Long-Term Remissions in Metastatic Malignant Melanoma Following Chemotherapy and Tamoxifen Maintenance

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Malignant melanoma with distant metastases is regarded as an incurable disease with a short median survival time (< 6 to 12 months). Only a few long-term remissions after chemotherapy lasting 10 or more years have been reported [1]. In a retrospective evaluation, we observed 6 patients who developed a continuous remission following chemotherapy and tamoxifen maintenance therapy (20 mg orally per day for up to 10 years). The remission duration varied from 1 to 16 years (median 8.6 years).

In the last 17 years, we treated in our institution 23 patients with distant metastases with first-line chemotherapy (dacarbazine (DTIC) or bis-chloronitrosourea (BCNU)/cisplatin/DTIC/tamoxifen (BCDT)) outside of a clinical trial. The primary diagnoses were cutaneous malignant melanomas; only 1 patient (no. 5 in the table) had a malignant melanoma of the anus.

12 out of 23 patients reached a partial remission or stable disease and were afterwards treated with tamoxifen 20 mg per day after giving informed consent (table 1). 6 out of these 12 patients developed a continuous remission as mentioned above, 4 of these showed a complete remission, and 2 patients had a continuous partial remission lasting for 62 and 13 months, respectively. No relevant side effects were observed. The patients were seen regularly for a follow-up every 3–6 months. The examination included a chest radiograph, abdominal ultrasonography, blood tests including the serum tumor marker S100 and, from time to time, a computed tomography (CT) scan or magnetic resonance (MR) tomography.

As shown in table 1, no obvious prognostic factors can be detected, probably due to the small number of patients.

It is remarkable that patients 1 and 2 developed progressive disease under tamoxifen maintenance (after 17 and 7 months, respectively), but remained in complete remission following local therapy (exstirpation of a kidney metastasis and an adrenal body in patient 1; irradiation of the lumbar spine, the sacrum and the right humerus in patient 2) and continuation of tamoxifen therapy.

Four out of these 6 patients had liver metastases, usually indicating a particularly poor prognosis. 2 of them (patients 1 and 2) have shown a continuous complete remission for 16 and 13 years, respectively. Up to now, to our knowledge, there has been only 1 case published with a continuous complete remission of liver metastases for 10 years (following vindesine and interferon) [1].

As potential action mechanisms of tamoxifen in malignant melanoma, induction of apoptosis and inhibition of angiogenesis [2], inactivation of the insulin-like growth factor-1 receptor [3], or inhibition of tumor cell invasion and metastasis through suppression of the PKC/MEK/ERK and PKC/PI3K/Akt pathways [4] have been discussed. Tamoxifen monotherapy in metastatic melanoma has been reported to induce remissions in about 5% of the patients, in some cases after progression of the disease in the first months of therapy [5]. In combination with chemotherapy, tamoxifen failed to exert an additional therapeutic effect in most studies [6]. But, to our knowledge, no results are published about tamoxifen maintenance following chemotherapy.

Given the good tolerability and low costs of the drug, it would be worthwhile to start a clinical trial with a larger number of patients to investigate the potential of tamoxifen maintenance in metastatic malignant melanoma, if possible.

Disclosure Statement

The authors declare no conflict of interest.

Table 1. Patient characteristics

No.	Sex	Age ^a , years	Time to distant metastases ^b , months	Metastatic manifestations	PS (ECOG) ^c	LDH ^d , U/l	Pretreatment	Chemotherapy and result	Remission duration, months
1	m	73	23	liver, skin	0	292	none	BCDT 3 ×: NC	190 +
2	m	50	0	liver, spleen, lung, bone, nodes ^e	2	normal	none	BCDT 1 × ^f , vindesin, CPL/DTIC: PR	156 +
3	f	65	81	vena cava tumor thrombus, (adrenal body exstirpated)	1	normal	none	DTIC 6 ×: PR	142 +
4	m	61	23	liver, lung	1	normal	IFN	BCDT 4 ×: PR	65 +
5	f	63	3	liver, lung, nodes	1	319	none	BCDT 4 ×: PR	27 +
6	m	69	30	lung, skin, nodes	2	normal	none	DTIC 6 ×: PR	13 +
7	f	63	24	lung, skin	1	normal	none	BCDT 2 ×: PR	18
8	f	55	10	lung, nodes	0	normal	IFN	BCDT 4 ×: NC	7
9	f	57	7	nodes + M. psoas, bone	1	327	IFN	BCDT 3 ×: NC	6
10	f	63	56	lung, spleen, nodes	0	normal	none	BCDT 4 ×: PR	2
11	m	52	21	jejunum	0	normal	IFN, RT	DTIC/Carbo 2 ×, BCDT 1 ×, DTIC 1 ×: NC	2
12	m	51	55	liver, bone	2	357	None	BCDT 4 ×: PR	1

^aAge at relapse.^bTime from diagnosis of the primary tumor to first distant metastasis.^cPerformance status (Eastern Cooperative Oncology Group) at relapse.^dLDH at relapse (normal up to 240 U/l).^eLymph nodes.^fBCDT 1 × means 3 weeks of treatment.

LDH: Lactate dehydrogenase; BCDT: BCNU/cisplatin/dacarbazine/tamoxifen; IFN: interferon-α; RT: radiotherapy; CPL: cisplatin; DTIC: dacarbazine; Carbo: carboplatin; NC: no change; PR: partial remission.

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