Prophylactic cranial irradiation in extensive disease small cell lung cancer: An endless debate

PROPHYLACTIC CRANIAL IRRADIATION IN EXTENSIVE STAGE SMALL CELL LUNG CANCER: WHAT IS THE CURRENT EVIDENCE AND WHAT REALLY MATTERS TO PATIENTS?

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OPINION STATEMENT:

Extensive disease Small cell lung cancer (ED-SCLC) represents a very aggressive malignancy in which brain metastases are quite common. Clinical trials on prophylactic cranial irradiation (PCI) have showed a clear decrease in the risk of developing brain metastases but conflicting results regarding a possible survival advantage.

In particular the JCOG study didn't show any survival benefit in favour of PCI compared to brain MRI monitoring thus this has led to an important shifting in oncology practice. By review extensively literature on the role and importance of PCI in ED-SCLC it emerges clearly that PCI could still pllay a crucial role in the treatment of ED-SCLC. Given the conflicting results in term of OS, empowering the patient, by giving him-her the appropriate information is the way forward to offer a correct patient-related treatment.

INTRODUCTION

Small-cell lung cancer (SCLC) represents nearly 13% of all newly diagnosed lung cancers. Most patients present with extensive disease (ED) and, without treatment, median survival remains poor, ranging from 2 to 4 months [1]. At diagnosis, at least 18% of SCLC patients already present brain metastases (BM), the rate could increase up to 25% with more accurate brain imaging such as magnetic resonance imaging (MRI). Furthermore, the incidence of BM increases considerably during the course of the disease, reaching 80% in patients surviving 2 years after diagnosis [2]. The development of BM can be associated with severe neurological symptoms and significant impairment of health-related quality of life, with a median overall survival (OS) lower than 6 months. The blood-brain barrier is poorly penetrated by most of the anticancer drugs, making systemic treatment slightly ineffective to prevent such a

complication. One landmark achievement to prevent the development of BM was the introduction of prophylactic cranial irradiation (PCI) more than 40 years ago [3]. Since the publication of a meta-analysis in 1999 [4], PCI has been recommended as standard of care in SCLC patients responding to initial systemic treatment. This meta-analysis included 987 patients: and the use of PCI confirmed an absolute increase in the 3-year OS rate of 5.4%, along with a significant decrease of BMs incidence (from 58.6% to 33.3% after 3 years). Even if patients with ED were only 15% of the whole population, the majority had limited disease (LD), the observed benefit was similar in the two subgroups.

In 2007, the European Organisation for Research and Treatment of Cancer (EORTC) published the results of a study about the role of PCI in ED-SCLC patients who had responded to chemotherapy [5]. PCI reduced the incidence of symptomatic BM, decreasing the cumulative risk at 1 year from 40.4% in the control group to 14.6% in the PCI group and prolonged the 1-year OS (27% in PCI group versus 13% in the control arm, hazard ratio [HR] = 0.68, p=0.003). The trial, along with the previous meta-analysis, strengthened the role of PCI in the ED population and PCI became standard care in metastatic patients with its use being recommended in international guidelines [6, 7]. Notably, an analysis of patterns of care in the USA showed high adherence to guidelines; namely, 98% of radiation oncologists recommended PCI for patients with ED-SCLC [8].

Over the past year the role of PCI in ED-SCLC has been readdressed [9] and conflicting results as far as OS is concerned have been reported. Takahashi and colleagues ran a phase III trial where patients were randomised, at the end of their standard first-line chemotherapy and in the absence of progression, to PCI or brain MRI monitoring. The study did not show any difference in terms of OS between the 2

arms, with a median OS of 11.6 months (in the PCI arm) versus 13.7 months (in the observation arm) (HR = 1.27; 95% confidence interval [CI] 0.96-1.68, p=0.94). The study was interrupted early and based on these findings, the role of PCI has been challenged and become controversial.

The aim of the present review is to critically analyze separately prospective and retrospective trials reporting results in terms of intracranial control and OS in ED-SCLC patients with the intention of clarifying the role and finding a possible place for the use of PCI in this setting.

MATERIALS AND METHODS

An extensive review of the literature has been performed between April and September 2018 throughout *PubMed.* Articles reporting on “PCI in ED-SCLC” and “metastatic SCLC” have been identified and analyzed. In order to have a “modern view” of the literature, and avoid studies in which patients were treated with non-standard radiotherapy (RT) doses or non-platinum containing regimes, only publications after 2000 have been considered. The following keywords have been entered to identify potential articles:[small cell lung cancer] AND [extensive disease] AND [PCI]. We found and screened 332 articles. Review articles, commentaries, case reports and abstracts have been excluded. Studies targeting limited stage (LS)-SCLC or reporting on patients treated with concomitant therapy (systemic treatment

and/or thoracic RT), and reports without clear comparison between PCI treated pts and observed population were excluded. The final reference list, based on originality and relevance to the broad scope of this review, contained 8 full-text articles, including prospective and retrospective trials that were included in the qualitative synthesis. Quantitative analysis was done on the final list of 6 articles. The flowchart is presented in Fig. 1

RESULTS

We have identified and included 6 studies in the review, 2 prospective [5, 9] and 4 retrospective [10-13]. All the retrospective series favor PCI in terms of OS and intracranial control. The 2 prospective trials report conflicting results with regards to OS, while both favor PCI in terms of local control.

Dose and fractionation vary slightly between the series (total PCI dose ranges from 24 to 30 Gy), with 25 Gy in 10 fractions being the most common schedule (table 1).

Brain screening for BM at diagnosis was always performed in both prospective and retrospective trials with the exception of one prospective study [5] where screening for BM was performed only in 29% of patients. MRI was the preferred imaging modality. Computed tomography (CT) scan instead of MRI was used in a minority of cases and mostly due to MRI contraindication (pacemakers, artificial implants, etc). Only in one prospective study brain imaging was systematically performed after systemic treatment and before PCI [9]. In two studies there was no standardized protocol and only a few patients had brain imaging, either CT or MRI [11, 13].

Information regarding brain imaging modalities before PCI is missing in two studies [10, 12].

Median follow up across studies was 23 months (range, 9-36).

Retrospective studies:

Within the retrospective studies, the largest one [10] used the American National Cancer Database and evaluated a total of 4257 SCLC metastatic patients (3784 not receiving PCI and 473 receiving PCI). In this large cohort, patients treated between 2010 and 2012 with chemotherapy for metastatic SCLC and without BM have been analyzed. After propensity score matching on factors associated with receipt of PCI and OS, results in the overall cohort favored PCI with improved median survival (13.9 vs 11.1 months; p <0.001), 1-year probability of survival (61.2% vs 44%, p< 0.001) and 2-year probability of survival (19.8 % vs 11.5%, p< 0.001). The benefit was confirmed even after excluding patients with less than 6 months or with less than 9 months survival (median survival for patients surviving at least 6 months: 14% vs 11%; median survival for patients surviving at least 9 months: 15% vs 13%; p< 0.001).

More recently a publication from Ontario [11] reports results of 155 patients with ED-SCLC and without baseline BM. Authors found a statistically significant difference in OS (HR 0.55; 95% CI 0.39-0.77; p =0.0005) and time to BM (HR 0.40; 95% CI 0.23-0.66; p= 0.0004) with the use of PCI. Median survival for the PCI and non-PCI groups was 13.5 and 8.5 months, respectively. Furthermore, the authors found a significant increase in 1 and 2-year OS in the PCI group (HR 0.41; 95% CI 0.29-0.57; p<.0001). The median time to develop BM was also found to be longer in the PCI group (23.8

months vs 10.2 months) with an HR of 0.36 (95% CI 0.21-0.60; p< .0001). A survival difference with PCI was observed in both patients that received post-chemotherapy brain imaging (HR 0.55; 95% CI 0.35-0.88; p=0.012) and those who did not (HR 0.48; 95% CI 0.29-0.77; p=0.0025).

Furthermore Chen et al [12] reviewed 204 ED-SCLC patients who had any response after 4 to 6 cycles of chemotherapy. PCI was performed in 45 patients (22.1%) and the remaining 159 (77.9%) were observed. PCI significantly prolonged median OS (16.5 vs 12.6 months [HR 0.63, 95% CI 0.41-0.96; p=0.033]). Also, the risk of developing BM was lower in the PCI group (HR 0.48; 95 % CI 0.30-0.76; p=0.001), with 1-year incidence of BM of 17.1% vs 55.9% in the PCI and control group, respectively. PCI was a favorable independent predictor for OS in multivariate analysis. In this trial, brain imaging was mandatory prior to initial treatment.

Nicholls et al [13] reported their institutional experience and analyzed retrospectively patients with SCLC (both ED and LD) treated between January 2008 and December 2013. Of the 129 ED patient population, 13% received PCI. Median OS in the ED-SCLC cohort receiving PCI was 13.6 months compared to 5.6 months in patients not receiving such treatment (p< 0.001).

Prospective Studies

At present, there are only two prospective trials available. The first one is the EORTC study published in 2007 by Slotman et al [5]. The primary endpoint of the trial was the time to development of symptomatic BM, while secondary endpoints were survival, quality of life, toxic effects, and treatment costs. Cumulative risk of developing symptomatic BM within 1 year was 14.6 % in the PCI group, compared to 40.4% in

the control arm. Although OS was a secondary endpoint of the study, patients in the PCI group showed longer OS, with a median survival of 6.7 months compared to 5.4 months (p=0.003). In this study, brain imaging was not mandatory before enrolment and not routinely performed during follow-up (unless patients presented symptoms suggestive of BM).

The second one was run by the Japan Clinical Oncology Group (JCOG): a prospective trial readdressing the role of PCI in ED-SCLC [9]. In this phase III trial, patients were randomised to PCI or observation with active monitoring. Conversely from the EORTC trial, the primary endpoint was OS, while time to BM was among secondary endpoints. This study did not demonstrate any difference in median OS between patients receiving PCI (11.6 months) and those assigned to the observation arm (13.7 months) (HR 1.27; 95% CI 0.96-1.68, p=0.94]. However, the cumulative incidence of BM at 6,12 and 18 months was lower in the PCI group compared to the observation group (15%, 32.9% and 40.1% vs 46.2%, 59% and 63%, respectively).

In the current literature, reports on quality of life (QoL) and adverse events (AE) are inconsistent and reported only in three publications [9, 12, 14]. In the EORTC trial [5, 14], there was no statistically significant difference in global health status between the two groups from baseline to 9 months (p=0.10). Most common side effects in the PCI group were hair loss and fatigue, that were significantly higher compared to control arm (p<0.001). No significant differences were found between the study groups in role functioning (p=0.17), cognitive functioning (p=0.07) or emotional functioning (p=0.18). In the JCOG trial [9], Mini-mental state examination (MMSE) scores were assessed at baseline, after 6 and 12 months, without significant differences between the two groups. Toxicity scores of grade 3 or higher were similar

between the irradiated or observed group. The most frequent grade 3 AE were anorexia (5% in the PCI group vs 2% in the observation cohort), malaise (3% in the PCI group vs 1 % in the observation cohort) and muscle weakness (1% in the PCI group vs 5% in the observation cohort). Impact on QoL was not addressed in this trial. Chen et al [12] report acute and late adverse events in the irradiated population. Grade 3 or worse acute toxicities were overall low (2.2 % grade 3 headache, no grade 4 acute side effect, no grade 3 or 4 late effects). The most frequent grade 2 acute side effect was headache (6.7%) and nausea or vomiting (4.4%).

DISCUSSION

Due to the high likelihood to develop BM and the clinically relevant consequences that this event implies, the prevention and control of BM are of paramount importance in patients with SCLC. Consensus has been reached in the setting of LD-SCLC, where, according to international guidelines [6, 7], PCI is part of standard treatment, providing a benefit in terms of survival and local control. However, in the ED-SCLC, the indication to deliver PCI is not universally established. So far, on the basis of the results from the EORTC trial [5], most guidelines [6, 7] recommended PCI for ED-SCLC patients who achieved at least a partial response. However, after the publication of the JCOG trial [9], PCI in this setting has become more controversial due to the uncertainty of OS benefits and practice has been shifting. For example in the recent Impower 133 [15], a trial comparing in ED-SCLC chemotherapy vs chemotherapy plus Atezolizumab, PCI was optional and only 10% of the centers opted for it

The EORTC study [5] was the cornerstone and first randomized trial. It showed that PCI reduces by two to three folds the risk to develop symptomatic BM, and prolongs OS with improved 1-year survival reaching 30% in the treated population versus 13% in the non-PCI group. Key criticism to the EORTC trial is that patients were not systematically screened for BM (unless symptoms suggested so). This pragmatic approach may have led to treat with PCI some patients that already had BM, and this could imply that the OS improvement could be due to the treatment of existing disease, and not to a true prophylactic effect. However, according to Hochstenbag et al [16], the proportion of patients with asymptomatic BM detected by follow-up MRI is rather small, about 15%, and it seems unlikely that this small proportion can justify the observed OS benefit.

The JCOG study [9] found, in the first analysis based on 163 patients, no benefits in terms of OS with a median survival of 10.1 months in the PCI group compared with 15.1 months in the control group (p=0.091). This finding led to the premature termination of the trial for futility. At the final analysis, with a longer follow-up of almost 12 months, the difference in median survival was less important (2 months difference vs 5 observed in the first analysis), leading the Authors to conclude that “prophylactic cranial irradiation is not essential” for patients with ED-SCLC if they are regularly assessed by MRI during follow-up, and treated for symptomatic metastases when required. Unlike the EORTC trial [5], all patients had brain MRI before the enrolment, and was performed during follow-up every 3 months for the first year, and every 6 months thereafter.

These results raise two important considerations. First, routine brain MRI imaging follow-up every 3 months would come with a considerable socioeconomic impact, which would not easily be applicable in clinical practice in the vast majority of the

countries. Second, when comparing 1-year OS between the two trials, patients enrolled in the JCOG [9] had a much better survival in both the PCI arm and the control arm than in the EORTC trial [5] (53.6 % vs 13.3% in the non-PCI arm, 48.4% vs 27.1% in the PCI arm). This may be partially explained by different genetics between Asian and Caucasian populations [17], but also by a possible selection bias. Indeed, the proportion of patients who were offered second-line chemotherapy was higher in the JCOG [9] compared to the EORTC [5] trial: within the JCOG [9], 40 patients in the observation arm (36%) and 29 patients in the PCI group (26%) were offered fourth-line chemotherapy. This is quite an exceptional event in SCLC patients and does not reflect daily practice.

In the cited retrospective series, as far as OS concerns, there's a clear advantage in favour of PCI.

It is worth discussing the systemic review and meta-analysis by Maeng et colleagues [18] , who used as primary endpoint OS. They analyzed 5 trials, 2 of them prospective. In pooled estimates, PCI did not statistically improve OS (HR = 0.82; 95%, CI: 0.60, 1.11; p = 0.19). However, the PCI group had a significant advantage in 1-year survival (37.1% versus 27.1%; 95% CI: 0.80–0.95; p= 0.002), progression-free survival (HR = 0.83; 95% CI: 0.70–0.98; p = 0.03) and decreased risk of BM (HR = 0.34; 95% CI: 0.23–0.50; $p < 0.001$) compared to the non-PCI group.

One more meta-analysis by Ge et colleagues [19] was recently published, assessing 14 papers, of which again only 2 were prospective. The results showed that PCI significantly improved overall survival (HR = 0.57; 95%, CI: 0.47-0.69; $p < 0.001$) and BM (RR =0.47, 95%CI: 0.33, 0.69; $p < 0.01$). However, this study had many flaws: an extremely heterogeneous population, the different PCI doses, and PCI timings.

Development of symptomatic BM is responsible for low QoL, significant morbidity, including hospitalization, and a median survival of only 4 to 6 months [20-22]. The EORTC and JCOG trials [5, 9] have shown that PCI significantly reduces by 2- to 3-fold the incidence of BM. In the Japanese trial [9] the cumulative incidence of BM at 6, 12 and 18 months was significantly higher in the observation arm. In this group, 83% of patients (compared to 46% in the PCI arm) needed radiotherapy; also in the EORTC trial, cranial irradiation was ultimately offered to 59% of patients with symptomatic BM in the non-PCI cohort vs 8.3% in the PCI cohort [5].

The results from retrospective series are in line with these findings. Chen et al [12] found a significantly increased BM-free survival (p=0.002) with 1-year incidence of BM of 17% vs 56% in the PCI and non-PCI group, respectively. The median time for the development of BM was also found to be longer in the PCI group (23.8 months vs 10.2 months) by the Ontario study [11].

Although the CALGB 30504 study [23] was not included in our final list because of the presence of a possible confounding factor (i.e. the use of an anti-angiogenic tyrosine kinase inhibitor), we find it is worth taking into consideration the post-hoc unplanned analysis. This trial was a phase II randomized trial of sunitinib vs placebo in ED-SCLC patients responding to platinum-based chemotherapy. Brain imaging was required at pre-enrollment. PCI was delivered at the discretion of the treating physician. Results showed a trend for improved progression-free survival (PFS) and OS in patients receiving PCI and sunitinib, with a quite remarkable central nervous system progression in the non-PCI group (27% vs 12%, p=0.05).

Thus, the burden of brain failure is relevant and must be considered, for both the patients QoL that deteriorates with such an event [24] and the balance of cost/benefit.

Over the past decade concerns regarding the possible decline of the neurocognitive functions (NCF) in patients treated with PCI have surfaced. However, there is no robust data to demonstrate any difference in NCF with or without PCI [25]. In a review by Tallet et al [26] on NCF in patients, after whole-brain radiotherapy, (patients were offered PCI or therapeutic WBRT), most studies assessing NCF in the setting of PCI showed a very low incidence of neurocognitive impairment at one year. MMSE was the only parameter assessed within the Japanese trial [9], and it did not show any difference after 12 and 24 months. Furthermore, most patients already have abnormal neuropsychology testing after chemotherapy and before PCI, stressing the importance to assess the chemotherapy impact on NCF. QoL was tested in the EORTC trial [5] and the impact of irradiation on functioning scales was moderate. Finally, neuro-toxicity induced by cranial irradiation may be reduced by hippocampal sparing. A prospective study suggested a potential benefit of this technique in limiting the neuropsychological sequelae of brain radiation for patients treated with PCI for LD-SCLC [27]. However, the safety of hippocampal-avoidance PCI still needs to be further validated in terms of risk of brain failure in the SCLC population.

To comment on doses and schedules, wide variation is seen among studies with doses ranging from 20 to 30 Gy resulting in different biologically equivalent doses (up to 39 Gy with an α/β of 10 Gy). Twenty-five Gy in 10 fractions is nowadays the standard. Higher dose do not translate into higher local control, and are associated with a possible negative impact on NCF [28]. The use of higher doses and dose per fraction in the past could, therefore, have had an impact on toxicity without any benefits in terms of disease control.

International guidelines, such as Version 1.2019 National Comprehensive Cancer Network (NCCN) guidelines [29] suggest to consider PCI or MRI brain surveillance in ED-SCLC with complete or partial response to first line chemotherapy.

CONCLUSIONS

Despite contradictory findings about a possible OS advantage in favour of PCI in the literature and the need to run further prospective trials, our review has further confirmed that PCI plays a role in reducing the incidence of developing BM in ED-SCLC patients responding to first-line platinum-based chemotherapy.

We would strongly encourage oncologists and radiation oncologists to consider all the factors and evidence we have gathered in this review, and to share them openly with the patients in order to make an informed choice based on the evidences rather than personal belief

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