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New approaches and consequences for elderly cancer patients with focus on melanoma
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Chapter 7

Prophylactic brain irradiation in patients with metastatic melanoma responding to systemic therapy: a feasibility study and future perspectives

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Abstract

Approximately 20–55% of patients with stage IV disease will die due to brain metastases. This study was set up in 2000 to evaluate whether prophylactic brain irradiation (PBI) could help prevent or postpone the occurrence of brain metastases in patients with stage IV melanoma responding to systemic treatment with chemo-immunotherapy. This is the first study evaluating prophylactic irradiation in metastatic melanoma.

Thirty patients with histologically confirmed distant metastatic melanoma were included and initially treated with dacarbazine, carboplatin and interferon- α . Sixteen patients showed non-progressive disease on systemic treatment and were offered to receive PBI. Thirteen patients actually received PBI.

Patients who responded to chemo-immunotherapy, therefore eligible for PBI, survived longer (median 16.9 versus 6.9 months) and developed more often brain

metastases (5 versus 2 patients) than the non-responders. In the PBI-group, two patients developed clinical brain metastases within 10 months (13%, 95% CI 0–31%). The stopping rule was not reached. Most common side-effects were headache and alopecia.

This study shows that PBI is feasible. It might however only be meaningful in patients with metastatic melanoma surviving long enough to actually be at risk for brain metastases.

As the perception of radio-resistance for melanoma is changing, as well as the finding that melanoma cells are heterogeneously radio-responsive, more defined prophylactic irradiation schedules should be studied in patients with metastatic melanoma with a high risk of brain metastasis. Given the growing systemic treatment arsenal available, the optimal time-window for PBI will be challenging.

Introduction

The incidence of melanoma is, more than any other human cancer, increasing steadily every year ¹. Melanoma belongs to the tumor types with the highest chance to develop brain metastases, with an incidence of 5–20% in any stage, increasing to 40–50% in stage IV disease and even higher percentages are found in post-mortem studies ^{2–5}.

For melanoma patients with brain metastases, surgical resection or stereotactic radiosurgery (SRS) in case of limited disease and good performance status and whole brain radiation therapy (WBRT) and/or steroids in case of advanced disease is widely accepted as treatment option ⁶. Despite these local treatment options, brain metastases are a rather common cause of death from melanoma ⁷. Of those who die of melanoma, 20–55% is due to brain metastases ^{5,7,8}.

A continue rise in number of systemic therapies are available for patients with metastatic melanoma. On the one hand, drugs targeting the mitogen-activated protein kinases pathway are highly effective in patients with v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) mutated melanoma ⁹. On the other hand, immune checkpoint inhibitors against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), which induce autoimmunity and thereby cause antitumor activity, show encouraging long-term survival rates ¹⁰.

Given the fact that systemic treatments extend life expectancy of melanoma patients, insight and novel strategies to combat brain metastases will be important. Although *BRAF* inhibitors and immune checkpoint inhibitors have shown clinical activity in melanoma brain metastases ^{11–13}, and thereby may reduce the incidence, local preventive treatment strategies may be warranted as well. For small cell lung carcinoma (SCLC) several randomized trials and two meta-analyses showed improved survival and decreased incidence of brain metastases when patients received prophylactic brain irradiation (PBI) after a complete response to chemotherapy ¹⁴.

Strikingly no such data are available for melanoma. In analogy to the approach in SCLC, we performed a feasibility study in which patients with metastatic melanoma non-progressing on systemic therapy received PBI. The goal of the study was to find an indication whether PBI could help to prevent or postpone the occurrence of clinical symptoms of brain metastases in patients with stage IV melanoma responding to systemic treatment with chemo-immunotherapy.

Methods

A single center study was performed between 2000–2008 at the University Medical Center Groningen, Groningen, the Netherlands. Patients were eligible for the study if they had histologically confirmed distant metastatic melanoma, defined as metastases beyond the regional lymph nodes, with at least one evaluable metastatic lesion. Other criteria for inclusion in the study were an age \geq 18-year-old, no previous radiotherapy to the head and neck area and no previous or other current cancer. In case of clinical suspicion of brain metastases, a CT or MRI of the brain was performed – when brain metastases were found, the patient was excluded. All patients provided written informed consent. The medical ethics committee reviewed and approved the protocol (METc 2000/172).

Study design

The treatment consisted of dacarbazine 800 mg/m² and carboplatin with AUC of 5 both intravenously on day 1 and on day 1–5 the patients received 10 million E interferon- α 2b subcutaneously. This treatment regime was chosen because of the then good response per-

centages and its feasibility in the outpatient setting^{15,16}. This schedule was repeated every 21 days for 4–6 cycles. Thereafter, tumor response assessment was performed. Patients who showed no progressive disease, based on RECIST 1.0 criteria, were offered to receive PBI (PBI-group).

Radiation was administered with the use of two opposed lateral fields with a linear accelerator (6 MV). Each field was treated daily on a schedule of 4–5 fractions per week. The dose was specified to the midline. Each patient received a total of 30 Gy in 10 fractions (a standard WBRT schedule)¹⁷.

After the PBI, systemic treatment with dacarbazine, carboplatin and interferon was continued. Response evaluation took place after every 4th course of chemo-immunotherapy, or if progression was clinically suspected. Brain CT or MRI during follow-up was only performed if symptoms suggestive for brain metastases were present.

Toxicity was scored according to common terminology criteria for adverse events 4.0. We were able to perform full follow-up on all patients until death or until the final analysis.

Statistics

Based on literature, the median survival of patients with stable disease, partial or complete response to systemic therapy was at that time about 10 months. Approximately, 30–50% of patients responding to the chemo-immunotherapy combination will have clinical symptoms or die as a result of brain metastases^{8,15,18}. The general stopping rule was based on an incidence of brain metastases of 10% within 10 months using sequential analysis with two-sided $\alpha = 0.05$ as borders for stopping the study. This means that there is a 50% probability that the rule will be activated within the first 16 patients in case the real event rate is 20% and that there is < 20% probability that the rule will be activated within the first 25 patients in case the real event rate is $\leq 10\%$. Because of the small sample size non-parametric tests were used for statistical analysis. A significant difference was assumed for a probability value of < 0.05. The software package SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses.

All analyses were performed according to the intention-to-treat principle. In this study the stopping rule was not reached in the 13 included patients to receive PBI. However, the accrual for the study stopped because of new and promising trials with the CTLA-4 antibodies tremelimumab and ipilimumab and the BRAF inhibitor vemurafenib. Most patients eligible for this study were also eligible for these studies, which were supposed to have more potential benefit for these patients.

Results

Patient characteristics

Patient characteristics of the 30 patients eligible for this study are shown in Tables 1A and 1B. Sixteen patients (53%) showed non-progressive disease on systemic treatment: ten patients (33%) had a partial response and six patients were considered to have stable

disease. No complete responses were seen. Eventually three out of these 16 patients did not receive PBI; one patient refused radiation treatment, one patient left the country for an experimental systemic treatment abroad and one patient was found to have such minimal disease (only subcutaneous metastases) that the treating physicians decided not to offer PBI. The ‘non-PBI-group’ consists of the 14 patients who did not respond to chemo-immunotherapy: twelve patients had progressive disease and two showed a mixed response to therapy.

In the PBI-group, 1 patient had stage M1a disease (6.3%), 8 patients had M1b disease (50%) and 7 patients had M1c disease (44%). In the non-PBI-group, 4 patients had stage M1b disease (29%) and 10 patients had stage M1c disease (71%), $p = 0.25$ (χ^2 2.74, df 2). Median age of all patients was 50.4 years (range 24–74), the median age in the PBI group was 49.7 years (range 24–74), the median age in the non-PBI-group was 51.2 years (range 24–65), $p = 0.61$ (Mann-Whitney U). The PBI-group consisted of 8 males and 8 female patients, the non-PBI-group consisted of 11 males and 3, $p =$ female patients 0.10 (χ^2 2.63, df 1).

ID	Age (years)	Sex	M-stage	Response*	PBI [†]	PFS ^{††}	First relapse site	Brain [§]	BFS	Survival [¶]
1	31	Female	1c	PR	No	11,3	Bone	-	-	24,6
2	31	Female	1c	SD	Yes	6.8	Liver, lung	-	-	7.4
3	53	Male	1b	SD	Yes	10.9	Meningi-tis carcinomatosa	Yes	10.9	11.5
4	41	Male	1c	PR	Yes	23.5	Lymph node, skin	-	-	33.0
5	58	Female	1b	PR	Yes	7.1	Brain	Yes	7.1	10.3
6	69	Male	1b	PR	Yes	89.9	-	-	-	89.9
7	32	Male	1c	PR	Yes	8.2	Liver, spleen	-	-	8.5
8	73	Female	1a	PR	No	16,8	Lymph node	-	-	17,4
9	68	Female	1b	SD	Yes	5.8	Lung	-	-	7.4
10	43	Female	1c	SD	Yes	7.8	Lung	Yes	8.8	12.1
11	58	Male	1b	PR	Yes	12.3	Liver	Yes	18.1	20.6
12	50	Female	1b	SD	5x	9.3	Lymph node, bone	Yes	29.2	29.3
13	50	Female	1c	PR	Yes	7.8	Lung	-	-	14.7
14	24	Male	1b	PR	No	12,5	Bone	-	-	16,3
15	38	Male	1b	PR	Yes	17.0	Liver, lung, spleen	-	-	34.1
16	57	Male	1c	SD	Yes	36.1	-	-	-	36.1

Table 1: Patient characteristics of the PCI-group.

ID	Age (years)	Sex	M-stage	Response*	PBI [†]	PFS ^{††}	First relapse site	Brain [§]	BFS	Survival¶
17	36	Male	1b	PD	No	3,1	Lymph node	-	-	7,4
18	65	Male	1b	PD	No	3,9	Lymph node	-	-	14,2
19	41	Female	1c	PD	No	3,8	Liver	-	-	27,9
20	59	Male	1c	PD	No	3,3	Liver	-	-	4,0
21	47	Female	1c	PD	No	4,1	Lymph node	-	-	6,3
22	51	Male	1b	MR	No	5,5	Lung	-	-	6,3
23	53	Male	1b	PD	No	5,2	Bone	-	-	9,2
24	60	Male	1c	PD	No	4,6	Lung	Yes	8,2	10,9
25	43	Male	1c	PD	No	1,5	Liver	-	-	1,7
26	34	Male	1c	PD	No	3,4	Lung, liver	-	-	4,3
27	62	Female	1c	MR	No	13,0	Adrenal gland	Yes	17,0	21,6
28	52	Male	1c	PD	No	5,1	Spleen, bone, liver	-	-	10,2
29	58	Male	1c	PD	No	4,2	Liver	-	-	5,6
30	39	Male	1c	PD	No	2,6	Lung	-	-	4,7

Table 1: continued.

*PR = partial response; SD = stable disease; PD = progressive disease; MR = mixed response

[†]Prophylactic brain irradiation

^{††}Progression free survival in months measured from moment of stage IV

[§]Cerebral metastases at any moment during course of disease

^{||}Brain metastases free survival measured from moment of stage IV

[¶]Survival in months from moment of stage IV

Toxicity

Thirteen patients reported 21 side effects, see Table 2. Only 1 patient did not experience any side effect of the treatment at all. The most common side effect was headache: 54% reported either grade I or grade II headache ($n = 7$). Another common reported side effect was alopecia ($n = 5$). One patient experienced morning nausea and headache lasting for three weeks after treatment. One patient stopped with PBI after 5 fractions of 3 Gy because of severe fatigue. No delayed neurologic cognitive function disorders were reported, especially not in our two long-term survivors. However, this was not specifically tested.

Side-effect	Grade I	Grade II	Grade III	Total (%)
Headache	4	3	-	7 (54)
Nausea	-	3	-	3 (23)
Vomiting	1	1	-	2 (15)
Fatigue	2	-	1	3 (23)
Alopecia	-	5	-	5 (38)
Malaise	-	1	-	1 (8)

Table 2: Toxicity (n).

Survival

Median survival time of all 30 patients is 11.2 months. Survival in the PBI-group ranged 7.4–89.9 months, with a median survival of 16.9 months. In this group are 2 long-term survivors who are still alive at 36.0 and 89.7 months. In the non-PBI-group median survival was 6.9 months (range 1.7–27.9), $p = 0.001$ (Mann-Whitney U).

Brain metastases

Out of the 16 patients in the PBI-group, two developed clinical brain metastases within 10 months (13%, 95% CI 0–31%). The stopping rule was not reached. Eventually a total of 7 patients developed brain metastases in the course of their disease. Of those, 5 patients were treated with PBI and 2 were not. The first site of disease progression was mostly hepatic ($n = 10$), pulmonary ($n = 9$) or in distant lymph nodes ($n = 6$).

Discussion

The incidence of melanoma is increasing faster than any other cancer. The annual increase in incidence rate has been 3–7% for fair-skinned Caucasian populations¹⁹. Treatment of brain metastases in melanoma is a major challenge. Over the last years, the life expectancy of metastatic melanoma patients increased due to many new systemic therapies available. Therefore, more insight and new ways to combat brain metastases will become increasingly important. This study is, to our knowledge, the first study to determine the effect of PBI in preventing or delaying clinical symptoms due to brain metastases in stage IV melanoma patients.

In the 16 patients responding to systemic treatment 13 patients actually received PBI. Two patients (13%, 95% CI 0–31%) developed within 10 months clinical symptoms of brain metastases and were visualized by CT. Based on literature this percentage is expected to be around 30–50%¹⁷. The median overall survival in the PBI group is 16.8 (IQR 10.6–32.0) months and 5 patients survived more than 24 months. It has to be taken into

account that in the median survival for dacarbazine responders historically ranges from 9–12 months²⁰.

Eventually more brain metastases developed in the PBI group compared to the non-PBI group, respectively 5/16 versus 2/14. A plausible explanation is that the non-PBI did not respond on systemic treatment and died due to progression of existing metastases. All patients in the PBI-group were responders to systemic treatment and therefore in general survived longer which consequently meant they were longer at risk to develop brain metastases. This supports the idea that only a selected subgroup of patients, those who have a substantial risk to develop brain metastases and controlled disease elsewhere, will have potential benefit from PBI. The incidence of brain metastases in the PBI-group was 31% (95% CI 6–57%). This incidence is on the lower end of what is assumed to be the incidence of brain metastases in patients with stage IV melanoma. The stopping rule, based on an incidence of 10% within 10 months, was not reached.

Since brain metastases in melanoma patients are most often multifocal and have a high tendency to hemorrhage, WBRT as a prophylactic treatment may be useful in preventing or delaying symptoms due to brain metastases. However, melanoma traditionally has been regarded as a rather radio-resistant tumor but this should not be interpreted as radio-untreatable. Human melanoma has demonstrated in clinical trials a very wide range of radio-sensitivities²¹. In fact, adjuvant radiotherapy improves loco-regional control after surgery in high-risk patients^{22, 23}. Additionally, radiation therapy has been used successfully for primary therapy for ocular or other melanomas in poor surgical candidates, and for the palliation of metastases. Several retrospective studies have shown the efficacy of both linear-accelerator based SRS as well as gamma knife-based radiosurgery (GKRS). These studies have demonstrated 1-year local control rates of 49–90%^{24–26}, but are only indicated in oligo-metastatic brain disease. SRS is also found to improve quality of life²⁷.

Although formal evidence is lacking, it is broadly assumed that WBRT can palliate patients with brain metastases and possibly improve survival. In smaller studies, complete responses after radiotherapy have been described in patients with WBRT¹⁷. One retrospective review concluded that, compared to surgical excision or GKRS alone, the addition of WBRT improves overall survival by 7.3 months²⁸.

Because in our study WBRT was given in a prophylactic setting, side effects are of major concern. Most important side effects we observed were headache and alopecia. There was one patient who stopped treatment after 5 fractions because of severe fatigue. This is in concurrence with a study where alopecia and fatigue were the most common side effects of PBI²⁹. Neurocognitive impairment is a potential concern regarding long-term toxicity especially in elderly and patients who have been exposed to cisplatin^{30, 31}. The use of low fraction dose schedules and the avoidance of concomitant chemotherapy have reduced the incidence of neurotoxic effects of PBI in SCLC considerably. Two major trials that reported on neuropsychological evaluation after PBI in SCLC did not show a significant difference in cognitive function between the PBI group and the non-PBI group^{32, 33}. However, it is unknown whether the benefits of possible reduction in brain metastases outweigh the risks of short-term and long-term toxicity in melanoma patients treated with PBI. Furthermore, in

the current setting of new promising trials with systemic therapy, PBI can be a disadvantage because it could be a potential exclusion criterion.

While chemotherapy has shown only modest results in melanoma brain metastases, more positive results are observed for the current therapy entities³⁴. The clinical response rate of temozolomide, which has an excellent penetration of the blood brain barrier, is in the 10% range and a median survival of 8–9 months³⁵. One study showed a trend to a longer delay before brain lesions relapse with fotemustine monotherapy, but it did neither decrease the number of relapses in brain sites nor increase survival³⁶. Temozolomide given concurrently with radiation therapy as a combined approach has been tested for melanoma with mixed results³⁷.

A phase II trial was performed with the BRAF inhibitor dabrafenib in 172 melanoma patients harboring brain metastases with a V600E or V600K mutation in BRAF¹³. 89 patients had not received previous local treatment for their brain lesions, and 83 had progressive brain lesions after local treatments (surgery, WBRT or SRS). Median PFS and OS in V600E harboring patients were 16.1 and 33.1 weeks in locally untreated patients, and 16.6 and 31.4 weeks in locally treated patients, respectively. The response rates were 39% and 31% for the previously treated and untreated group. A pilot study was performed with the BRAF inhibitor vemurafenib in 19 patients with measurable intracranial disease. It showed > 30% tumor regression of melanoma brain metastases in 7/19 patients¹². A retrospective analysis of 22 patients assessable for response showed an intracranial response rate of 50% after vemurafenib, with a median intracranial PFS of 4.6 months (95% CI 2.7–7.9)³⁸. Initial it was unsure whether it is safe to combine BRAF inhibitors with PBI since photosensitivity is an adverse event of both vemurafenib and dabrafenib, but this is found to be exclusively UVA-dependent³⁹. At this moment, based on the limited available data, it is generally recommended to interrupt BRAF inhibitors during WBRT but not necessarily during SRS⁴⁰.

Immune checkpoint inhibitors are of interest due to their potential for long-term disease control. A phase II trial with the CTLA-4 antibody ipilimumab 10 mg/kg iv was conducted in 72 melanoma patients with brain metastases¹¹. 51 were neurologically asymptomatic without corticosteroids and 21 symptomatic on a stable dose of corticosteroids. The primary end point was global disease control, defined as complete response, partial response or stable disease after 12 weeks, and was achieved in 25% of asymptomatic and in 10% of symptomatic patients. Another phase II trial with ipilimumab 10 mg/kg dosed every 3 weeks for four times combined with fotemustine 100 mg/m² was performed in 86 melanoma patients, of which 20 harbored brain metastases⁴¹. Forty patients (47%) had confirmed stable disease or a response. Ten of them had brain metastases. At 24 weeks, 17 patients including six with brain metastases had ongoing disease control (20%). A phase II trial with the PD-1 antibody pembrolizumab 10 mg/kg iv every 2 weeks in 18 melanoma patients with asymptomatic brain metastases of maximal 20 mm without the need for corticosteroids showed a durable response rate of 22% ($n = 4$; 95% CI 7–48%)⁴². A retrospective report found that the PD-1 antibody nivolumab is safely combined with SRS⁴³. An interesting finding relates to the so-called abscopal effect: a response of non-irradiated

tumor lesions after radiotherapy. It depends, according to preclinical studies, on a functional immune system⁴⁴. The hypothesis assumes that eventually, irradiation leads to an increased antigen presentation due to inflammation. Thereby, it could potentiate the benefit from immune checkpoint inhibitors⁴⁵⁻⁴⁶. Currently, several prospective pilot studies try to validate this approach⁴⁷.

Unfortunately, despite all positive results of systemic therapies in melanoma brain metastases, most registration trials still exclude patients with unstable or symptomatic brain metastases.

In conclusion, this study emphasizes the high frequency of brain metastases in patients with metastatic melanoma and the need to prevent or postpone symptoms. It illustrates that PBI might only be meaningful in patients with metastatic melanoma surviving long enough to actually be at risk for symptomatic brain metastases and this has become more important due to the new available drugs. This study shows that PBI is feasible and it supports the thought that it might be helpful in delaying symptoms. We cannot exclude that combination with BRAF inhibition or checkpoint inhibition is more potent in preventing brain metastases. Recently, ipilimumab was the first drug that clearly demonstrated a survival advantage in the adjuvant setting⁴⁸. Results of more adjuvant studies with BRAF inhibition and other checkpoint inhibition are expected in the coming years. To justify PBI we first need answers how to select subgroups that will benefit by preventing symptomatic brain metastases, for example by evaluating endpoints on the rates of first relapse in the brain. The (pre-) clinical findings such as PTEN loss, BRAF and NRAS status, PI3K-AKT activation and lactate dehydrogenase levels might be useful to select patients prone to develop brain metastasis²⁴.

The impact of brain metastases in melanoma patients will likely accumulate prominently. Symptomatic brain metastases can be severely painful, highly invalidating due to a large spectrum of neurologic signs and symptoms causing general deterioration, and thus influencing quality of life poorly. Given increasing numbers of longer surviving patients, the impact on personal lives and health care services becomes ubiquitous. In spite of all potential new treatment methods for brain metastases, prevention of brain metastases through prophylactic treatment in patients with controlled metastatic disease elsewhere might become an important next step in the treatment of metastatic melanoma.

To position PBI treatment, we need PBI trials with or without systemic treatment in patients with a high probability of brain metastasis to define the selection of high-risk patients who will benefit in a field of spectacular changing treatment options.

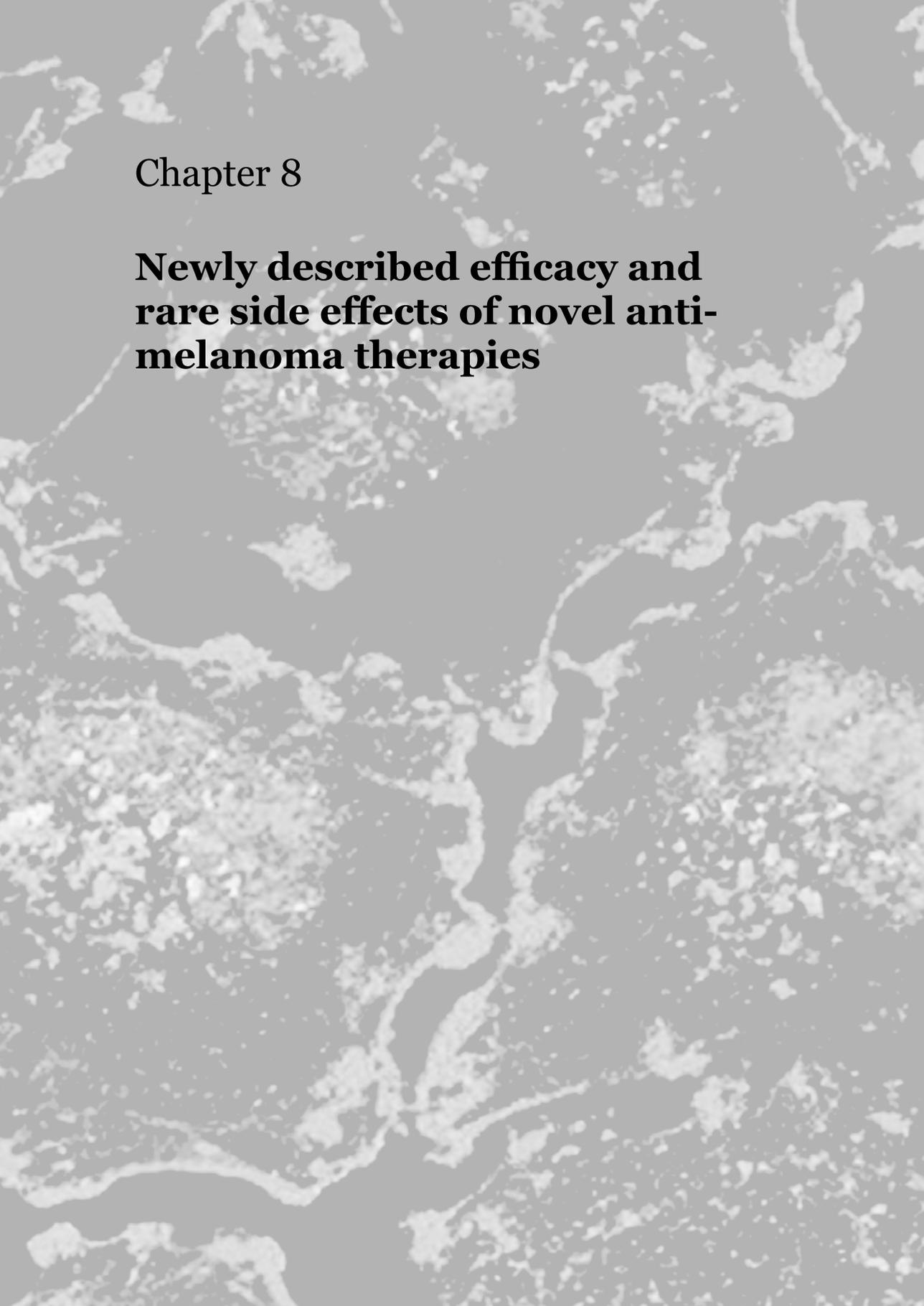
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A grayscale microscopic image of tissue, showing a complex network of cells and fibers. The image is used as a background for the text.

Chapter 8

Newly described efficacy and rare side effects of novel anti-melanoma therapies

