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CLINICAL STUDY

Preliminary experience of the concurrent use of radiosurgery and T-DM1 for brain metastases in HER2-positive metastatic breast cancer

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Abstract This is preliminary study assessing the efficacy and safety of concurrent use of radiation therapy (RT) and T-DM1 for the treatment of brain metastases (BM) in patients with HER2-positive metastatic breast cancer (BC). We retrospectively studied 12 patients treated for BM at the Institut Curie in 2014–2015 with T-DM1 and concurrent (4) or sequential (8) radiosurgery with or without whole brain irradiation. The following variables were studied: local control, clinical and radiological response as well as early and late side effects. The mean age of the population was 38 years at the time of diagnosis of BC and 46 years at of BM. All patients were with good PS. The response rate of the concurrent treatment group was 75 % with 1 complete response, 1 partial response, one stable disease and 1 progression. Comparatively, the response rate in the sequential group was as follows: two complete responses, two partial responses, six cases of stable disease and two cases of local progression. No patient experienced interruption of irradiation because of side effects. About 50 % of patients were asymptomatic after treatment. Radiation necrosis was observed in 50 % of patients in the concurrent group and 28.6 % of patients in the sequential group with a similar rate of oedema in the two groups. We found that the combination of T-DM1 and radiosurgery was feasible but can increase the incidence of radiation necrosis. Larger prospective studies with longer follow-up are needed to more clearly evaluate this association.

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Introduction

The incidence of breast cancer in France is approximately 48,763 cases per year [1], 20–25 % of whom present amplification or overexpression of Epidermal Growth Factor Receptor (HER2) [2], associated with decreased survival [3] and brain metastases in 20 % of cases [4].

Trastuzumab (Herceptin) was the first HER2-targeted agent developed in the 2000s. It increases the overall survival and the progression-free survival for locally advanced [5, 6] and metastatic breast cancer [7, 8]. Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate (ADC) currently approved as monotherapy for the second-line treatment for HER2-positive metastatic breast cancer pretreated by trastuzumab and taxanes.

This new agent is a combination of a targeted monoclonal antibody (trastuzumab), a stable linker and a cytotoxic agent (maytansine) [9]. T-DM1 binds to the HER2 receptor and delivers a direct chemotherapeutic effect and DM1 disturbs microtubule networks in the cell after internalization and lysosomal degradation of the complex, resulting in cell cycle arrest and apoptotic cell death [10]. Whole brain radiation therapy (WBRT) and radiosurgery for brain metastases can be performed concurrently with trastuzumab without increasing local toxicity [11], but few data are available concerning the toxicity of concurrent T-DM1 and brain radiation therapy. This preliminary study assessed the efficacy and safety of concurrent radiosurgery and T-DM1 for the treatment of brain metastases in patients with HER2-positive metastatic breast cancer.

Methods

We conducted a retrospective study of the first twelve female HER2+ breast cancer patients with brain metastases treated at the Institut Curie between 2014 and 2015 after the official marketing authorization of T-DM1 (out of clinical study). Four patients received radiosurgery concomitantly and eight patients received radiosurgery sequentially (with interval longer than 1 month) with T-DM1. All patients were treated with intravenous (IV) infusion of T-DM1 every 3 weeks (Day 1 = Day 21).

Patient characteristics at initial diagnosis of breast cancer

The mean age of the patients was 38 (range, 23–53) years and the majority presented grade II or III (75 %) invasive ductal carcinoma (IDC) (83.3 %). Hormone receptors were positive in 50 % of cases. Initial treatment consisted of breast-conserving surgery in five patients (41.66 %), radical mastectomy in eight patients (67 %) and no surgery was performed in one patient (8.33 %). Six patients received neoadjuvant chemotherapy and three patients also received trastuzumab concurrently. Seven patients (58.3 %) received adjuvant chemotherapy, and six of them (50 %) also received trastuzumab concurrently. Seven patients (58.3 %) received hormonal therapy after surgery. Radiotherapy consisted of post-surgery chest wall irradiation in eleven patients, with irradiation of the Internal Mammary nodes in six patients, supraclavicular lymph nodes in ten patients, infraclavicular nodes in three patients and axillary nodes in two patients. One patient was treated by exclusive breast radiotherapy.

Patient characteristics at brain metastatic progression:

Concurrent use was defined as use of systemic treatment with TDM 1 during the radiotherapy. Sequential treatment was defined as interruption of TDM 1 1 week or longer before the radio surgical procedure.

Brain metastatic progression was documented in all 12 cases using magnetic resonance imaging at a mean age of 46 years (range: 28–61). Four patients were symptomatic, ten had a good performance status (PS < 2) and four had multiple brain metastases. The main associated secondary sites were: liver (eight patients), lung (seven patients), bone (five patients), nodes (five patients) and no patients had carcinomatous meningitis. Treatment of local metastases consisted of surgery in four patients (33.3 %), not concomitantly with TDM1, whole brain radiation therapy in six patients (50 %), concomitantly with trastuzumab in three patients but not with T-DM1. Eighteen brain stereotactic radiation therapy sessions were performed in ten patients. Four of these patients were concomitantly treated with TDM1. All patients in this study received T-DM1 for a median duration of 5.1 months (range, 1–9.5). Six patients are still on treatment. The main reasons for discontinuation of treatment were: liver progression (three patients), brain progression (two patients), lung progression (one patient) and toxicity (one patient). One patient died after brain progression, another after multimetastatic progression.

Results

Response

After radiosurgery and concurrent T-DM1 (n = 4), a radiologic response was observed in 75 % (3 of the 4 patients) of patients, including one patient with a complete response, one patient with a partial response, one patient with local stable disease and one patient with progression after treatment. The median interval was 5.5 months (range, 1–15) for local progression and 6.5 months (range, 3–7) for brain progression.

Comparatively, the response rate in the sequential group (n = 8) was as following: two complete responses, two partial responses, six cases of stable disease and two cases of local progression. No patient experienced interruption of irradiation because of side effects.

The median interval was 12.5 months (1–24) for local progression and 19 months (1–65) for brain progression.

Toxicity

The acute radiosurgery-related toxicity was low for most patients with 50 % of asymptomatic patients in the concurrent group and 50 % in the sequential group. The most commonly reported adverse events in the concurrent group were radiation necrosis in 50 % of cases, alopecia in 25 % of cases and memory disorders in 25 % of cases. The most commonly reported adverse events in the sequential group were radiation necrosis in 28.6 % of cases, alopecia in 14.3 % of cases, intracranial hypertension in 7.1 % of cases, locomotor disorders, balance disorders and visual disorders in 21.4 % of cases. Patients with symptoms received steroids, mostly with the dose of 1 mg/kg (Solupred® at the dose 40–60 mg). The radiation necrosis rate was 33.3 % (4/12 treatments) in the sequential group and 50 % (2 of 4 treatments) in the concurrent group. The edema rate was 25 % in the concurrent group and 28.6 % in the sequential group.

Discussion

In this preliminary series, we found that combination of T-DM1 and radiosurgery is feasible but can be associated with radiation necrosis.

Patients treated with trastuzumab and new anti-HER2 targeted therapies obtained improved life expectancy and local brain control [12], but some patients need local treatment for brain metastases. It has already been demonstrated that a concomitant combination of trastuzumab and WBRT is feasible with low local toxicity, but few data are available concerning the combination of radiotherapy and new anti-HER2 targeted therapies.

Shoji Yomo et al. showed that lapatinib combined with radiosurgery achieved better response rates than radiosurgery alone with a response rate of 86 vs. 69 % ($p < 0.001$) with no increased toxicity [13]. A case report [14] of a 68-year-old patient with brain metastatic breast cancer, treated with concomitant whole brain radiation therapy and T-DM1 infusion, reported a local stability of brain metastases and no adverse effects after 6 months of follow-up. In our study, no patient received concomitant WBRT. Six patients received sequential WBRT with a median interval of 13.2 months between the two treatments. No adverse effects were observed.

Radiation therapy may therefore increase the local efficacy of T-DM1 as also demonstrated to show increased response rates [15]. We have previously shown that no increased toxicity was found of the concurrent use of TDM 1 and radiotherapy in patients with bone metastases [16].

Radio necrosis represents the main complication of stereotactic radiotherapy (SRT) for brain metastases. It may be observed in up to 34 % of cases at 24 months after treatment and associated with significant morbidity in 10–17 % [17].

In a study published in Neuro-Oncology [18] based on seventeen patients, four patients were treated with stereotactic radiosurgery and trastuzumab emtansine and thirteen with radiosurgery without T-DM1. The four patients treated with T-DM1 developed clinically significant edema, three had to stop treatment and 57 % developed radiation necrosis.

In our study, the radiation necrosis rate was 50 % in the concomitant group and 28.6 % in the sequential group, but no patients had to stop T-DM1. The edema rate was 25 % in the concurrent group and 28.6 % in the sequential group.

Conclusion

The T-DM1 and concomitant stereotactic radiosurgery combination appears to be well tolerated but could increase the risk of radiation necrosis according to published data with a rate of 6–11 %. Larger prospective studies with longer follow-up are needed to evaluate this association.

Compliance with ethical standards

Conflict of interest No conflicts of interest.

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