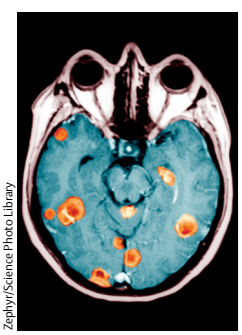
3 Hansen ML, Jepsen RM, Olesen JB, et al. Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. *Europace* 2015; **17:** 18–23.
4 Klein AL, Grimm RA, Murray RD, et al, for the Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001; **344:** 1411–20.
5 Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011; **123:** 131.
6 Piccini JP, Stevens SR, Lokhnygina Y, et al. Outcomes following cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. *J Am Coll Cardiol* 2013; **61:** 1998–2006.
7 Flaker G, Lopes RD, Al Khatib SM, et al. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *J Am Coll Cardiol* 2014; **63:** 1082–87.
8 Cappato R, Ezekowitz MD, Klein AL, et al, on behalf of the X-VeRT Investigators. Rivaroxaban *vs.* vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014; **35:** 3346–55.
9 Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; **383:** 955–62.
10 Coleman CM, Khalaf S, Mould S, et al. Novel oral anticoagulants for DC cardioversion procedures: utilization and clinical outcome compared with warfarin. *Pacing Clin Electrophysiol* 2015; **38:** 731–37.
11 January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; **130:** 2071–104.
12 Goette A, Merino JL, Ezekowitz M, et al. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomized, open-label, phase 3b trial. *Lancet* 2016; published online Aug 30. http://dx.doi.org/10.1016/S0140-6736(16)31474-X.

Whole brain radiotherapy in patients with NSCLC and brain metastases



Zephyr/Science Photo Library

Published Online
September 4, 2016
http://dx.doi.org/10.1016/S0140-6736(16)31391-5

See Articles page 2004

Radiation oncologists are often challenged because of the paucity of randomised trials supporting their clinical practice. In terms of brain metastases treatment, it should be emphasised that there have been five randomised trials assessing whole brain radiotherapy (WBRT): four studies[1–4] assessing stereotactic radiotherapy with or without WBRT for patients with four or less brain metastases, and the present trial by Paula Mulvenna and colleagues[5] in *The Lancet* assessing optimum supportive care with or without WBRT in a much poorer prognostic population of patients with non-small-cell lung cancer (NSCLC). None of these trials has shown any survival improvement with WBRT, but the first four have shown improved intracranial control with the addition of WBRT. It is only in small-cell lung cancer that prophylactic WBRT improves survival because emergence and development of brain metastases is prevented; but this does not apply to patients with NSCLC[6] Because of advances in the management of NSCLC, the risk of developing brain metastases seems to increase as survival is prolonged. NSCLC management in 2016 still represents a real challenge because detectable brain metastases might be responsible for life-threatening symptoms and serious impairment of quality of life, possibly ameliorated with WBRT.[7]

Mulvenna and colleagues are to be congratulated for conducting this non-inferiority phase 3 trial assessing the omission of WBRT in patients with NSCLC and brain metastases.[5] They chose quality-adjusted life-years (QALYs) as the primary outcome measure, and a group of 538 patients between 2007 and 2014 were randomly assigned to receive either WBRT (20 Gy in five daily fractions) and optimal supportive care, including dexamethasone (n=269), or optimal supportive care alone (n=269). The benefits in terms of length of life were adjusted to reflect the quality of life assessed with weekly questionnaires. 536 patients died by October, 2015. The authors concluded that there was no evidence of a difference in terms of QALYs, overall survival (hazard ratio [HR] 1·06, 95% CI 0·90–1·26), or quality of life; the median survival from randomisation was less than 3 months. The difference between the mean QALYs was 4·7 days (46·4 QALY days for the optimal supportive care plus WBRT group *vs* 41·7 QALY days for the optimal supportive care only group), with two-sided 90% CI of –12·7 to 3·3.

There is no question that this is a large and well designed trial, and that patients were well assessed, with more than 90% of the expected follow-up forms and more than 80% of the quality-of-life forms received. It should be emphasised that owing to poor survival, only 289 (53%, 149 WBRT patients and 140 optimal supportive care patients who were assessed for quality of life at 4 weeks) and 97 (18%, 54 WBRT patients and 43 optimal supportive care patients assessed at 12 weeks) of all enrolled patients answered quality-of-life questionnaires at 4 weeks and 12 weeks, respectively. Should we then consider that there is no place for WBRT

in such a group of patients with NSCLC because it gives little, if any, additional clinically significant benefit?

The limitations of the study include that it is generally accepted that the maximum benefit of radiotherapy is achieved 6 weeks after the end of the treatment. Given the median overall survival of 8 weeks and considering the time to deliver WBRT, about half of patients died before an optimum symptomatic assessment could be done. This might also explain why WBRT did not have any effect on steroid consumption, because patients did not live long enough for an effect to be seen. Of course, the decision to deliver WBRT should be put into perspective with the fatigue and neurocognitive toxicity it might generate. This trial raises another question: are the conclusions applicable to patients with NSCLC treated by today's standards? A one size fits all policy was applied to all eligible patients, ranging from those unsuitable for surgery or stereotactic cranial radiotherapy to any patient for whom there was uncertainty over the benefit of WBRT. As expected, the population was quite heterogeneous, but of poor outcome. The recursive partitioning analysis (RPA) and DS-GPA (Diagnosis Specific Graded Prognostic Assessment) prognostic classes taking into account Karnofsky performance status (KPS), age, presence of extracranial disease, and status of primary tumour or number of brain metastases were designed to select the patients most eligible for radiotherapy.[8] As an example, this trial confirms that WBRT should not be given to RPA class 3 patients, which represented more than a third of the enrolled population. There was no evidence that WBRT offered a survival advantage within any prognostic class, but this should be interpreted with caution. The results of this trial emphasise the robustness of prognostic factors such as age and KPS.[5] Improved survival with WBRT was indeed shown for younger patients, particularly those younger than 60 years, and there was a trend for better outcome in patients with a KPS of at least 70 and those with controlled primary NSCLC. It now seems clear that an elderly patient, with a KPS of less than 70 and uncontrolled primary, should not have WBRT. Indications of stereotactic radiotherapy have become broader, especially in elderly patients and in patients with expected longer term survival.[9,10]

As outlined by the authors, there have been considerable changes within the past 10 years in the systemic treatment of patients with advanced NSCLC, but also in the development and widespread use of stereotactic radiotherapy and MRI to strictly monitor some of these patients who might need several treatments. Identification of oncogenic driver mutations, and more sophisticated pre-treatment tumour characterisation has transformed the outcome of a subgroup of patients with metastatic NSCLC; survival has been increased by at least three times over the past 15 years in patients with epidermal growth factor receptor (*EGFR*)-mutated or anaplastic lymphoma kinase (*ALK*)-rearranged NSCLC. *EGFR* mutation as well as the absence of (or little) tobacco consumption, considered as a surrogate marker of these molecular abnormalities, were not captured in this study, and this is another key limitation to the interpretation of these results. The intracranial efficacy of targeted drugs such as EGFR tyrosine kinase inhibitors (TKI) or ALK inhibitors has been shown, justifying their use as first-line treatment in case of *EGFR* mutation or *ALK* rearrangement.[11,12] WBRT might also enhance penetration of some drugs, thus possibly improving their efficacy.[13]

Finally, this trial might not rule out use of WBRT in all patients with NSCLC and brain metastases. Is there still a place for WBRT in patients with NSCLC and brain metastases? Yes, we believe that optimised WBRT, given at the right time to appropriate patients, could lead to more individualised strategies. Both systemic and local treatments of brain metastases need to be discussed with patients, taking into account the results of this trial, classic prognostic factors, and the molecular status.

Cécile Le Pechoux, Frederic Dhermain, Benjamin Besse
Department of Radiation Oncology (CLP, FD) and Department of Medical Oncology (BB), Gustave Roussy Cancer Campus, Villejuif 94800, France; and Faculté de Médecine, Université Paris Sud, Le Kremlin-Bicêtre, France (BB)
cecile.lepechoux@gustaveroussy.fr

We declare no competing interests.

1 Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006; **295:** 2483–91.
2 Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009; **10:** 1037–44.
3 Kocher M, Soffietti R, Abacioglu U, et al. 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* 2011; **29:** 134–41.
4 Brown PD, Asher AL, Ballman KV, et al. NCCTG N0574 (Alliance): a phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1–3 brain metastases. *J Clin Oncol* 2015; **33** (suppl 15)**:** LBA4 (abstr).

5 Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* 2016; published online Sept 4. http://dx.doi.org/10.1016/S0140-6736(16)30825-X.

6 Le Pechoux C, Sun A, Slotman BJ, De Ruysscher D, Belderbos J, Gore E. Prophylactic cranial irradiation for patients with lung cancer. *Lancet Oncol* 2016; **17:** e277–93.

7 Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol* 2007; **25:** 1260–66.

8 Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012; **30:** 419–25.

9 Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014; **15:** 387–95.

10 Besse B, Adjei A, Baas P, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. *Ann Oncol* 2014; **25:** 1475–84.

11 Zhang I, Zaorsky NG, Palmer JD, Mehra R, Lu B. Targeting brain metastases in *ALK*-rearranged non-small-cell lung cancer. *Lancet Oncol* 2015; **16:** e510–21.

12 Heon S, Yeap BY, Lindeman NI, et al. The impact of initial gefitinib or erlotinib versus chemotherapy on central nervous system progression in advanced non-small cell lung cancer with EGFR mutations. *Clin Cancer Res* 2012; **18:** 4406–14.

13 Shi W, Dicker AP. CNS metastases in patients with non-small-cell lung cancer and ALK gene rearrangement. *J Clin Oncol* 2016; **34:** 107–09.

Antiplatelet strategies in elderly people: still a long way to go

Published **Online** August 28, 2016 http://dx.doi.org/10.1016/S0140-6736(16)31387-3

See **Articles** page 2015

Outcomes of patients with acute coronary syndrome undergoing percutaneous coronary intervention have been significantly improved with the potent $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor.[1,2] Elderly patients comprise a growing subset of the acute coronary syndrome population. This subset is characterised by multiple organ changes and various comorbidities, which altogether culminate in an increased risk of both ischaemic and bleeding complications after percutaneous coronary intervention. Platelet function testing has been established and validated to predict ischaemic and bleeding events in patients treated with percutaneous coronary intervention.[3,4] However, previous studies,[5,6] enrolling mostly low-risk patients with little use of potent antiplatelet drugs, have been unable to show clinical superiority of strategies that implemented platelet function testing for treatment guidance. Nevertheless, elderly patients undergoing percutaneous coronary intervention represent a high-risk cohort that might derive clinical benefit from platelet function testing to monitor and adjust the level of platelet inhibition.

In *The Lancet*, Guillaume Cayla and colleagues report the results of the randomised controlled ANTARCTIC trial,[7] which assessed the effect of platelet function monitoring with treatment adjustment in 877 elderly patients (aged ≥75 years) stented for an acute coronary syndrome. The investigators aimed to establish the superiority of a platelet function monitoring-guided treatment approach using the VerifyNow assay (monitoring strategy) with options to escalate (from 5 mg to 10 mg prasugrel) or de-escalate (from 5 mg prasugrel to clopidogrel 75 mg) the level of platelet inhibition, compared with a uniform treatment approach (control strategy) of prasugrel 5 mg daily with no testing or treatment adjustment. As a key result of the study, the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, stent thrombosis, urgent revascularisation, and bleeding complications after 12 months did not differ between the two treatment groups (hazard ratio 1·003, 95% CI 0·78–1·29; p=0·98); ischaemic complications (p=0·80) and bleeding events alone (p=0·77) were likewise non-significant. On the basis of these results, the investigators conclude that platelet function monitoring to adjust low-dose prasugrel treatment in elderly patients with acute coronary syndrome does not improve their clinical outcome. Cayla and colleagues are to be congratulated for this important and well conducted study of platelet function monitoring to guide treatment specifically in elderly patients, who are generally under-represented in clinical trials. However, some important caveats should be considered that might explain why ANTARCTIC did not show a net clinical benefit of the monitoring approach.

First, the study was designed with an initial treatment strategy of low-dose prasugrel for both groups. Platelet function monitoring in the monitoring group resulted in only 16 (4%) of 435 patients requiring intensification of treatment (up-adjustment to prasugrel 10 mg). In fact, the predominant consequence of testing was de-escalation of treatment with a change of treatment from low-dose prasugrel to clopidogrel in 171 (39%) patients, while 240 (55%) patients in the monitoring group remained on prasugrel 5 mg. In essence, ANTARCTIC therefore compared the effect of prasugrel 5 mg with a regimen in which low-dose prasugrel was replaced by clopidogrel 75 mg in less than half of patients. Against this background, invasively managed