Exp Oncol 2021
43, 3, 257–260

Experimental ONCOLOGY

SAFETY PROFILE AND CLINICAL OUTCOME OF ADJUVANT RADIATION THERAPY AND INTERMEDIATE-DOSE INTERFERON IN COMPARISON WITH INTERMEDIATE-DOSE INTERFERON ALONE IN PATIENTS WITH MELANOMA METASTASES IN REGIONAL LYMPH NODES AND UNFAVORABLE PROGNOSTIC FACTORS

M. Kukushkina, S. Korovin, S. Diedkov, V. Ostafiichuk, A. Diedkov*
National Cancer Institute, Kyiv 03022, Ukraine

***Aim*: To assess the safety profile and efficacy of adjuvant radiation therapy and intermediate-dose interferon in comparison with intermediate-dose interferon alone in patients with synchronous and metachronous skin melanoma metastases in regional lymph nodes with unfavorable prognostic factors. *Materials and Methods*: 96 patients with synchronous and metachronous skin melanoma metastases in regional lymph nodes (stage III according to American Joint Committee on Cancer) and unfavorable prognostic factors were randomized in 2 groups: one of them (n = 45) received regional radiation therapy 50–55 Gy and intermediate dose of α2b-interferon (RT + IFN) in adjuvant setting and another one (n = 51) intermediate dose of α2b-interferon alone (IFN). *Results*: The most common adverse events in both groups were pyrexia and fatigue but grades 3–4 were observed more frequently in the RT + IFN group than in the IFN group (24.4 and 42.2% *vs* 11.8 and 27.5% respectively). 3-year recurrence-free survival was 78.5% in the RT + IFN group and 73.8% in the IFN group ($p = 0.72$), 3-year progression-free survival was 63.2% in the RT + IFN group comparing with 57.2% in the IFN group ($p = 0.59$) and 3-year overall survival was 77.1% and 66.7%, respectively ($p = 0.29$). Median of recurrence-free, progression-free and overall survival was not reached in any group. *Conclusions*: Radiation therapy and intermediate-dose interferon in adjuvant setting tends to improve recurrence-free, progression-free and overall survival comparing with intermediate-dose interferon alone in patients with synchronous and metachronous skin melanoma metastases in regional lymph nodes and unfavorable prognostic factors but it needs further investigation in larger groups of patients.**

***Key Words*: melanoma, regional lymph node metastases, radiation therapy, α2b-interferon.**

DOI: 10.32471/exp-oncology.2312-8852.vol-43-no-3.16524

Although skin melanoma represents only 4% of all malignancies, its incidence is continuing to rise all over the world [1]. In 1982, 1.115 new cases of skin melanoma were identified in Ukraine, in 2019 it raised to 3.008 and 10.0% of them were at stages III–IV [2]. Skin melanoma is one of the most aggressive forms of skin cancers. It tends to short remission, lymphogenic and hematogenous metastases. Melanoma preferentially metastasizes to lymph nodes, leading to hypotheses that it spreads through the lymphatic vasculature [3]. Surgery is the standard of care for localized melanoma and regional lymph node metastases, but patients with stage III (T1–4N1–3M0) disease are at high risk of relapse after definitive surgery [4] so they need treatment in the adjuvant setting to prevent distant metastases [5]. The risk of disease progression increases in the presence of some unfavorable prognostic factors (more than three lymph nodes metastases and/or extracapsular tumor spreading).

According to the existing standards of care, immunotherapy (IT) with nivolumab or pembrolizumab or targeted therapy with dabrafenib and trametinib (for BRAF-V600E/K-positive tumors) can be used in the adjuvant setting [6–9]. However, treatment with pembrolizumab, dabrafenib and trametinib is not refunded or reimbursed in Ukraine, and nivolumab is not registered. So unfortunately, innovative treatment is not affordable for Ukrainian patients [10].

As it is mentioned in the European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow-up for skin melanoma, adjuvant α2b-interferon (IFN) can no longer be routinely proposed in the adjuvant setting but its use might be confined to particular settings like patients with an ulcerated stage IIC primary melanoma and if the approved new drugs are not accessible [6].

It is proved that adding radiation therapy (RT) to the surgical treatment reduces the number of local recurrences [11]. However, the question about benefits of combining intermediate doses α2b-IFN with RT compared with α2b-IFN monotherapy in patients at high risk of disease progression requires further study.

The aim of the prospective randomized study is to assess the safety profile and 3-year recurrence-free (RFS), progression-free (PFS) and overall survival (OS) of adjuvant RT and intermediate-dose α2b-IFN in comparison with intermediate-dose α2b-IFN alone in patients with synchronous and metachronous skin melanoma metastases in regional lymph nodes

Submitted: June 10, 2021.
*Correspondence: E-mail: mkukushkina07@gmail.com
Abbreviations used: CT – computed tomography; IFN – interferon; IT – immunotherapy; MRI – magnetic resonance imaging; OS – overall survival; PFS – progression-free survival; RFS – recurrence-free survival; RT – radiation therapy.

(stage III according to melanoma staging system by the American Joint Commission on Cancer, 8th edition) with unfavorable prognostic factors (metastases in more than three lymph nodes and/or extracapsular tumor spreading).

MATERIALS AND METHODS

This study was approved by the Ethical Committee of Ukrainian National Cancer Institute. All patients included in the study signed informed consent form before any protocol-specific procedure.

96 patients with synchronous and metachronous skin melanoma metastases in regional lymph nodes with unfavorable prognostic factors were randomized in 2 groups: group 1 (n = 45) received regional RT 50–55 Gy and intermediate dose α2b-IFN in adjuvant setting and group 2 (n = 51) intermediate dose α2b-IFN alone. All patients were initially staged by physical examination, as well as computed tomography (CT) scan of the chest, abdomen and pelvic and brain magnetic resonance imaging (MRI).

According to study design (Fig. 1), skin melanoma patients with synchronous and metachronous macroscopic lymph node involvement and unfavorable prognostic factors were randomized 1:1 in 2 groups after complete lymph node dissection: group 1 received intermediate dose of α2b-IFN and regional RT 50–55 Gy (2 Gy fraction per day) and group 2 — intermediate dose α2b-IFN. α2b-IFN was administrated in both groups at a dose of 9 MU per day subcutaneously for 22 days (induction period) followed by 52 weeks of 3 MU subcutaneously three times per week (maintenance period).

All patients were monitored by means of clinical examination, chest, abdomen and pelvic CT scans and brain MRI every 3 months during the first 2 years and every 6 months during 3 years.

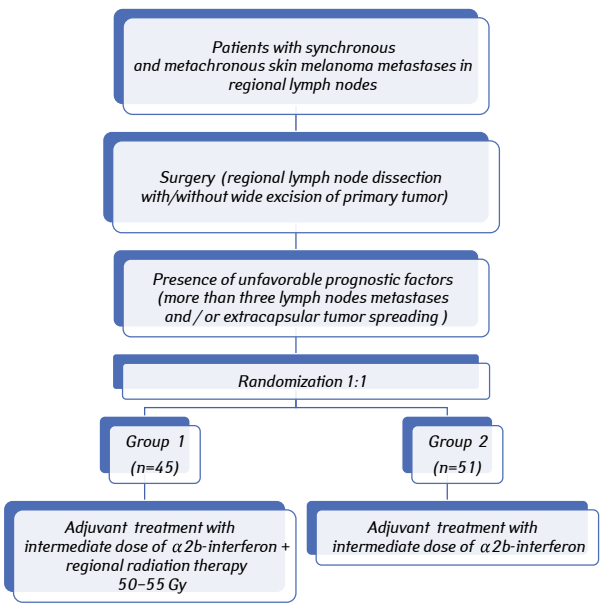

Fig. 1. Study design

Inclusion criteria for enrollment:

1. Patients with histologically confirmed synchronous and metachronous skin melanoma metastases in regional lymph nodes after complete lymph node dissection and unfavorable prognostic factors (more than three lymph nodes metastases and/or extracapsular tumor spreading).

2. Patients are ⩾ 18 years old at the time of signing the informed consent form.

3. Patients have fully recovered from surgery.

4. ECOG performance status of 0 or 1 at the time of randomization.

5. Patients with adequate bone-marrow reserve, adequate renal function and adequate hepatic function as assessed by standard laboratory criteria.

Exclusion criteria for enrollment:

1. Patients suffer from a mucous or ocular melanoma.

2. Patients with in-transit or satellite metastases.

3. Patients with a history of autoimmune disease, congenital or hereditary immunodeficiency.

4. Patients with previous or concomitant malignancies at other sites.

5. For female patients: the patient is pregnant or lactating.

Safety profile of treatment was assessed according to Common Terminology Criteria for Adverse Events version 5.0, efficacy by 3-year RFS in comparison groups.

Data analysis was performed using StatPlus software. For statistical analyses, quantitative parameters were summarized by mean, standard error, median, minimum and maximum, and qualitative parameters by frequencies and percentages. Time-dependent variables, RFS, PFS, and OS were analyzed using the Kaplan — Meier method. Any differences in survival were computed using the log-rank test. Durations of RFS, PFS, and OS were calculated based on the date of the first day of adjuvant therapy until the date of local recurrence, or until the date of any type of disease progression (local recurrence and/or metastases), or until the date of death, respectively. All data were considered to be statistically significant when the *p* value was 0.05 or less.

RESULTS

Demographic and pathologic features of the RT plus IFN and IFN groups are presented in Table 1. A greater proportion of female patients and patients with metastases in axillar lymph nodes assigned to RT plus IFN group than to IFN. Extracapsular spreading was more frequent in the IFN group; however, cohorts were similar regarding the number of lymph node metastases.

Safety profile was assessed according to Common Terminology Criteria for Adverse Events v.5.0. Adverse events (AEs), including grades 3–4, were more common among patients in the RT + IFN group than among patients in the IFN group. The most common AEs in both groups were pyrexia and fatigue but

Table 1. Baseline characteristics of the patients

Characteristics	RT+ α2b-IFN (n = 45)	α2b-IFN (n = 51)
Sex		
• Female	34 (75.6%)	26 (51.0%)
• Male	11 (24.4%)	25 (49.0%)
Age		
• Mean	53.7 ± 13.9	54.9 ± 12.1
• Median (range)	56.0 (27–82)	57.1 (27–78)
Primary site		
• Trunk	23 (51.2%)	29 (56.9%)
• Upper limbs	6 (13.3%)	5 (9.8%)
• Lower limbs	10 (22.2%)	14 (27.5%)
• Unknown	6 (13.3%)	3 (5.9%)
Lymph node metastases site		
• Supraclavicular	5 (11.1%)	3 (5.9%)
• Axillar	24 (53.3%)	16 (31.4%)
• Ileo-inguinal	16 (35.6%)	32 (62.7%)
Number of lymph node metastases		
• Mean	4.9 ± 2.1	4.8 ± 2.5
• Median (range)	4.0 (1–12)	4.0 (1–14)
Number of cases with extracapsular spreading	27 (60.0%)	41 (80.4%)

Table 2. Treatment-related adverse events

Event	RT + α2b-IFN (n = 45)		α2b-IFN (n = 51)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
	Number of patients with event (%)			
Pyrexia	45 (100)	11 (24.4)	51 (100)	6 (11.8)
Fatigue	41 (91.1)	19 (42.2)	44 (86.3)	14 (27.5)
Pain	28 (62.2)	5 (11.1)	31 (60.8)	3 (5.9)
Myalgia	4 (8.9)	2 (4.4)	3 (5.9)	1 (2.0)
Arthralgia	5 (11.1)	2 (4.4)	6 (11.8)	1 (2.0)
Nausea	17 (37.8)	4 (8.9)	20 (39.2)	3 (5.9)
Anemia	28 (62.2)	2 (4.4)	19 (37.3)	2 (3.9)
Leucopenia	21 (46.7)	3 (6.7)	18 (35.3)	1 (2.0)
Thrombocytopenia	15 (33.3)	3 (6.7)	12 (23.5)	2 (3.9)

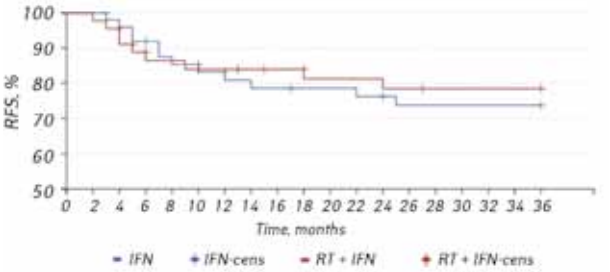

Fig. 2. 3-year recurrence-free survival

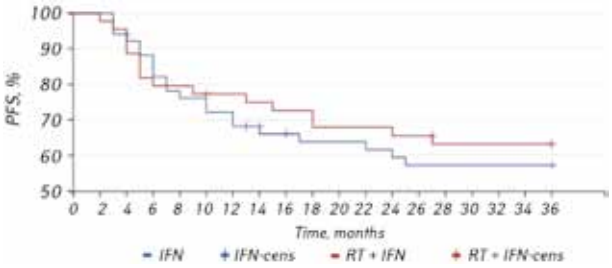

Fig. 3. 3-year progression-free survival

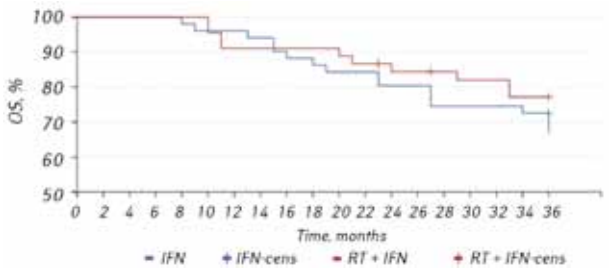

Fig. 4. 3-year overall survival

grades 3–4 were observed more frequently in the RT + IFN group than in the IFN group (24.4% and 42.2% *vs* 11.8% and 27.5%, respectively). As expected, hematological toxicity, particularly anemia and leucopenia, was revealed frequently among patients who received RT + IFN than IFN alone. At the same time, frequency of the pain, myalgia and arthralgia were very similar (Table 2).

3-year RFS did not differ significantly between the two groups: it was 78.5% in the RT + IFN group and 73.8% in the IFN group ($p = 0.72$) (Fig. 2). 3-year PFS was 63.2% in the RT + IFN group comparing with 57.2% in the IFN group ($p = 0.59$) and insignificant difference in 3-year OS (77.1% and 66.7% respectively, $p = 0.29$) (Figs. 3, 4). Median of RFS, PFS and OS was not reached in any group.

DISCUSSION

Adding RT to surgical treatment reduces the number of local recurrences. In particular, one of the largest randomized studies showed a reduction in the frequency of local recurrences from 41% to 10% [11], although its impact on OS is uncertain. In order to prevent distant metastases various treatments have been used (RT, chemotherapy, IT) [12, 13].

Until recently, only recombinant α2b-IFN was included into the guidelines for treating stage IIB-III melanoma in the United States and Europe [14]. However, the meta-analysis published in 2017 proved its low efficacy: the absolute difference in event-free survival after 5 and 10 years was 3.5% and 2.7%, and in OS — 3.0% and 2.8%, respectively, in favor of IFN under observation [15]. At the same time, the efficacy of combined RT and α2b-IFN compared with α2b-IFN monotherapy is underestimated.

Radiation seems to synergize with IT via several mechanisms, such as increasing the visibility of tumor antigens, activating the cGAS-STING pathway, and modulating the tumor microenvironment [16]. The efficacy of RT is associated with the induction of a type I IFN response [17] triggered via a cytosolic DNA sensing mechanism involving cGAS (Cyclic GMP-AMP synthase) and STING (STimulator of INterferon Genes) [18, 19] and this response is dose-dependent, as high dose irradiation can induce a mechanism leading to degradation of cytosolic DNA, thereby preventing the activation of cGAS/STING signaling [20]. Therefore, combination of IFN and RT needs to be investigated in further clinical trials.

Our study has demonstrated that RT and α2b-IFN are associated with higher frequency of grade 3-4 pyrexia and fatigue compared with IFN therapy alone (24.4% and 42.2% *vs* 11.8% and 27.5%, respectively).

RT and intermediate-dose IFN in adjuvant setting tends to improve recurrence-free, progression-free and OS on 4.7%, 6.0% and 10.4%, respectively, comparing with intermediate-dose IFN alone in patients with synchronous and metachronous skin melanoma metastases in regional lymph nodes with unfavorable

prognostic factors, but it needs further investigation in larger groups of patients.

REFERENCES

1. **Korovin S, Fedorenko Z, Michailovich Y, *et al.*** Burden of malignant melanoma in Ukraine in 2002–2013: incidence, mortality and survival. Exp Oncol 2020; **42**: 324–9. doi: 10.32471/exp-oncology.2312-8852.vol-42-no-4.15334.

2. **Fedorenko Z, Michailovich Y, Goulak L, *et al.*** Cancer in Ukraine 2019-2020. Bull Nat Cancer Registry of Ukraine 2021; **22**: 38–9.

3. **Emmett MS, Symonds KE, Rigby H, *et al.*** Prediction of melanoma metastasis by the Shields index based on lymphatic vessel density. BMC Cancer 2010; **10**: 1–8. doi: 10.1186/1471-2407-10-208.

4. **Ben-Ami E, Schachter J.** Adjuvant treatment for stage III melanoma in the era of targeted medicine and immunotherapy. Melanoma Manag 2016; **3**: 137–47. https://doi.org/10.2217/mmt-2016-0002.

5. **Schuitevoerder D, Vining CC, Tseng J.** Adjuvant therapy for cutaneous melanoma. Surg Oncol Clin 2020; **29:** 455–65. doi: 10.1016/j.soc.2020.02.009.

6. **Michielin O, Van Akkooi A, Ascierto P, *et al.*** Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019; **30**: 1884–901. doi: 10.1093/annonc/mdz411.

7. **Michielin O, van Akkooi A, Lorigan, P, *et al.*** ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. Ann Oncol 2020; **31**: 1449–61. doi: 10.1016/j.annonc.2020.07.005.

8. **Garbe C, Amaral T, Peris K, *et al.*** European consensus-based interdisciplinary guideline for melanoma. Part 2: treatment–update. Eur J Cancer 2019; **126**: 159–77. doi: 10.1016/j.ejca.2019.11.015.

9. **Coit DG, Thompson JA, Albertini, *et al.*** Cutaneous melanoma, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019; **17**: 367–402. doi: 10.6004/jnccn.2019.0018.

10. **Kandolf Sekulovic L, Guo J, Agarwala S, *et al.*** Access to innovative medicines for metastatic melanoma worldwide: Melanoma World Society and European Association of Dermato-oncology survey in 34 countries. Eur J Cancer 2018; **104:** 201–9. doi: 10.1016/j.ejca.2018.09.013.

11. **Agrawal S, Kane J, Guadagnolo B, *et al.*** The benefits of adjuvant radiation therapy after therapeutic lymphadenectomy for clinically advanced, high-risk, lymph node-metastatic melanoma. Cancer 2009; **115**: 5836–44. doi: 10.1002/cncr.24627.

12. **Gogas H, Kirkwood J, Sondak V**. Chemotherapy for metastatic melanoma: time for a change? Cancer 2007; **109**: 1–10. doi: 10.1002/cncr.22427.

13. **Korovin S, Kukushkina M**. Adjuvant therapy of patients with metastases of skin melanoma in regional lymph nodes. Oncologiya 2007; **9**: 377–9 (in Russian).

14. **Dummer R, Hauschild A, Lindenblatt, N, *et al.*** Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; **26**: 126–32. doi: 10.1093/annonc/mdv297.

15. **Ives N, Succiu S, Eggermont A, *et al.*** Adjuvant interferon-α for the treatment of high-risk melanoma: an individual patient data meta-analysis. Eur J Cancer 2017; **82**: 171–83. doi: 10.1016/j.ejca.2017.06.006.

16. **Wang Y, Deng W, Li N, *et al.*** Combining immunotherapy and radiotherapy for cancer treatment: current challenges and future directions. Front Pharmacol 2018; **9:** 185. doi: 10.3389/fphar.2018.00185.

17. **Burnette BC, Liang H, Lee Y, *et al.*** The efficacy of radiotherapy relies upon induction of type I interferon-dependent innate and adaptive immunity. Cancer Res 2011; **71**: 2488–96. doi: 10.1158/0008-5472.CAN-10-2820.

18. **Ishikawa H, Ma Z, Barber GN.** STING regulates intracellular DNAmediated, type I interferon-dependent innate immunity. Nature 2009; **461**: 788–92. doi: 10.1038/nature08476.

19. **Deng L, Liang H, Xu M, *et al.*** STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. Immunity 2014; **41**: 843–52. doi: 10.1016/j.immuni.2014.10.019.

20. **Vanpouille-Box C, Alard A, Aryankalayil MJ, *et al.*** DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun 2017; **8**: 15618. doi: 10.1038/ncomms15618.

ПРОФІЛЬ БЕЗПЕКИ ТА КЛІНІЧНИЙ РЕЗУЛЬТАТ АД'ЮВАНТНОЇ ПРОМЕНЕВОЇ ТЕРАПІЇ ТА СЕРЕДНІХ ДОЗ ІНТЕРФЕРОНУ ПОРІВНЯНО З СЕРЕДНЬОДОЗОВОЮ ІНТЕРФЕРОНОТЕРАПІЄЮ В МОНОРЕЖИМІ У ПАЦІЄНТІВ З МЕТАСТАЗАМИ МЕЛАНОМИ В РЕГІОНАРНИХ ЛІМФАТИЧНИХ ВУЗЛАХ З НЕСПРИЯТЛИВИМИ ПРОГНОСТИЧНИМИ ФАКТОРАМИ

М. Кукушкіна, С. Коровін, С. Дєдков, В. Остафійчук, А. Дєдков

Національний інститут раку, Київ 03022, Україна

Мета: Оцінити профіль безпеки та клінічний результат ад'ювантної променевої терапії та середніх доз інтерферону порівняно з середньодозовою інтерферонотерапією в монорежимі у пацієнтів з метастазами меланоми в регіонарних лімфатичних вузлах з несприятливими прогностичними факторами. ***Матеріали та методи:*** 96 пацієнтів із синхронними та метахронними метастазами меланоми шкіри в регіонарних лімфатичних вузлах (стадія III за American Joint Committee on Cancer) з несприятливими прогностичними факторами були рандомізовані у 2 групи: одна з них (n = 45) отримувала променеву терапію на ділянку регіонарного лімфоколектору 50–55 Гр та середні дози α2b-інтерферону (ПТ + ІФН) у ад'ювантному режимі, друга (n = 51) лише терапію середніми дозами α2b-інтерферону (ІФН). ***Результати:*** Найбільш поширеними побічними ефектами в обох групах були гіпертермія та втома, але ступінь 3–4 спостерігався частіше у групі ПТ + ІФН, ніж у групі ІФН (24,4 та 42,2% проти 11,8 та 27,5% відповідно). 3-річна безрецидивна виживаність (БРВ) становила 78,5% у групі ПТ + ІФН та 73,8% у групі ІФН (p = 0,72), 3-річна виживаність без прогресування (ВБП) становила 63,2% у групі ПТ + ІФН порівняно з 57,2% у групі група ІФН (p = 0,59) та 3-річна загальна виживаність (ЗВ) становила 77,1 та 66,7% відповідно (p = 0,29). Медіана БРВ, ВБП та ЗВ не була досягнута в жодній групі. ***Висновки:*** Променева терапія та середньодозова інтерферонотерапія в ад'ювантному режимі демонструють тенденцію до покращення БРВ, ВБП та ЗВ порівняно із середньодозовим інтерфероном в монорежимі у пацієнтів із синхронними та метахронними метаномами шкіри у регіонарних лімфатичних вузлах з несприятливими прогностичними факторами, але потрібні подальші дослідження у великих групах пацієнтів.

Ключові слова: меланома, регіонарні метастази в лімфатичні вузли, променева терапія, α2b-інтерферон.

Copyright © Experimental Oncology, 2021