Editorial

Brain metastases: costs for care need to be spend more effectively!

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Brain metastases are a very common problem in many cancers and usually result in considerable morbidity and mortality (1). Among the most common malignancies, symptomatic brain metastases of lung cancer have a high incidence, both at the time of diagnosis of the disease, and at a later stage during therapy or follow-up after therapy.

Large scale reports on incidence and prognosis of brain metastases are lacking. A recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database, covering a 4-year period, shows that of the patients presenting with brain metastases at the time of diagnosis, often lung cancer is the primary tumour. Small cell lung cancer presents as highest (15.8%), followed by adenocarcinoma (14.4%), and other non-small cell lung cancer (NSCLC) (12.8%) (2). In the Swedish Family Cancer database (3) the nervous system was the most frequently mentioned site of metastases (39%).

During the course of their disease many patients with lung cancer will have to face the morbidity of symptomatic metastases, often causing severe neurological symptoms, profound impairment in cognition, poor performance status, loss of autonomy, and poor quality of life (4).

The moment of becoming symptomatic during the course of the disease may vary widely. It ranges from at the time of diagnosis of lung cancer till at the time of widespread tumour progression after systemic therapy. The first sign of metastatic disease can be a single lesion in an, up till then, low stage case after radical therapy such as surgery or stereotactic ablative radiotherapy (SABR). Whereas in a stage IV patient with disease apparently responding to (palliative) chemotherapy, immunotherapy or both, multiple metastatic lesions may become symptomatic. The presentation may differ based on specific characteristics such as histological or molecular features, and its course may be influenced by systemic or loco-regional therapy.

The group of non-squamous NSCLC differs based on the presence of molecular changes. *Anaplastic lymphoma kinase* (*ALK*) gene rearrangements seem to be present in up to 5% without difference between races (5), whereas mutations in the *epidermal growth factor receptor* (*EGFR*) are found in 50% of Asians, but in only 10% of Caucasians (6).

All these features make it very difficult to come to generalizable conclusions on what might be beneficial—or lacking benefit—for an individual patient (7). Currently a patient needs to be characterized much further than having only as diagnosis "NSCLC", as the outcome of those with driver mutations and brain metastases will be completely different than those without these molecular changes. The 1st and 2nd generation EGFR-tyrosine kinase inhibitors (TKIs) have not been evaluated in a systemic way for its efficacy in patients with an EGFR mutation and brain metastases, although a number of responses in small series have been reported (8). The more recent studies with the 3rd generation EGFR-TKI osimertinib (9), shows a much higher potential against brain metastases, and likely will delay local therapy for a considerable period. This may reduce the risk of long-term sequelae of local therapy, for instance radiation-induced cerebral necrosis (10), and osteonecrosis as a long-term side effect of high-dose corticosteroids (11).

A comparable situation and development has been seen

for patients with a rearrangement in ALK where alectinib has proven to be the better TKI with considerable potential against brain metastases (12).

Whether a comparable success story will unroll with the recently introduced immunotherapeutic possibilities still needs to be seen, at least some observations give hope to a change in perspectives (13).

All this will generate not only hope and progress but also result in considerable costs, likely higher than based on recent observations (1), but spent for potential more benefit for the individual patient. Improved control of non-central nervous system (CNS) disease by better systemic therapy (14-16), will result in longer overall survival, maybe better CNS-control and hopefully prevention of brain metastases to become symptomatic.

Unfortunately, not all patients will benefit from these improvements brought by systemic therapy and for those the prognosis remains grim. This emphasizes the need for shifting costs by different approaches. First of all, it is needed to keep patients out of hospital for as long as possible, as in-patients generate high costs. The most important reasons for becoming hospitalized are the disabling symptoms of brain metastases. Detection and/or treatment at a much earlier moment during the course of the disease is therefore needed, especially for those with otherwise still reasonable survival prospects with good quality of life.

Historically, the best oncological example for early treatment of brain metastases is small cell lung cancer, the guidelines incorporated—for more than 4 decades—a standard approach to delay brain metastases of becoming symptomatic by adding "prophylactic" cranial irradiation (17). Even for those with less favourable outcome based on extent of disease prophylactic therapy improved outcome (18). Unclear is if a different approach by regular screening of the brain by MRI could be as beneficial for these patients (19,20). This will add to costs earlier but might be a way to prevent the so often occurring serious disabling symptoms leading to high costs related to the need for hospitalization.

Whether the latter approach could be incorporated in the regular follow-up of NSCLC patients might be a topic of research, it might at least give some more insight in who are at highest risk of developing (symptomatic) brain metastases and through that lead to a more tailored use of prophylactic irradiation of the brain for those at highest risk (21). Although overall survival might not be affected, it might reduce costs in a significant way by reducing costs for care of those with disabling symptoms (1).

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Footnote

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