, stable disease) to first-line chemotherapy, PCI had a suppression effect on symptomatic brain metastases as well as a survival-prolonging effect. Slotman et al. carried out a prospective comparative study in which 283 patients with ES-SCLC who showed any positive response to first-line treatment were allocated to a PCI group and a non-PCI group (EORTC study) [10]. The time period until the occurrence of symptomatic brain metastases was considered as the primary endpoint. The cumulative incidence of symptomatic brain metastases was significantly lower in the PCI group, with a hazard ratio of 0.27 (95% confidence interval: 0.16–0.44, $p < 0.001$), and the one-year cumulative rate of brain metastasis was successfully reduced from 40.4% (non-PCI group) to 14.6% (PCI group). The median disease-free survival (DFS) was also prolonged from 12.0 weeks (non-PCI group) to 14.7 weeks (PCI group), and the hazard ratio was 0.76 (95% confidence interval: 0.59–0.96, $p = 0.02$), showing significantly favorable results in the PCI group. The percentage of cases with the brain as the site of first recurrence was 9.1% in the PCI group and 35% in the non-PCI group. The median OS was prolonged from 5.4 months (non-PCI group) to 6.7 months (PCI group); the hazard ratio was 0.68 (95% confidence interval: 0.52–0.88, $p = 0.003$), which was significantly better in the PCI group; and the one-year survival rate also increased from 13.3% (non-PCI group) to 27.1% (PCI group).

A phase III study for further validation was carried out in Japan: the primary endpoint was the OS while the secondary endpoints were time to brain metastasis, progression-free survival (PFS), and safety [11]. A total of 330 cases were planned to enroll in the study, but the results of an interim analysis denied the superiority of the treatment effect in the PCI group over that in the non-PCI group; therefore, the study was considered invalid and was discontinued. A total of 224 cases were enrolled: the median OS was 13.7 months in the non-PCI group and 11.6 months in the PCI group, and the hazard ratio was 1.27 (95% confidence interval: 0.96–1.68, $p = 0.094$), which showed no significant difference, whereas in the non-PCI group, favorable results were found: the one-year cumulative rate of brain metastasis was 59.0% in the non-PCI group and 32.9% in the PCI group, showing a significant decrease in the PCI group. The median PFS was 2.4 months in the non-PCI group and 2.3 months in the PCI group, and the hazard ratio was 0.98 (95% confidence interval: 0.75–1.29, $p = 0.75$), showing that there was no difference. Grade 3–4 anorexia and malaise occurred more frequently in the PCI group.

In the phase III study of PCI compared with observation in patients with locally advanced non-small cell lung cancer, there were no significant differences in global cognitive function or QOL after PCI, but there was a significant decline in memory at 1 year [12].

Differences between the EORTC study and Japan study

In the EORTC study, the protocol specified that screening of brain metastases through CT or MRI had to be carried out only when there were findings suspected of brain metastasis. As a result, confirmation of the absence of brain metastasis through MRI (or CT) was not performed before chemotherapy or before PCI; and after protocol treatment, tests aimed at detecting brain metastases were not performed until the presence of symptoms suspected of brain metastasis was confirmed. In addition, the radiation therapy schedule could be selected from the following: 20 Gy/5 fractions or 8 fractions, 24 Gy/12 fractions, 25 Gy/10 fractions, 30 Gy/10 fractions or 12 fractions. Also, in some cases, non-platinum based chemotherapies were used for induction chemotherapy [10].

In the Japan study, patients with MRI findings confirming the absence of brain metastasis were randomly assigned to the PCI group and the non-PCI group. PCI was carried out on all patients with a radiation dose of 25 Gy/10 fractions, and detection of brain metastases was carried out through evaluations using MRI once every 3 months. As a post-treatment, radiation therapy against newly developing brain metastases was performed on 83% of patients in the non-PCI group and 46% of patients in the PCI group. Patients who underwent second-line, third-line and fourth-line chemotherapy accounted for 83%, 61%, and 36% of the non-PCI group, respectively, and 88%, 50%, and 26% of the PCI group, respectively, showing that third and fourth-line chemotherapy were performed more frequently in the non-PCI group [11].

Impact on the results due to differences between the two studies

Significance of the screening of metastatic brain tumors using head MRI before PCI

In a previous report published by Manapov et al., 40 patients with LS-SCLC who achieved CR to concurrent chemoradiotherapy and were indicated for PCI were subjected to contrast-enhanced head MRI before receiving PCI, and the findings revealed asymptomatic brain metastases in 13 cases (32.5%) [13]. In the EORTC study, MRI was not carried out before PCI, therefore it could not be ruled out that patients with asymptomatic brain metastasis may have been included among the participants, and that the study results may have been influenced by the treatment effect in patients with asymptomatic brain metastasis.

Significance of detection during the asymptomatic phase and diagnostic imaging tests after protocol treatment

In the EORTC study, screening of brain metastases was not performed until there were symptoms leading to suspicion of brain metastasis; meanwhile, in the Japan study, screening of brain metastases was performed once every 3 months. The time until progression (DFS and PFS) was roughly the same in both studies, and the duration of survival after progression was involved in the differences in the survival period. Reports on the EORTC study did not indicate any data on the treatment received after exacerbation, but the duration of survival after progression was estimated on the basis of the median values of DFS and OS, and was shorter than that found in the Japan study. In addition, findings from the

Please cite this article in press as: Nosaki K et al. Is prophylactic cranial irradiation (PCI) needed in patients with extensive-stage small cell lung cancer showing complete response to first-line chemotherapy?. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.04.010