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Original article

Impact of pemetrexed on intracranial disease control and radiation necrosis in patients with brain metastases from non-small cell lung cancer receiving stereotactic radiation

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ABSTRACT

Background: Pemetrexed is a folate antimetabolite used in the management of advanced adenocarcinoma of the lung. We sought to assess the impact of pemetrexed on intracranial disease control and radiation-related toxicity among patients with adenocarcinoma of the lung who received stereotactic radiation for brain metastases.

Materials/Methods: We identified 149 patients with adenocarcinoma of the lung and newly diagnosed brain metastases without a targetable mutation receiving stereotactic radiation. Kaplan–Meier plots and Cox regression were employed to assess whether use of pemetrexed was associated with intracranial disease control and radiation necrosis.

Results: Among the entire cohort, 105 patients received pemetrexed while 44 did not. Among patients who were chemotherapy-naïve, use of pemetrexed ($n = 43$) versus alternative regimens after stereotactic radiation ($n = 24$) was associated with a reduced likelihood of developing new brain metastases (HR 0.42, 95% CI 0.22–0.79, $p = 0.006$) and a reduced need for salvage brain-directed radiation therapy (HR 0.36, 95% CI 0.18–0.73, $p = 0.005$). Pemetrexed use was associated with increased radiographic necrosis. (HR 2.70, 95% CI 1.09–6.70, $p = 0.03$).

Conclusions: Patients receiving pemetrexed after brain-directed stereotactic radiation appear to benefit from improved intracranial disease control at the possible expense of radiation-related radiographic necrosis. Whether symptomatic radiation injury occurs more frequently in patients receiving pemetrexed requires further study.

Central nervous system (CNS) metastases remain a significant clinical challenge in the care of patients with advanced non-small cell lung cancer (NSCLC) and are responsible for substantial morbidity and mortality in this population [1–3]. An estimated 20% of patients with NSCLC have CNS metastases at the time of diagnosis [1,3] and a significant percentage of remaining patients will develop brain metastases later in their disease course [2]. For the minority of NSCLC patients who have targetable mutations or rearrangements in genes including *EGFR*, *ALK*, or *ROS1*, the development of tyrosine kinase inhibitors with the ability to penetrate the blood–brain barrier has transformed the management of CNS metastases [4–6]. However, such advances in drug development do not benefit all NSCLC patients for whom radiation therapy, with or without preceding neurosurgical resection, has remained the primary treatment modality for CNS disease.

For patients with a limited number of brain metastases, stereotactic radiation delivered as either stereotactic radiosurgery (SRS: focused radiation given in a single day) or stereotactic radiotherapy (SRT: focused radiation administered over >1 day) has afforded

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more precise treatment of metastatic lesions while avoiding the potentially significant neurocognitive side effects and decreased quality of life associated with whole brain radiation (WBRT) [7–10]. The main adverse effect associated with stereotactic radiation is radiation necrosis (i.e. radiation-induced breakdown of the blood–brain barrier with or without associated neurologic symptomatology) [11].

For advanced NSCLC patients with adenocarcinoma histology without a targetable mutation, National Comprehensive Cancer Network guidelines suggest numerous therapeutic options all of which include a platinum agent, however the optimal choice of second agent in addition to a platinum agent remains unclear [12]. Regimens containing pemetrexed, an antimetabolite analog of folic acid, appear to be more effective in patients with adenocarcinoma and less effective than regimens without pemetrexed in patients with squamous cell carcinoma [13,14]. Pemetrexed has been shown to benefit patients with non-squamous NSCLC when used as part of a first-line platinum doublet regimen [14], as maintenance therapy [15], or as second line monotherapy [16] following platinum doublet therapy with other agents. Pemetrexed does have some ability to cross the blood–brain barrier [17], and there are limited data to suggest that in some cases, pemetrexed can result in stabilization of CNS disease in patients with NSCLC [18,19].

The overlap in therapeutic efficacy and treatment morbidity in patients who receive stereotactic radiation for brain metastases and pemetrexed-based chemotherapy remains poorly characterized. A related drug, methotrexate, has intracranial activity in a number of malignancies but also possesses known neurologic toxicity, particularly in patients who receive brain-directed radiation therapy [20,21]. Accordingly, we sought to characterize the impact of pemetrexed use on both intracranial disease control and radiation necrosis among patients with advanced adenocarcinoma of the lung and newly-diagnosed brain metastases managed with brain-directed stereotactic radiation.

Materials and methods

Patient identification and clinical/radiographic characteristics

Under an IRB-approved research protocol, we retrospectively identified 237 patients with adenocarcinoma of the lung who received stereotactic radiation for newly diagnosed brain metastases at Brigham and Women's Hospital/Dana-Farber Cancer Institute between January 2001 and December 2015 Among the entire cohort, 124/237 (52%) were treated for brain metastases during the initial staging workup, while 113/237 (48%) were treated for brain metastases occurring at a later point. Patients who underwent neurosurgical resection of intracranial lesions were included if at least one brain metastasis was not surgically resected. Patients receiving WBRT as part of the initial management strategy were excluded. We excluded patients with *EGFR* mutations ($n = 53$) and *ALK* rearrangements ($n = 11$) as well as those without brain-directed imaging available post-treatment ($n = 24$) leaving 149 patients in the final cohort. If mutation/rearrangement status for *EGFR/ALK* was unknown we included the patient in the cohort. One patient with a *ROS1* rearrangement was included in the final analysis.

Radiation treatment

Lesions that were <2 cm and 2–3 cm were typically treated with SRS using a dose of 20 Gy and 18 Gy, respectively. Patients with targets >3 cm were generally managed with 5-fraction SRT (25–30 Gy). The margin for the planning target volume was generally 0–1 mm for intact tumors and 2 mm for surgical cavities; a clinical target volume expansion was not used [22]. All stereotactic radiation was delivered on a linear accelerator.

Imaging assessment and validation

For brain metastases that enlarged after stereotactic radiation, delineation of necrosis (Fig. 1A) versus disease progression (Fig. 1B) was made by a team of CNS radiation oncologists with final validation of all data by a senior author (AAA) based on the following factors: pathology reports (if the enlarging lesion was resected), dual-phase positron emission tomography studies, and radiographic assessment over time on magnetic resonance imaging (MRI)-based imaging of the brain. Features on MRI suggestive of radiation necrosis included lack of sustained growth in the absence of CNS-active therapy, development of a T1 hypointense center, a large edema to enhancing disease ratio, and poorly delineated borders on T1 post contrast imaging [23]. All MRI studies from a given patient were fused together to ensure consistency of evaluation utilizing MIM® Software (v6.5, Cleveland, OH).

Because the distinction between radiation necrosis and tumor progression was frequently based on the results of radiographic findings alone, we conducted a sensitivity analysis to test the accuracy of such determinations. We used a separate database of 1685 patients with brain metastases secondary to a primary tumor of any histology to identify 30 patients managed with a craniotomy for an enlarging, enhancing lesion after stereotactic radiation in which pathology findings revealed either tumor recurrence alone or radiation necrosis alone. The senior author reviewed the associated imaging after being provided a brief clinical vignette outlining the patient's pre-surgical history but not the pathology results and decided as to the reason for enlargement (tumor progression vs. necrosis) while remaining blinded to the results of the pathology after resection and all patient-identifying information. In total, 27 of 30 cases were assessed correctly (kappa = 0.76) increasing the confidence that patients in the current study who were assigned a diagnosis of tumor recurrence versus radiation necrosis based on MRI imaging alone were classified with an acceptable degree of accuracy. If a diagnosis of radiation necrosis was made for any patient in this cohort, we distinguished radiographic necrosis from radiographic and symptomatic necrosis based upon the presence versus absence of associated neurologic symptoms (including patients who received dexamethasone and/or bevacizumab for radiation-related inflammation) correlating with the anatomic location of the lesion in question.

Statistical analysis

The entire cohort was used to assess the relationship between pemetrexed use and radiation necrosis. Pemetrexed dose was typically 500 mg/m^2 given every 3 weeks. Timing of pemetrexed administration was recorded with specific reference to SRS/SRT delivery (i.e. before, during, or after). The median number of cycles of pemetrexed received was 5 (IQR 2–9).

For endpoints relating to intracranial disease control, we limited assessments to patients who were chemotherapy-naïve prior to stereotactic radiation and compared outcomes in cohorts who received a pemetrexed-containing regimen versus any alternative regimen post-radiation. The rationale for this was to remove any confounding factors or bias which may exist in patients who have had multiple prior chemotherapy regimens. Among patients who were censored, time to radiographic necrosis and time to new brain metastases were defined from the diagnosis of brain metastases to the last MRI exam. The outcomes of time to symptomatic necrosis and time to salvage-brain directed radiation therapy utilized the date of last follow up or date of death as the end date. Statistical analysis was performed using SAS statistical software

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