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Biomodulatory metronomic therapy in stage IV melanoma is well-tolerated and may induce prolonged progression-free survival, a phase I trial

Editor

Generally, redirecting hallmarks of cancer by communicative reprogramming leads to long-term tumour control in histologically quite different neoplasias[1,2]: A recently published randomized phase II trial on metastatic melanoma revealed significant impact of pioglitazone, a peroxisome proliferator-activated receptor$_\gamma$ (PPAR$_\gamma$)[3,4] agonist, on inflammation control, progression-free survival and overall survival when added to immunemodulatory and angiostatic acting metronomic low-dose chemotherapy.[5–7]

In the present phase I trial we studied tolerability and efficacy of the original combination pioglitazone daily 60 mg p.o, etoricoxib daily 60 mg p.o., plus low-dose trofosfamide daily 50 mg three times p.o., and supplemented temsirolimus i.v. weekly at two dose levels, cohort 1, 15 mg, cohort 2, 25 mg (PETT schedule) (Fig. 1).[8,9] All medications were given continuously from day 1 until progression.

Main inclusion criteria were age >18 years, histologically diagnosed metastatic melanoma with BRAF (the human gene that codes for the serine/threonine protein kinase B-Raf) wild-type, and LDH level >0.8 ULN, measurable lesions, and subjects had to receive study medication as first-line therapy.

Dose-limiting toxicity (DLT) was defined as any toxicity within the first 3 weeks of treatment with CTCAE (NCI-CTCAE version 4.0) grade ≥3 and a causal relationship to the administration of one of the study drugs. At the end of phase I, patients were followed according RECIST criteria for progression-free and overall survival. Computed tomography or magnetic resonance imaging (RECIST criteria) was performed every 8 weeks. The trial is approved by the local ethic committee and registered at ClinicalTrials.gov (NCT01614301).

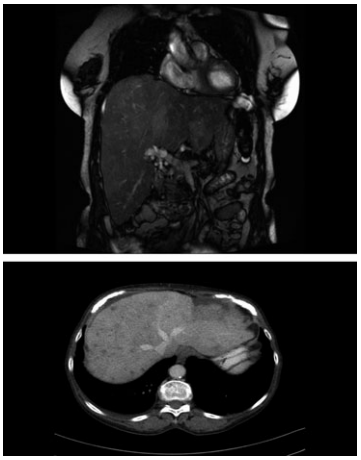

Figure 1 Hepatomegaly due to far advanced diffuse and multifocal metastases in patient No. 5 (Table 1) with uveal melanoma. Hepatomegaly did not decrease during PETT therapy, but disease could be stabilized for 1 year paralleled by a steep decrease of MIA in serum (Table 1).

Six elderly female patients (68–86 years old) with stage IV melanoma of uveal (n = 2) or cutaneous origin (n = 4), diffuse and multifocal liver metastases (n = 4) or tumour growth per continuitatem (n = 2) were enrolled during phase I. Local pretreatment and metastatic sites at study inclusion are listed in Table 1.

The 25 mg dose of temsirolimus was chosen for the randomized phase II part of the study as no DLTs occurred in cohort 1 or 2. Two severe adverse events (SAEs) were observed during phase I part of the study, one due to pneumonia and another to pleural effusion. Both SAEs resolved during continuation of study medication. Grade 3 (no grade 4) toxicities during the follow-up phase are listed in Table 1. According to scheduled dose reductions, trofosfamide was reduced to 50 mg twice daily in four patients. Due to oedema, the dose of pioglitazone was reduced to 30 mg daily in two patients.

Progression-free survival was 4–13 months, with four disease stabilizations, one mixed response (no objective response in the radiation field) and one partial response (PR) (Table 1). One stable disease in a patient with diffuse as well as measurable liver metastases of uveal melanoma was associated with a steep decline of melanoma inhibitory activity (MIA) and an improvement of Eastern Cooperative Oncology Group (ECOG)status from ECOG 2 to 1 (Fig. 1, Table 1). PR was not associated with a significant decline of MIA (Table 1). Interestingly, two patients with extensive metastatic liver involvement from uveal melanoma had a comparatively long progression-free survival.

In all patients, progression took place at the original metastatic sites. Patients, who were prior irradiated, presented with progression in the radiation field.

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Table 1 Characteristics of patients enrolled in phase I part of the study

Patient no/age (year)	Histology, initial stage	Prior treatment	Clinical status before	Metastatic sites at study inclusion	Treatment duration (months)	Best response/ tumor marker initially	Grade 3/4 toxicities following phase I (NCI-CTCAE version 4.0)	Overall survival (months)/outcome
1/68 y	**Primary metastatic melanoma** Stage IV	• IFNα, 9 months • Radiation left axilla 60 Gy, • Radiation 60 Gy paravertebral left	ECOG 0	- Axilla left - Chest wall left (*per continuitatem lung*)	8	SD MIA 16/21 ng/mL	- Neutropaenia 3 - Anemia 3	13 Progression in the radiation field
2/83 y	**Mixed desmo-plastic melanoma** Glandula parotis pT4 pN1a	• R0 resection	ECOG 1	- Mandible and parotis right - Lung right - Liver Seg VII/VIII and diffuse infiltration	9 MIA 8.1–8.5	SD S-100 0.45/0.1 μg/L	No	14 Progression at metastatic sites
3/71 y	**Uveal melanoma** right eye, **(metastatic)** T3, N0, M1c Stage IV	• Local proton therapy • SIRT therapy: Right hepatic lobe	ECOG 0	- Multiple liver lesions Seg IVb/III and diffuse liver infiltration	13	PR MIA 8.6/8.5 ng/mL	- Edema 3 - Supra-ventricular tachykardia (SAE) - Synkope (SAE) - Pain left arm - Neutropaenia 3	20 Progression liver
4/71 y	**Superficial spreading melanoma** dorsal, pT1a, R0, N0, M0, Stage Ia	For metastatic disease: • Radiation of thoracic vertebra 11 • and chest wall	ECOG 0	- Adrenal gland, per continuitatem kidney right - Superficial spreading melanoma - Bone metastases	4 Inhibition of further spreading	SD MIA 22/23 ng/mL	Perianalnumbness, Anal and urinary incontinence: - Anaemia 3 - Leukopaenia 3	8 Progression in the radiation field and vertebra 11
5/79 y	**Uveal melanoma, (right eye, metastatic)** Multiple liver metastases Stage IV	• Silikonoil tamponade	ECOG 2	- Seg V/VI, III and diffuse infiltration - Bone metastasis left femur	12	SD MIA 465/82 ng/mL	- Anaemia 3 - Edema 3 - Dehydration 3	13 Progression at original metastatic sites
6/86 y	**Melanoma DIG II left** pT2a N3 M0 R0, Stage IIIb	• Excision, coverage with allo-plastic material • Systematic lymph-adenectomy left groin level I and **radiotherapy left groin**	ECOG 0	- Lymphnodes left iliacal, paraaortal - **Pericardial effusion, pericardial tumor, per continuitatem lung** - Skin involvement	5	Mixed response S-100 0.45/0.1 μ/L	No	14 Progression in the radiation field

ECOG, Eastern Cooperative Oncology Group performance status; SIRT, selective internal radiation therapy; MIA, melanoma inhibitory activity; SD, stable disease; PR, partial response; SAE, severe adverse event.

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To our knowledge, this is the first report describing the use of PETT schedule, to successfully control both, metastatic growth in cutaneous and uveal melanoma by simultaneously targeting multiple hallmarks of melanoma: Communicative reprogramming may overcome (molecular-)genetic heterogeneity among melanomas of quite different origin as well as at different metastatic sites.[2,5] PETT schedule provides a modest toxicity profile and omits maximal tolerable dosages of single drugs by concertedly modulating melanoma plus adjacent stroma cell functions.[3,5,8,10] These promising data with PETT combination therapy are currently studied in a randomized phase II trial in second-line.

A.R., C.H. designed the research, analysed the data and wrote the paper; C.H., M.V., Ch.H., M.L., M.B., S.H. and A.R. treated the patients; W.H. critically reviewed the manuscript.

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Disseminated fusariosis with endophthalmitis after skin trauma in acute lymphoblastic leukaemia

Editor

A 46-year-old male patient with acute lymphoblastic leukaemia diagnosed 1 month prior who was currently undergoing chemotherapy (1 cycle of mitoxantrone) was admitted to the emergency room due to malaise and fever he had been experiencing over the past 24 h, and febrile neutropenia was diagnosed. Imipenem (500 mg, i.v., q6 h) and vancomycin (1000 mg, i.v., bid) were initiated. At 1 week before admission, he fell on his left knee and developed an asymptomatic violaceous nodule (Fig. 1a). Two days later, he developed other disseminated lesions on his face, trunk, arms and legs. Some of them were ulcerated and covered with necrotic crusts (Fig. 1b).

Skin biopsy showed a lymphohistiocytic infiltrate with thrombosis. PAS and Grocott staining revealed the presence of filamentous fungal structures within the vascular spaces (Fig. 2a). According to these findings, disseminated aspergillosis was suspected, and treatment with amphotericin B deoxycholate (75 mg, i.v., qd) was initiated. Four days later, he developed pneumonia and bronchoscopy, and cultures were performed. *Fusarium* spp. was isolated from the skin and later from lung tissue cultures (Fig. 2b,c) (*Fusarium solani* by PCR). He was referred to ophthalmology due to eye redness and decreased visual acuity. A diagnosis of bilateral endogenous endophthalmitis presumably due to *Fusarium* spp. was made, and treatment with topical amphotericin B was started. Progressive worsening of his eye occurred, which led to total vision loss. Disseminated fusariosis was diagnosed based on these clinical findings, and amphotericin B deoxycholate (75 mg, i.v., qd) was administered for 1 month. His skin and lung lesions resolved within 2 weeks after resolution of neutropenia. He was discharged from the hospital with voriconazole (200 mg, o.d., bid) and was followed up for 8 months, during which time he had no relapse. He continues chemotherapy (Capizzi regimen) for his acute lymphoblastic leukaemia.

Fusarium species are fungal pathogens commonly found in the soil, plants and air.[1,2] More than 50 species have been described, but only some of them cause human infection, the most common of which are *Fusarium moniliforme, Fusarium solani* and *Fusarium oxysporum.*[3]

In severely immunocompromised patients (mainly those with haematological malignancy, those who have received bone marrow or solid organ transplant, and those on chemotherapy), *Fusarium* spp. may cause disseminated disease.[1,4] *Fusarium* infection is the second most common opportunistic infection in these patients after *Aspergillus* infection, and most of these infec-

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