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Radiosensitization by BRAF inhibitor therapy—mechanism and frequency of toxicity in melanoma patients

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Background: Recent evidence suggests that ionizing radiation may be associated with unexpected side-effects in melanoma patients treated with concomitant BRAF inhibitors. A large multicenter analysis was carried out to generate reliable safety data and elucidate the mechanism.

Methods: A total of 161 melanoma patients from 11 European skin cancer centers were evaluated for acute and late toxicity, of whom 70 consecutive patients received 86 series of radiotherapy with concomitant BRAF inhibitor therapy. To further characterize and quantify a possible radiosensitization by BRAF inhibitors, blood samples of 35 melanoma patients were used for individual radiosensitivity testing by fluorescence in situ hybridization of chromosomal breaks after *ex vivo* irradiation.

Results: With radiotherapy and concomitant BRAF inhibitor therapy the rate of acute radiodermatitis ≥2° was 36% and follicular cystic proliferation was seen in 13% of all radiotherapies. Non-skin toxicities included hearing disorders (4%) and dysphagia (2%). Following whole-brain radiotherapy, rates of radiodermatitis ≥2° were 44% and 8% ($P < 0.001$) for patients with and without BRAF inhibitor therapy, respectively. Concomitant treatment with vemurafenib induced acute radiodermatitis ≥2° more frequently than treatment with dabrafenib (40% versus 26%, $P = 0.07$). In line with these findings, analysis of chromosomal breaks *ex vivo* indicated significantly increased radiosensitivity for patients under vemurafenib ($P = 0.004$) and for patients switched from vemurafenib to dabrafenib ($P = 0.002$), but not for patients on dabrafenib only. No toxicities were reported after stereotactic treatment.

Conclusion: Radiotherapy with concomitant BRAF inhibitor therapy is feasible with an acceptable increase in toxicity. Vemurafenib is a more potent radiosensitizer than dabrafenib.

Key words: radiosensitization, radiotherapy, radiation, BRAF, vemurafenib, dabrafenib

introduction

BRAF inhibitors are a standard treatment of patients with metastatic BRAF V600-mutated melanoma [1–3]. Frequently, radiotherapy is also required in these patients [4]. Recently, radiosensitizing effects of both BRAF inhibitors vemurafenib and dabrafenib have been described [5–10]. In addition, after sequential radiotherapy and BRAF inhibitor treatment, radiation recall phenomena have been reported [11–13]. However, some cancer centers reported good tolerability [14, 15].

Currently, there is no standard approach with regard to interruption of the systemic therapy with BRAF inhibitors, while patients undergo radiotherapy. Since the interruption in treatment could potentially lead to progression, an analysis of toxicity was called for. The aim of this study was to provide

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reliable data on the frequency and severity of radiosensitizing effects of vemurafenib and dabrafenib in a sufficient number of patients as basis for rational decisions on treatment algorithms.

methods

patients

In total, 161 metastatic melanoma patients from nine German, one Austrian and one Swiss skin cancer centers were analyzed, retrospectively. Toxicity of 177 radiotherapies in those 161 patients was fully documented. Among these patients, 86 radiotherapies were applied in 70 patients with concomitant BRAF inhibitor therapy. Patients' characteristics are shown in Table 1. Regarding the sites of the radiotherapies, the largest subgroup received WBRT with or without stereotactic boost ($n = 32$). These patients were compared with a control group of melanoma patients treated with WBRT without BRAF inhibitors between 1998 and 2014 at the University Hospital Erlangen ($n = 91$) (Table 1).

Individual radiosensitivity was studied in 35 blood samples of melanoma patients with or without BRAF inhibitor therapy. Approval by the Ethics Committee at the University of Erlangen was obtained and all patients gave written informed consent. Blood samples were taken during necessary blood draw at regular follow-up visits.

materials

Acute radiodermatitis of the 177 radiotherapies was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [16]. Other toxicities were documented descriptively.

Individual radiosensitivity was determined in freshly drawn heparinized peripheral blood from 35 melanoma patients. After dividing the blood sample in two aliquots, one was not irradiated and the other irradiated with a dose of 2 Gy. Ionizing radiation was generated by a 6-MV linear accelerator (Mevatron, Siemens, Germany) with a dose rate of 2.2 Gy per min. After irradiation, lymphocytes were stimulated with phytohemagglutinin and cultured for 48 h. The preparation for three-color fluorescence *in situ* hybridization (FISH) followed a previously described standard technique [17]. Chromosomal aberrations were

Table 1. Patient characteristics

	Radiotherapy with concomitant BRAFi		WBRT without BRAFi	
Number of patients	70 patients		91 patients	
Radiotherapies per patient				
One	56 patients		91 patients	
Two	12 patients			
Three	2 patients			
Number of radiotherapies	86	100%	91	100%
Mean age (range), years	53 (19–85)		60 (25–87)	
Male	50	58.8%	61	67%
Irradiated sites				
WBRT	32	37%	91	100%
Bone metastases	19	22%		
STX brain	18	21%		
Lymph node metastases	8	9%		
Soft tissue metastases limbs	4	5%		
Mediastinal metastases	3	4%		
Others	2	2%		
STX	19	22%		
WBRT dosage				
Mean dose	33.6 Gy		33.0 Gy	
With boost	8	25% of WBRT	26	29% of WBRT
Prior radiotherapy of the same site				
All patients	12	14%		
Subgroup WBRT	5	16% of WBRT	26	29% of WBRT
Concomitant therapy				
Vemurafenib 960 mg b.i.d.	51	59%		
Vemurafenib reduced dose	12	14%		
Dabrafenib 150 mg b.i.d.	20	23%		
Dabrafenib reduced dose	3	4%		
Fotemustine			21	23%
Temozolomide			16	18%
Others			13	14%

Characteristics of 86 radiotherapies in 70 patients with any radiotherapy and concomitant BRAF inhibitor therapy and 91 patients with WBRT without BRAF inhibitor therapy.
BRAFi, BRAF inhibitor; STX, stereotactic radiotherapy; WBRT, whole-brain radiotherapy.

Table 2. Adverse events

Adverse events in 86 radiotherapies (100%)		
Skin toxicity		
Acute radiodermatitis ≥ CTCAE 2°	31	36%
Follicular cystic proliferation[a]	11	13%
Hand–foot syndrome (irradiated area)	1	1%
Impaired wound healing	1	1%
Hyperpigmentation	1	1%
Other toxicities		
Hearing disorder	3	4%
Dysphagia	2	2%
Hemorrhagic intracranial metastasis	1	1%
Polyneuropathy	1	1%
Taste disorder	1	1%

Adverse events in 86 radiotherapies of 70 patients treated with radiotherapy and concomitant BRAF inhibitor therapy.
[a]Includes one case of cutis verticis gyrate-like toxicity as the maximal form of FCP.
FCP, follicular cystic proliferation.

scored as breaks per metaphase (B/M). At least 200 metaphase spreads were scored for the unirradiated control and 100 metaphases after 2 Gy. The 0 Gy value was subtracted to correct the influence of spontaneous aberrations. The assessment was carried out in a blinded manner.

statistical analysis

Data analysis was carried out using SPSS 19.0 (IBM Corporation, Armonk, NY) and the Mann–Whitney *U*-test. Two-sided *P* values were evaluated and a *P* value of <0.05 was considered statistically significant.

results

toxicity analysis of all radiotherapies

Any acute or late toxicity appeared in 57% of radiotherapies with concomitant BRAF inhibitor therapy. Skin toxicity appeared frequently whereas other toxicities were rare (Table 2). There were no differences in skin toxicity based on the sites of radiotherapy. The most frequent toxicities were acute radiodermatitis with radiodermatitis ≥2° in 36% (Figure 1A and B) and follicular cystic proliferation (FCP) in 12.8% (Figure 1C). One case of hand–foot syndrome occurred after irradiation of the foot (Figure 1D) and one patient developed a maximal form of FCP, which has been

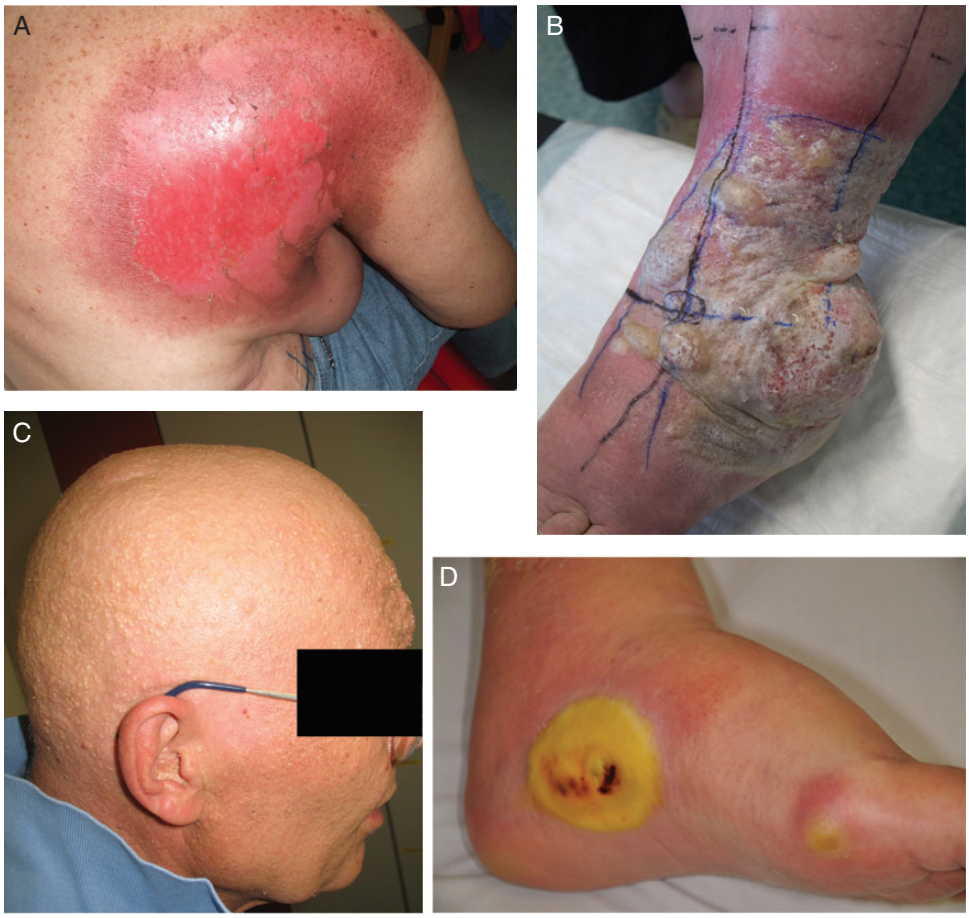

Figure 1. Skin toxicities of patients treated with radiotherapy with concomitant BRAF inhibitor therapy. (A) Acute radiodermatitis 3° of a patient treated for axillary metastases. (B) Acute radiodermatitis 3° of a patient treated for a soft tissue metastasis of the ankle. (C) Follicular cystic proliferation (FCP) of a patient after whole-brain radiotherapy. (D) Hand–foot syndrome of a patient treated for a soft tissue metastasis of the foot.

described before as cutis verticis gyrate-like toxicity [10, 13]. But despite this high rate of acute skin toxicities, no severe sequelae were reported after a mean follow-up time of 6.6 months [95% confidence interval (CI) 4.8–8.3 months]. Non-skin toxicities were rare and included hearing disorders (4%) and dysphagia (2%). BRAF inhibitor therapy was interrupted due to toxicity in 9% and irradiation was interrupted in 4% of all cases.

The frequency of radiodermatitis was further analyzed depending on the type of BRAF inhibitor. In patients treated with vemurafenib ($n = 63$), acute radiodermatitis ≥°2 occurred in 40%, whereas in the dabrafenib group ($n = 23$) in only 26% ($P = 0.07$) (Figure 2A). FCPs only appeared in patients taking vemurafenib. In several patients, the BRAF inhibitor dose was reduced precautionary due to the upcoming radiotherapy ($n = 5$) or after prior adverse events induced by the BRAF inhibitor ($n = 10$). These dose reductions did not reduce radiation-induced skin toxicity during concomitant treatment compared with full dosage ($P = 0.4$) (Figure 2B).

The largest subgroup of patients treated with radiotherapy and concomitant BRAF inhibitors received WBRT. These 32 patients were compared with 91 patients treated with WBRT only. In patients receiving WBRT with concomitant BRAF inhibitor therapy acute radiodermatitis ≥°2 according to CTCAE criteria occurred in 44% of cases compared with 8% of patients with WBRT only ($P < 0.001$) (Figure 2C) [16].

Rates of acute radiodermatitis of conventionally fractioned radiotherapies ($n = 67$) and stereotactic treatments ($n = 19$) were also compared. No increased skin toxicity and no other severe adverse events were reported after stereotactic radiotherapy with concomitant BRAF inhibitor therapy (Figure 2D). In contrast, acute radiodermatitis ≥°2 was reported in almost every other patient (46%) who received a conventionally fractioned radiotherapy with concomitant BRAF inhibitor therapy ($P < 0.001$).

individual radiosensitivity *ex vivo*

Individual radiosensitivity was assessed in peripheral blood lymphocytes of melanoma patients after *ex vivo* irradiation. Three-color FISH was used to analyze the cells' ability to respond to ionizing radiation-induced DNA damage. Misrepair,

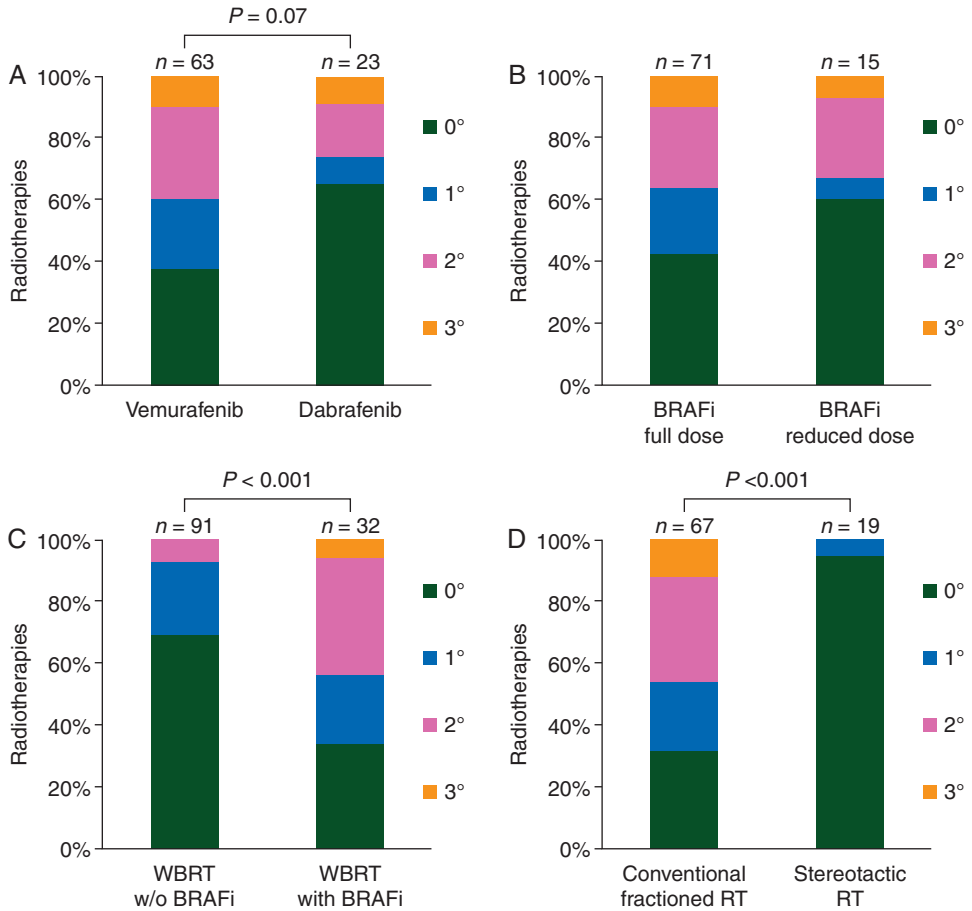

Figure 2. Acute radiodermatitis of patients treated with radiotherapy with concomitant BRAF inhibitor therapy. Acute radiodermatitis of 86 radiotherapies (RT) with concomitant BRAF inhibitor therapy divided in subgroups of BRAF inhibitor (BRAFi) type (A) and BRAF inhibitor dose (B). Acute radiodermatitis after WBRT of 32 patients with and 91 patients without concomitant BRAF inhibitor therapy (C). Acute radiodermatitis of 86 conventionally fractioned or stereotactic radiotherapies with concomitant BRAF inhibitor therapy (D). Grading of skin toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (1° Faint erythema or dry desquamation; 2° Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema; 3° Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion; 4° Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated).

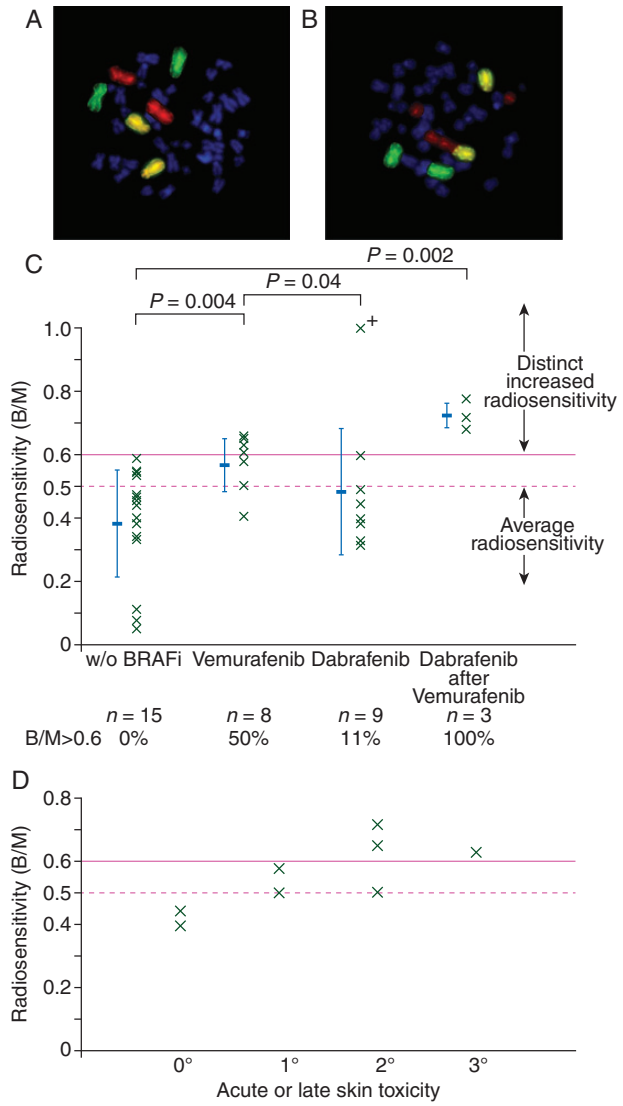

Figure 3. Individual radiosensitivity testing of melanoma patients with or without BRAF inhibitors *ex vivo*. Three-color FISH painting of chromosomes 1 (red), 2 (green) and 4 (yellow). (A) A metaphase without aberrations and (B) a metaphase with one dicentric chromosome and two acentric fragments are displayed. The aberrations were scored as 2 breaks per metaphase (B/M). (C) Lymphocytes were irradiated *ex vivo* with 2 Gy. B/M found in nonirradiated metaphases were subtracted from those scored in the irradiated samples. B/M values of patients treated with vemurafenib, dabrafenib and dabrafenib after vemurafenib were compared with melanoma patients without BRAF inhibitor therapy. [+]The patient with a dramatically increased B/M value of 1.0 developed 17 HPV acanthomas and one squamous cell carcinoma 3 months after start of therapy with dabrafenib. (D) Correlation of acute and late skin toxicity of irradiated patients with their B/M values.

impaired signaling and dysfunctional cell cycle control results in chromosomal aberrations. Color changes along chromosomes indicate these aberrations (Figure 3A and B). The chromosomal aberrations were expressed as mean breaks per metaphase (B/M value) and were scored in the blood of melanoma patients without BRAF inhibitor therapy ($n = 15$), patients taking vemurafenib ($n = 8$) or dabrafenib ($n = 9$) and patients who were switched from vemurafenib to dabrafenib ($n = 3$). B/M values of <0.5 indicate an average radiosensitivity and B/M values between 0.5 and 0.6 increased radiosensitivity. Patients with B/M values higher than 0.6 have a clearly increased radiosensitivity with an increased risk for severe toxicities during radiotherapy [17–19]. In the control group, the B/M values of none of the patients were higher than 0.6 B/M (Figure 3C). In contrast, 50% (4/8) of patients under vemurafenib had strongly increased B/M values. Interestingly, the B/M value was increased only in 11% (1/9) of patients under dabrafenib. The patient of the dabrafenib group with the dramatically increased B/M value of 1.0 developed 17 HPV acanthomas and 1 squamous cell carcinoma 3 months after start of therapy with dabrafenib. Patients who were currently taking dabrafenib and had previously been treated with vemurafenib, had very high B/M values, even though vemurafenib treatment was stopped on average 5.2 months before. Patients under vemurafenib ($P = 0.004$) and patients who were switched from vemurafenib to dabrafenib ($P = 0.002$) had significantly increased B/M values compared with patients without BRAF inhibitor therapy. Patients taking vemurafenib had significantly higher B/M values than patients under therapy with dabrafenib ($P = 0.04$). There was no correlation of B/M values with BRAF inhibitor dose, dose per body weight or dose per body mass index. Eight of the patients in which a radiosensitivity testing was carried out were also treated with radiotherapy. Patients with average B/M values had no skin toxicities, whereas patients with increased B/M values suffered much more frequently from acute and late skin toxicities ≥2° (Figure 3D).

discussion

This analysis of a large patient cohort showed an increased rate of acute radiodermatitis ≥°2 of 36% in patients treated with radiotherapy and concomitant BRAF inhibitor therapy. Despite the high rate of acute radiodermatitis, no severe skin-related late toxicities were reported during an average follow-up time of 6.6 months. FCPs, a characteristic late reaction of concomitant BRAF inhibitor therapy and WBRT [9, 13], was reported in 13% of our patient cohort. Other reactions like hand–foot syndrome are reported here for the first time after radiotherapy. In our patients, these skin reactions were strictly limited to the irradiated areas. But it has to be considered, that BRAF inhibitors frequently induce follicular dermatitis and hyperkeratosis without ionizing radiation [1–3, 20]. It can be speculated that some of these adverse events might have also happened without ionizing radiation. Reports on radiation-induced visceral reactions such as pneumonitis or anorectitis [7, 11] and potentially liver toxicity exist [5]. However, in this patient population, nonskin toxicity was rare. Another finding of the study was that radiation-induced toxicity only appeared in patients, who received conventionally fractioned radiotherapy with concomitant BRAF inhibitor therapy. No skin or other toxicity appeared after stereotactic treatment. This is in line with previous case reports [15] and an earlier retrospective analysis of 12 patients ($n = 3$ WBRT; $n = 3$ WBRT + stereotactic boost; $n = 6$ stereotactic radiotherapy) with no reported toxicities except for brain necrosis in 1 patient [14].

So far, it was unclear whether additional toxicity was induced by BRAF inhibitors and if so, whether this increased toxicity was mediated by an immunologic boost [21] or whether the effect was direct. To establish the pathogenic mechanism, the radiosensitivity in patients taking BRAF inhibitors was investigated *ex vivo* and clearly showed a radiosensitizing effect of vemurafenib but not of dabrafenib. These *ex vivo* findings are in line with the patient data that also showed a higher rate of acute radiodermatitis ≥°2 in vemurafenib-treated patients (40%) compared with dabrafenib-treated patients (26%). Interestingly, photosensitization is almost exclusively reported in vemurafenib-treated patients [22]. One might speculate that this is a consequence of the very selective binding affinity of dabrafenib to mutant BRAF, whereas vemurafenib also has a low affinity to CRAF, wild-type BRAF and possibly other enzymes [23].

The radiosensitizing effect of BRAF inhibitors probably also sensitizes melanoma cells, maybe even to a greater extent than keratinocytes. *In vitro* the radiosensitizing effect of BRAF inhibitors in BRAF-mutated melanoma cells has already been shown [24, 25]. This might enhance the antitumor effect of both radiotherapy and BRAF inhibitors, which is especially valuable for patients with multiple brain metastases, when no stereotactic radiotherapy is possible. Both, whole-brain radiotherapy and BRAF inhibitor therapy improve cerebral tumor control [26–28]. Nevertheless, the prognosis of melanoma patients with multiple brain metastases is still poor. Synergistic effects of ionizing radiation and BRAF inhibition within a concomitant treatment regime could improve the prognosis of these patients.

Whether the BRAF inhibitor therapy should be interrupted during radiotherapy, has to be discussed in light of these data. Radiation recall phenomena have been reported up to 1 month after radiotherapy [11–13]. Consequently, if maximal safety is favored, therapy interruption of systemic treatment would last several weeks and might lead to progression of nonirradiated metastases. Whereas when radiotherapy is carried out with concomitant BRAF inhibitor therapy, systemic tumor control is maintained. Furthermore, a radiosensitizing effect might improve (local) tumor control. Our data demonstrate that stereotactic radiotherapy with concomitant BRAF inhibitor therapy does not increase the risk of toxicity. Patients receiving conventionally fractioned radiotherapy with concomitant dabrafenib have a moderately increased risk of acute radiodermatitis compared with a larger increase in patients taking vemurafenib. Thus, in patients with planned radiotherapy, the choice of BRAF inhibitor with respect to toxicity favors dabrafenib. Switching patients from vemurafenib to dabrafenib before starting radiotherapy cannot be recommended, as these patients showed the highest individual radiosensitivity *ex vivo*. Particularly, patients under treatment with vemurafenib should be monitored closely for skin and noncutaneous radiation toxicities and receive early supportive care, if necessary. Nevertheless, the results of this analysis show the feasibility of radiotherapy with concomitant BRAF inhibitor therapy.

disclosure

Seventeen authors report collaborations with different pharmaceutical companies, partially with the manufacturers of BRAF inhibitors, outside the project of this manuscript. All remaining authors have declared no conflicts of interest.

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The impact of docetaxel-related toxicities on health-related quality of life in patients with metastatic cancer (QoliTax)

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Background: Docetaxel is a widely used cytotoxic agent. This study evaluates the impact of docetaxel toxicities on patient's health-related quality of life (QoL).

Patients and methods: We conducted a multicenter, prospective, non-interventional trial, in which the QoL was assessed using the EORTC QLQ-C30 questionnaires at baseline and every 4 weeks up to 40 weeks in patients receiving a docetaxel-based chemotherapy for metastatic disease. Treatment-related adverse events were correlated with the corresponding QoL scores. Uni- and multivariate analyses were applied.

Results: From January 2008 to June 2011, a total of 2659 patients were included. The majority of patients (48.1%) had prostate cancer, followed by breast (17.1%) and non-small-cell-lung cancer (15.8%). Patients received a median of 5 docetaxel cycles with the median dose of 75 mg/m^2. The presence of grade 3/4 diarrhea showed the strongest effect on global health status/QoL average scores (50.91 versus 33.06), followed by vomiting (50.91 versus 35.17), dyspnea (50.94 versus 35.81), mucositis/stomatitis (50.88 versus 36.41), nausea (50.91 versus 36.68), infection (50.90 versus 37.14), fatigue (50.90 versus 43.82) and anemia (50.91 versus 41.03), $P < 0.05$ for all comparisons. Grade 3/4 leukopenia/neutropenia, alopecia, constipation, neurotoxicity and nail disorders had no significant impact on the global health status/QoL or other items.

Conclusion: In this large non-interventional trial, docetaxel-associated grade 3 or 4 toxicities were shown to have a strong detrimental effect on patient's QoL. Notably, diarrhea and vomiting had the strongest negative impact on QoL measures. This has to be kept in mind while making therapeutic decisions and providing optimized supportive treatment measures.

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