Oligoprogression in metastatic melanoma – The clinical value of stereotactic irradiation and electrochemotherapy

Doctoral (PhD) thesis

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Introduction

The incidence of melanoma, especially in the fair-skinned population, has shown a gradual increasing trend over the past fifty years. Although it represents only a small percentage of all malignant skin tumors, its high propensity for metastasis makes it accountable for nearly 90% of skin cancer-related deaths. However, the mortality of melanoma shows a decreasing trend according to the latest data, attributed to successful prevention efforts, precise molecular pathological mapping of melanoma, and the emergence of new innovative targeted and immunotherapeutic modalities.

Clinical trials also confirm that new innovative therapies have significantly extended the survival of advanced melanoma patients. However, the therapeutic response is heterogeneous and not always durable, thus supplementary local therapeutic modalities may be necessary.

In our study, we evaluated the data of melanoma patients treated with systemic therapy initiated at the National Oncology Institute Dermato-oncology Department, with or without previously started systemic therapy, due to oligoprogression, using local therapeutic modalities, stereotactic radiotherapy, and electrochemotherapy. Systemic treatment was supplemented with stereotactic (30 patients) and electrochemotherapy (23 patients) in 53 patients. Between 2018 and 2020, among 30 patients treated for metastatic melanoma, stereotactic irradiation was applied in 28 cases (93%) alongside systemic therapy, and in 2 cases (7%) as monotherapy for brain and visceral metastases using CyberKnife, VitalBeam2, and TruBeam devices. Between 2016 and 2021, 23 patients were treated with electrochemotherapy for cutaneous-subcutaneous metastases using IGEA CLINIPORATOR®. We analyzed the effectiveness and side effects of therapies in relation to systemic innovative therapies.

Material and Methods

Patients

In my study, systemic treatment was supplemented with stereotactic irradiation (30 patients) and electrochemotherapy (23 patients) in a total of 53 patients. I analyzed the effectiveness and side effects of the therapies.

Between 2018 and 2020, among 30 patients treated for metastatic melanoma, systemic therapy was administered in 28 (93%) cases, and stereotactic irradiation was applied as monotherapy in

2 (7%) cases for brain and other organ metastases using CyberKnife, VitalBeam2, and TruBeam devices.

Between 2016 and 2021, 23 patients were treated with electrochemotherapy using the IGEA CLINIPORATOR® for cutaneous-subcutaneous metastases.

Statistical Analysis

Evaluation of PFS and OS was conducted using the Kaplan-Meier method and log-rank analysis, and simple data analysis was performed. Survival times were calculated from the start of systemic therapy. For patients treated only with radiation therapy, survival times were calculated from the start of radiation therapy. Results were considered significant if the p-value was less than 0.05. All statistical analyses were conducted using Statistica 13.4 software (TIBCO Software, Palo Alto, CA, United States).

Results

Stereotactic irradiation

Stereotactic irradiation was administered to 22 patients for brain metastases, 4 patients for pulmonary metastases, and 4 patients for other visceral metastases, alongside systemic therapy. Initial LDH levels were normal in 18 patients, elevated in 10 patients, and unknown in 2 patients. 20 patients received radiation therapy once, while 10 patients received two or more courses of radiation therapy. The radiation dose was delivered in a single fraction in 16 patients and in multiple fractions in 14 patients.

21 patients were treated using the CyberKnife device, 6 patients using VitalBeam2, and 3 patients using the TruBeam device. In 10 patients (33%), stereotactic radiation was the first-line therapy followed by systemic therapy initiation, while in 20 patients (67%), radiation therapy was administered following initiation of systemic therapy. Among these, 8 patients (27%) received targeted Braf-MEK inhibitor therapy, 8 patients (27%) received checkpoint inhibitor immunotherapy, and 4 patients (13%) received chemotherapy. Following stereotactic radiation therapy, systemic therapy was continued in 16 patients (53%), systemic therapy was not initiated in 4 cases (13%), and therapy switch was required in only 3 cases (10%). 17

patients (57%) received systemic therapy before radiation therapy, 8 patients (27%) received simultaneous systemic and radiation therapy, 3 patients (10%) did not require continuation of systemic therapy after radiation therapy, and 2 patients (7%) did not require systemic therapy either before or after radiation therapy.

The median follow-up was 20 months, with a minimum follow-up of 4 months. Regarding the treated tumors, complete remission was achieved in 6 cases (20%) and partial remission in 14 cases (47%). Stable disease was observed in 3 patients (10%), while progression of treated lesions was noted in 7 patients (23%). In terms of systemic disease, complete remission was seen in 6 cases (20%), partial remission in 12 cases (40%), stable disease in 2 cases (7%), and progression in 10 cases (33%). At the time of the study (October 2020), 14 patients (47%) were still receiving systemic treatment or were under observation, while 16 patients (53%) deceased. The median progression-free survival (PFS) was 12.5 months. Stratifying by patient groups, a median PFS of 13 months was observed in patients who received systemic therapy before radiation therapy, and a median PFS of 16 months was observed in those who started stereotactic radiation and systemic therapy simultaneously. Patients who did not receive systemic therapy after radiation therapy had a median PFS of 9 months, while those who underwent radiation therapy as their sole treatment had a median PFS of 11.5 months. The median overall survival (OS) was 20 months, calculated from the initiation of systemic therapy or radiation therapy (the latter applied to two patients who did not require systemic treatment at all).

According to the Kaplan-Meier curve in our study, the presence of brain metastases significantly negatively affected PFS, while the M stage and LDH levels at the start of therapy were not significant predictors of PFS or OS.

A total of 27 side effects were observed, affecting 16 patients (53%). Among them, 9 patients (30%) received targeted therapy, 3 patients (10%) received immunotherapy, and 3 patients (10%) received chemotherapy, while 1 patient (3%) did not receive systemic therapy alongside stereotactic radiation therapy. Most of the side effects were related to brain metastases, such as nausea, vomiting, headache, dizziness, aphasia, and epileptiform seizures. Side effects related to non-brain metastases included coughing, dry eyes, sweating, pain, esophageal irritation, and pneumonitis. All were of grade 1 severity except for pneumonitis in one case, which was grade

2. Pneumonitis resulting from radiation therapy was described on CT scans. With one month of oral steroid therapy supplemented with antibiotics, the observed abnormalities regressed.

Electrochemotherapy

Between 2016 and 2021, 23 melanoma patients, 10 males (43%) and 13 females (57%), underwent electrochemotherapy at our Institute. The median age was 74.5 years (range: 33-90, 57). In 13 cases (57%), cutaneous and subcutaneous metastases on the lower limbs were treated, in 5 cases (22%) on the head and neck region, in 4 cases (17%) on the upper limbs, and in 1 case (4%) on the trunk. The median size of metastases was 1 cm. In 16 patients (70%), one treatment was sufficient, while 6 patients (26%) received two, and 1 patient (4%) received three ECT treatments. Before ECT, 7 patients (30%) received chemotherapy, 6 patients (26%) received immunotherapy, and 2 patients (9%) received targeted therapy. Electrochemotherapy was used as first-line treatment in 8 patients (35%).

Among the 23 patients treated with ECT, complete remission (CR) was observed in 12 cases (52%), partial remission (PR) in 6 cases (26%), stable disease (SD) in 1 case (4%), and progressive disease (PD) in 4 cases (17%). The overall response rate (ORR) (CR+PR) was 78%. The median local PFS was 9 months. After the intervention, systemic therapy was continued in 8 patients (35%) with previously initiated effective systemic therapy in other tumor locations, while 4 patients (17%) did not require additional systemic therapy, two of whom had not received systemic treatment previously. The median OS was 17 months. Therapy switch occurred in 5 cases (22%), with progression of treated lesions in four patients and progression in a different location in one patient. Repeating ECT was necessary in 8 patients (35%), with a variable time interval between treatments ranging from 1 to 9 months.

Side effects of treatment were observed in 8 cases (35%) among all treated patients, including grade 1 erythema and pain at the treated site in 5 patients (22%), bacterial superinfection at the treated site in 2 cases (9%), and grade 3 edematous reaction around the treated lesion in 1 case (4%). No systemic side effects of treatment were observed. Antibiotic therapy was initiated for bacterial superinfections, topical soothing ointments were applied for erythematous reactions, and oral nonsteroidal medications were used to alleviate treatment-related pain. With symptomatic therapy, patients' symptoms resolved quickly. Overall, side effects were well-tolerated, with no permanent changes observed. It is crucial to determine the precise indications

for ECT, as potential septic conditions can be life-threatening in the case of superinfection of an extensive tumor process.

From our results, we concluded that both stereotactic irradiation and electrochemotherapy, alongside systemic innovative treatments, improve the disease outcome of melanoma patients with tolerable side effects.

Key findings

1. In cases of oligoprogression, in addition to systemic therapy supplemented with stereotactic irradiation, we achieved a median progression-free survival (PFS) of 12.5 months and a median overall survival (OS) of 20 months, which corresponds to data reported in international literature.
2. We successfully utilized the CyberKnife device, which is available in Hungary at the National Institute of Oncology, for determining precise radiation doses in the treatment of melanoma metastases. A median radiation dose of 18 Gy proved to be safe.
3. We conducted data analysis regarding the radiotherapy of melanoma extracranial metastases using CyberKnife and other LINAC devices, for the first time in Hungary, in terms of efficacy and safety. Out of eight patients treated with SBRT, we observed a therapeutic response in 75%.
4. We analyzed the effectiveness and safety of innovative therapies such as electrochemotherapy and systemic treatments, available for about ten years
5. We found that electrochemotherapy treatment, used alongside innovative therapies, improves patients' quality of life and can enhance the effectiveness of innovative therapies, with tolerable side effects

Articles on which the thesis is based

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