Brain metastases: the need for a more tailored approach in non-small-cell lung cancer patients

Pablo Martínez · Enriqueta Felip

Brain metastases are quite common in cancer patients and their incidence has increased over the last two decades. That may be due to both improvements in diagnostic methods and longer survival of metastatic patients. The most common primary site for patients with brain metastases is the lung and approximately 20% of patients with non-small-cell lung cancer (NSCLC) will develop brain metastases at some point in the course of their disease.

Most patients with brain metastases are symptomatic at diagnosis and their presence should be suspected in any patient with a history of lung cancer who presents with a new neurological sign or symptom. Magnetic resonance imaging is the test of choice for diagnosing brain metastases because of its superior resolution and accuracy compared with computed tomography.

Overall, the outcome for NSCLC patients who develop brain metastases remains poor, with an average survival of 3–6 months. A number of prognostic indexes have been proposed and validated with a view to predicting more accurately the prognosis of patients with brain metastases [1]. Essentially, all these index scores help us to better select patients for the different options available to treat brain metastases: surgery, stereotactic radiosurgery, whole brain radiotherapy, chemotherapy and corticosteroids. However, these index scores are less than perfect and more precise prognostic tools are clearly needed.

For patients with single or 1–3 brain metastases as the only site of disease, or with systemic disease which can be radically treated, the main objective is to completely eradicate or control the brain lesion. Surgical resection is usually employed for potentially resectable lesions, which are symptomatic and/or affecting silent areas of the brain as surgery can provide immediate relief in patients with a good baseline performance status. Another advantage

of surgical resection is the pathologic confirmation of the malignant nature of the lesion. Postoperative radiotherapy has demonstrated a decrease in the recurrence of brain metastases, a decrease in the mortality due to neurological deterioration and a delay in neurologic clinical deterioration [2, 3].

Radiosurgery has emerged as a non-invasive option to treat patients with 1–3 brain metastases, providing similar local control rates to surgery [4–6]. However, no randomised trial has compared the two approaches. Stereotactic radiosurgery is preferable to open surgery in patients with brain metastases with lesions no greater than 30–35 mm who have no symptomatic oedema or mass effect and those unlikely to achieve complete surgical resection.

Whole brain radiotherapy is the standard of care in patients with multiple brain metastases. Several randomised trials have explored different doses and fractions; a total of 30 Gy in 10 fractions is considered appropriate in the majority of patients [7]. In patients with brain metastases and symptomatic extracranial metastatic disease, starting treatment with systemic chemotherapy and delaying whole brain radiotherapy could be an option with no detrimental impact on the final outcome.

Despite the above-mentioned treatment approaches, the majority of NSCLC patients treated for brain metastases relapse or develop new symptomatic brain lesions. It is clear that we need effective tools to help us decide which patients would benefit from a more aggressive approach. Hashimoto et al. [8] reported that in NSCLC patients with brain metastases undergoing brain surgery followed by radiotherapy, the status of the MGMT promoter region would be able to identify two groups of patients with different prognoses. In that study, the differences in patients' survival, according to the status of the promoter region of MGMT, were not statistically significant, probably due to the small sample size. Although, as the authors admit in the discussion, the study has some methodological limitations, the manuscript highlights the impact of brain metastases in NSCLC patients and the need for more tailored treatment in this group of patients. The study of Hashimoto et al. opens the door to the analysis of the potential role of the status of the promoter region of MGMT as a prognostic/

P. Martínez · E. Felip (✉)
Medical Oncology Department
Vall d'Hebron University Hospital
P. Vall d'Hebron, 119-129
ES-08035 Barcelona, Spain
e-mail: efelip@vhebron.net

predictive factor in a larger number of patients. In patients in whom we are contemplating using more aggressive treatment approaches, it is essential to have prognostic and predictive tools that allow us to select the most appropriate treatment in each individual case.

In summary, the optimal treatment for patients with brain metastases is an area open to discussion in which

many questions are yet to be answered and in which a more tailored approach is required. The analyses of molecular markers requires further investigation and it is to be hoped that in the near future more studies, such as the one published in this issue by Hashimoto et al., will provide us with clearer rules to guide us in the treatment of our NSCLC patients with brain metastases.

References

1. Sperduto P, Berkey B, Gaspar L et al (2008) A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys* 70:510
2. Patchell R, Tibbs Ph, Regine W et al (1998) Post-operative radiotherapy in the treatment of single metastases to the brain. A randomized trial. *JAMA* 280:1485
3. Kocher M, Soffiatti R, Abacioglu U et al (2011) Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 29:134
4. Muacevic A, Kreth FW, Horstmann GA et al (1999) Surgery and radiotherapy in the treatment of solitary cerebral metastases of small diameter. *J Neurosurg* 91:35–43
5. Schoggl A, Kitz K, Reddy M et al (2000) Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastasis. *Acta Neurochir (Wien)* 142:621–626
6. O'Neill BP, Iturria NJ, Link MJ et al (2003) A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases. *Int J Radiat Oncol Biol Phys* 55:1169–1176
7. Borgelt B, Gelbert R, Kramer S et al (1980) The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group (RTOG). *Int J Radiat Oncol Biol Phys* 6:1–9
8. Hashimoto K, Narita Y, Matsushita Y (2012) Methylation status of O⁶-methylguanine-DNA-methyl transferase promoter region in non-small-cell lung cancer patients with brain metastasis. *Clin Transl Oncol* 14:31–35