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Editorial Comment

The management of cerebral metastasis from germ cell cancer; walking the tightrope

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With the introduction of cisplatin-based chemotherapy in the 1980s, metastatic germ cell cancer became a model for a highly curable malignant disease. Today, approximately 80% of patients with overt metastatic disease can be cured by chemotherapy followed by adjunctive surgery to remove post-chemotherapy remnants.[1] Prognostic factors have enabled a further prediction in the likelihood of survival, ranging from over 90% in patients who present with good prognostic features, *versus* 50% in patients presenting with poor prognosis disease.

Although the chemotherapy has attracted most attention, a major contributor is the complete surgical resection of post-chemotherapy residuals.[1] In all risk categories, many patients still have radiological residuals after the completion of the chemotherapy and it has become a standard procedure to resect such remnants. Extensive data from the literature have demonstrated a 10–20% chance of small foci or even gross viable cancer within these post-chemotherapy residuals, and complete resection adds to the eventual feasibility of cure.[1–3] In view of discordant findings up to 40% in retroperitoneal, chest, and other site histologies, there is a general consensus that such surgery requires removal at all remaining sites.[1,4] Patients with intermediate or poor prognosis disease more often present with more bulky disease and multiple sites, and may therefore have a greater need for post-chemotherapy surgical procedures. In 1999, a report by EORTC and MRC investigators provided the strongest evidence to date that the expertise of the treating centre has a significant impact on treatment outcome.[5] A 15% better survival at 2 years could be attributed to better protocol chemotherapy dose adherence and to more frequent of post-chemotherapy surgery. National and international consensus guidelines are now recommending the referral of poor prognosis patients to expert centres. Only then, the best achievable expertise can be provided, both ensuring interventions that are needed, as well as avoiding treatments that are less likely to contribute to the eventual outcome, and that may just add to toxicity associated with the treatment.

The management of patients with cerebral metastases from non-seminomatous germ cell cancer must be seen exactly in this light. The frequency of poor risk germ cell cancer (15% of patients with metastatic disease) is rare in community hospitals and even in university hospitals, the incidence of patients presenting or relapsing with cerebral metastases is even rarer. The International Germ Cell Cancer Collaborative Group Database of 5202 patients comprised no more than

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63 patients (1.3%) presenting with cerebral metastases.[6] Of note, the greater majority of these patients had neurological symptoms that had led to imaging. The true incidence may be higher since at the time brain imaging was not required in the standard workup. Today CTscan or MRI is performed in most patients who present with poor prognosis disease. A German cohort study has shown that 84% of the patients presenting with cerebral metastases qualified for poor prognosis disease by serum tumour marker values or extracranial disease alone, irrespective of the presence of cerebral metastasis.[7] Since brain metastases is considered extremely rare in patients who otherwise present with good risk disease, current guidelines do not recommend brain imaging in good risk patients, unless in the case of symptoms.

If we consider intermediate and poor prognosis germ cell cancer a rare disease entity and a plea is made for referral and treatment in specialised centres, this is even more so the case in patients with brain metastases from germ cell cancer. Even in expert centres the clinical experience is limited and the available literature is based on small retrospective series. The largest database was built by Dr. Fossa et al.[8] By collecting data from several large centres in Europe and detailed analyses of a total of 139 cases, she was the first to provide evidence against the use of whole brain radiation therapy (WBRT) in all patients presenting with cerebral metastases who received standard induction chemotherapy. Until then, based on scarce data, most authors had recommended either chemotherapy plus whole brain irradiation (WBRT), or concomitant WBRT and chemotherapy, despite the development of leukoencephalopathy in many patients, that is characterised by concentration difficulties and cognition impairment, as well as ataxia and sensory motor changes, occurring 5–15 years after treatment.[9,10] A substantial number of reports on solid tumours, including germ cell cancer, have shown responsiveness of brain metastases to chemotherapy.[10–14] Despite the widely held belief that systemic chemotherapy does not reach the brain no blood brain barrier is present in brain metastases. The free penetration is also evidenced by the enhancement of brain metastases on CT and MRI imaging and the similar responses to chemotherapy of brain metastases as compared with extra-cerebral tumour localisations.[10–14]

As a result, patients presenting with cerebral metastases that is part of widespread metastatic germ cell cancer, may best be treated upfront by standard chemotherapy, followed by repeated imaging and additional surgery or radiation therapy by identical criteria as developed from extracerebral disease sites.[1] An excellent review on this shifting paradigm in the management of brain metastases from germ cell cancer has recently been published by Dr. Forquer et al.[15] Using Dr. Fossa's analysis as a backbone, these authors have separated patients into three groups. The first group consists of those patients with the known cerebral metastases at the time of the initial diagnosis. The second group are those patients who obtain a complete response, but develop a relapse isolated in the brain. The third group are those patients treated with cisplatin-based chemotherapy who relapse with systemic disease plus brain metastases. Today, there is a general consensus that patients who present with cerebral metastasis at initial diagnosis are best served with upfront chemotherapy, unless there is a need for immediate decompression surgery.[15,16] Following the completion of chemotherapy, those patients who have obtained radiological CR, may be followed closely, since there seems no survival benefit by additional WBRT.[8] Those patients who have residual lesions qualify for diagnostic procedures along the same algorithm as defined for extracranial disease, that is to resect residuals whenever possible.[1] In many cases such exploratory surgery may be conducted first at extracranial sites (as findings may require additional systemic therapy). If no viable cancer is found, patients with a solitary residual lesion in the brain may as yet undergo surgery, if viable cancer is found at that time, or in the case of multiple residual brain lesions not accessible by surgery, patients may be treated with additional WBRT.[8,15,16] Patients in the second group (isolated brain relapse following cisplatin-based chemotherapy) may still obtain long-term progression-free survival by surgery and radiotherapy. Such isolated relapse, however, is a rare presentation, since most patients who relapse in the brain also have systemic recurrence. This concurrent systemic and cerebral relapse in most patients with a brain relapse is one of the strongest arguments not to proceed with additional WBRT in patients who have a radiological CR following upfront cisplatin-based chemotherapy; those patients who relapse are likely to have systemic relapse again requiring systemic chemotherapy. The treatment outcome in this (third) group heavily depends on prognostic factors for relapsed disease.[1,17,18] Although these factors have been identified mainly in extracranial disease, today there is no reason to believe that there is a difference in tumour characteristics or intrinsic chemosensitivity between brain metastasis and extracerebral disease. Therefore, the majority of patients relapsing within 2 years following an initial CR to 3 or 4 cycles of BEP chemotherapy may again respond to salvage regimens such as TIP (paclitaxel, ifosfamide and cisplatin), or high-dose chemotherapy.[1,17,18] It is important, though, to emphasise that the frequency of residual viable cancer in post-chemotherapy surgical specimens in the salvage setting is higher (40–50%, as opposed to the 10% following initial chemotherapy).[19] This warrants either exploratory surgery, or stereotactic radiosurgery, or additional WBRT, especially if there is no complete radiological remission in the brain.

In this issue of the EJC, Dr. Oechsle et al., further contribute to the existing data.[20] These authors report a retrospective analysis of patients enroled on a dose-intensified cisplatin, etoposide, ifosfamide (VIP) study who had either presented with cerebral metastases or who had relapsed after the initial treatment. The data lend further support to the above treatment algorithm; of a total of 434 patients with poor prognosis germ cell cancer treated in the framework of the dose-intensified chemotherapy protocol, 50 (12%) were found to have brain metastasis by CT or MRI imaging. Of these 50 patients, 24 had clinical symptoms that led to the diagnosis, in the others the imaging was done at the discretion of the local investigator. Hence, the detection of asymptomatic lesions was augmented. All 50 patients started chemotherapy without prior surgery or radiation therapy. In 70% of the patients the cerebral metastases responded to the chemotherapy, 6% remained unchanged and 14% had disease progression in the brain. Subsequent WBRT was performed in 20 (40%) and post-chemotherapy surgery was done in 4 patients (8%).

Long-term progression-free survival was obtained in 22 patients (44%). Of these, 12 had received post-chemotherapy WBRT to control residual lesions. After a median of 6 months (range 1–15 months) 21 patients relapsed, of whom only 2 had an isolated brain recurrence, whereas 19 relapsed either cerebral and extracerebral simultaneously or exclusively outside the brain. Hence, the eventual outcome was dominated by the overall effectiveness of the chemotherapy to eradicate all sites of the disease, rather by the additional measures to consolidate the cerebral metastases. The second part of this retrospective study provided information of 77 patients who relapsed after the dose-intensified VIP protocol, of whom 19 were found to have cerebral metastasis at the time of relapse. Of these patients 5 had cerebral metastases diagnosed also at the initial presentation, in the remaining 14 patients the cerebral metastases had most likely gone undetected at presentation (as well as residuals after the chemotherapy), as all had initially presented with widespread pulmonary metastases and very high HCG levels, which have been associated with the highest incidence of brain metastasis. In 13 of these patients an isolated cerebral relapse was found. Presumably, most of these isolated relapses resulted from previously unrecognised and residual brain metastases, emphasising the need for diagnostic brain imaging in patients presenting with poor prognosis disease. The apparent control at the extracranial sites and solitary relapse in the brain should be considered a missed opportunity to improve control by further treatment, should residual lesions have been detected on post-chemotherapy brain imaging.

Hence, in 2008, patients presenting with poor prognosis germ cell cancer should have an MRI of the brain in the work-up. Those patients who present with brain metastasis and who obtain a radiological CR by cisplatin-based chemotherapy may be spared additional WBRT, thereby avoiding debilitating leukoencephalopathy in the long-term survivors.[8,10] An active approach not to miss asymptomatic cerebral metastases that do not completely respond is imperative, since residual lesions require additional diagnostic and consolidation measures. With the increasing knowledge in the recent years walking the tightrope of managing these patients is definitely becoming firmer.

Conflicts of interest statement

None declared.

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