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Clinical Trial Note

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Randomized phase III trial of adjuvant therapy with locoregional interferon beta versus surgery alone in stage II/III cutaneous melanoma: Japan Clinical Oncology Group Study (JCOG1309, J-FERON)

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Abstract

The Dermatologic Oncology Group of Japan Clinical Oncology Group has started a randomized phase III trial to confirm the superiority of adjuvant therapy with locoregional interferon beta in overall survival over surgery alone for patients with pathological stage II/III cutaneous melanoma (JCOG1309). Patients in the interferon beta arm receive intra- or subcutaneous injections of interferon beta directly into the surgical site at a flat dose of 3 million units once per day. Treatment is repeated for 10 consecutive days every 8 weeks for a total of 3 courses during the induction phase, then 1-day injection every 4 weeks for 2.5 years. A total of 240 patients will be accrued from 17 Japanese institutions within 6.5 years. Primary endpoint is overall survival. Secondary endpoints are relapse-free survival, distant metastasis-free survival, pattern of recurrence, and adverse events. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000017494 [http://www.umin.ac.jp/ctr/index.htm].

Key words: melanoma, adjuvant therapy, interferon beta, randomized controlled trial

Introduction

High-dose or pegylated interferon (IFN) alfa has been shown to improve relapse-free survival (RFS) in patients with surgically resected cutaneous melanoma; however, its efficacy in terms of overall survival (OS) is marginal, and the incidence of severe adverse events (AEs) is relatively high (1–5). Although one study using low-dose IFN alfa showed a benefit in OS with tolerable toxicity (6), all other phase III randomized controlled trials (RCTs) using low-dose or intermediate-dose IFN alfa have failed to show any OS benefit.

The primary site of cutaneous melanoma is often located away from its regional node field; thus, the lymphatic route between the primary site and the regional node field is usually still untreated even after definitive surgery with curative intent. Since almost half of Japanese patients with cutaneous melanoma developed the primary lesions on the lower limb (7), which are likely to have a longer lymphatic route than those in other anatomical sites, it would be reasonable to focus on the untreated lymphatic route as a therapeutic target of adjuvant therapy. To improve the outcome by adjuvant therapy and to lower its systemic toxicity, we have proposed injecting IFN beta directly into the surgical site, similar to the procedure used for sentinel lymph node (SLN) biopsy, so that the injected IFN beta would be drained through the untreated lymphatic route to the regional node field. Previously published study showed that the locally injected IFN beta achieved a clinical response in 50.0% of patients and 75.4% of skin metastases (8), and the other study showed that the locally injected IFN beta was drained well to the regional lymph nodes (9), although these studies were based on the results from a small number of patients and were published only in Japanese. The Dermatologic Oncology Group of Japan Clinical Oncology Group (JCOG-DOG) hypothesized that the locally injected IFN beta would reach clinically occult residual melanoma cells along the untreated lymphatic route and might induce systemic immunity in a manner similar to that induced by intralesional immune therapy (10). To develop an effective and safe adjuvant therapy for patients with resected cutaneous melanoma, the JCOG-DOG began a phase III RCT of adjuvant therapy with locoregional IFN beta versus surgery alone in stage II/III cutaneous melanoma (JCOG1309) in May 2015.

Currently, clinical trials of new agents in the adjuvant setting, such as immune checkpoint inhibitors or BRAF/MEK inhibitors, are ongoing. These agents seem to be promising because their efficacy in the metastatic setting has already been shown. However, these agents have some disadvantages; the costs of these emerging therapies are extremely high, immune-related AEs can occasionally be serious, some endocrine-related AEs can last for long periods of time during which hormone replacement therapy must be continued, and the incidence of BRAF mutation in Asian populations is relatively low. Recently, the EORTC18071 trial, in which patients with postoperative stage III cutaneous melanoma were randomly assigned to receive ipilimumab at a dose of 10 mg/kg or placebo, showed that ipilimumab resulted in a significantly longer OS than placebo (11,12). However, the JCOG-DOG decided not to consider adjuvant ipilimumab (10 mg/kg) as a standard of care because of its severe toxicity and high cost. Since ipilimumab was efficacious in the adjuvant setting, anti-PD-1 antibody might also be capable of activating T cells effectively in the absence of measurable metastatic disease. Even if the presently ongoing phase III trials of adjuvant therapy with anti-PD-1 antibodies or ipilimumab (3 mg/kg) show that it is associated with a significantly improved OS with tolerable toxicity, the JCOG1309 study will be continued by revising the protocol to limit the enrolled subjects to patients with stage II or IIIA disease, in whom immunity is less likely to be activated against clinically occult melanoma cells than in patients with more advanced stage disease.

The study protocol was approved by the JCOG Protocol Review Committee in March 2015 and the institutional review board at each institution prior to starting patient accrual. Patient enrollment began in May 2015. This trial has been registered at the UMIN Clinical Trials Registry: UMIN000017494 [http://www.umin.ac.jp/ctr/index.htm].

Protocol digest of JCOG1309

Objectives

The objective of this study is to confirm the superiority of adjuvant therapy with locoregional IFN beta over surgery alone in terms of OS in patients with pathological stage II/III cutaneous melanoma.

Study setting

A multi-institutional, two-arm, open-label, randomized phase III trial.

Endpoints

The primary endpoint is OS. OS is defined as days from randomization to death from any cause, and it is censored at the last day when the patient is alive. The secondary endpoints are RFS, distant metastasis-free survival (DMFS), pattern of recurrence, and AEs. RFS is defined as days from randomization to relapse or death from any cause, and it is censored at the last day when the patient is alive without any evidence of relapse. DMFS is defined as days from randomization to distant metastasis or death from any cause, and it is censored at the last day when the patient is alive without any evidence of distant metastasis.

Eligibility criteria

Inclusion criteria

1. Histologically confirmed primary cutaneous melanoma.
2. Pathological stage II or III according to the 7th AJCC-TNM classification.
3. Patients must have undergone curative surgery within 9 weeks prior to registration.
4. Primary melanoma must have been completely resected with clear margins.
5. Patients who underwent SLN biopsy must fulfill one of the followings:
   (a) SLNs were examined using immunohistochemistry (HMB-45 and/or MART-1/Melan A) in addition to routine H&E staining and were histologically confirmed as being negative for metastasis.
   (b) Patients with positive SLNs must have undergone an adequate complete lymph node dissection (CLND). The number of harvested lymph nodes must be equal to or more than 15 in the neck, 10 in the axilla and 5 in the groin.
6. Patients with clinically positive lymph nodes must have undergone an adequate CLND. The number of harvested lymph nodes must be equal to or more than 15 in the neck, 10 in the axilla and 5 in the groin.
7. No history of previous treatment for malignancy.
8. No history of treatment using any kind of interferon.
9. No plan of postoperative radiation
10. Age between 20 and 80 years.
11. ECOG performance status of 0 or 1.
12. Patients must have adequate organ and marrow function as defined below within 28 days prior to registration:
    (a) Absolute neutrophil count $\geq 1200/mm^3$
    (b) Hemoglobin ≥ 8.0 g/dL
    (c) Platelets $\geq 10 \times 10^4 /mm^3$
    (d) Total bilirubin ≤ 2.0 mg/dL
    (e) AST ≤ 100 IU/L
    (f) ALT ≤ 100 IU/L
    (g) Creatinine ≤ 1.5 mg/dL
13. Written informed consent.

Exclusion criteria

1. Patients with a concurrent malignancy (within 5 years) except for carcinoma in situ, intramucosal cancer or basal cell carcinoma that was curatively treated with local therapy.
2. Patients with ongoing or active infections requiring systemic therapy.
3. Patients with a fever of equal to or higher than 38°C.
4. Pregnant, possibly pregnant, or lactating women. Women within 28 days after having given birth.
5. Patients with a psychiatric illness or social situations that would limit compliance with study requirements.
6. Patients who are receiving the systemic administration of steroids or other immunosuppressants.
7. Patients with unstable angina pectoris or a history of cardiac infarction within 6 months.
8. Patients with uncontrolled diabetes mellitus or receiving continuous treatment with insulin.
9. Patients with a positive HIV antibody status.
10. Patients with interstitial pneumonia, severe pulmonary fibrosis or emphysema.
11. Patients with a history of autoimmune hepatitis.
12. Patients who are taking the herbal drug Shosaikoto.
13. Patients who have a history of allergy to materials included in IFN beta, materials derived from cows or biological drugs.

Randomization

After confirming the fulfillment of the eligibility criteria, registration is performed using a web-based system of the JCOG Data Center. Patients are randomized 1:1 to receive IFN beta or surgery alone using a minimization method balancing the arms in terms of institution, pathological stage (IIA/IIB/IIIA vs. IIC/IIIB vs. IIIC), and primary site of melanoma (head and neck vs. trunk vs. limbs).

Treatment methods

Patients in the IFN arm receive intra- or subcutaneous injections of IFN beta at a flat dose of 3 million units into the surgical site once a day. Treatment is repeated for 10 consecutive days every 8 weeks for a total of 3 courses during the induction phase; treatments are then repeated as 1-day injection every 4 weeks for 2.5 years during the maintenance phase.

Follow-up

All randomized patients will be followed up for at least 5 years after patient accrual is completed. A physical examination will be performed at least once every month for the first 3 years, every 3 months from the third to fifth years, and every year thereafter to determine whether a local recurrence, in-transit metastasis, or regional node recurrence has occurred. A blood test will be performed at least once every month for the first 6 months, and every 3 months from the seventh month until the third year. An enhanced computed tomography examination of the head, cervix, chest, abdomen and pelvis will be performed at least every 6 months for the first 5 years.

Study design and statistical analysis

This study is designed as a randomized phase III trial to confirm the superiority of locoregional IFN beta over surgery alone in terms of OS in patients with pathological stage II/III cutaneous melanoma. The planned total sample size is 240 to observe required events of 88 to detect a 10% improvement in 5-year OS in the IFN arm from 70% in the surgery alone arm with a power of 70%, a one-sided alpha-level of 5%, the planned accrual period is 6.5 years, and the follow-up period is 5 year for primary analysis. Stratified log-rank test with pathological stage and primary site of melanoma as stratification factors will be performed to test the superiority of locoregional IFN beta following curative surgery over surgery alone. All the statistical analyses will be performed at the JCOG Data Center.

Interim analysis and monitoring

Two interim analyses are planned. The first interim analysis will be performed after half of the planned number of patients have been enrolled. The second interim analysis is planned after the planned patient accrual and the completion of the protocol treatment for all patients. The Lan-DeMets method with the O'Brien&Fleming-type α spending function will be used to adjust for the multiplicity of the interim analyses (13). The Data and Safety Monitoring Committee of the JCOG will review the interim analysis reports independently from the group investigators and group statistician. At the interim analyses, the trial will be terminated if the IFN beta arm is superior to the surgery alone arm in terms of OS with an adjusted significance level. The early termination will also be considered for safety reasons if treatment-related deaths occur in four or more patients in the IFN beta arm. In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate and improve the study's progress, data integrity, and patient safety. For quality assurance, site visit audits will be performed by the JCOG Audit Committee (not on a study-specific basis but for the study group).

Participating institutions (from north to south of Japan)

Hokkaido University Hospital, Asahikawa Medical University Hospital, Faculty of Medicine, University of Tsukuba, Saitama Medical University International Medical Center, Saitama Medical University, National Cancer Center Hospital, The University of Tokyo Hospital, Niigata Cancer Center Hospital, Toyama Prefectural Central Hospital, Shinshu University school of medicine, Shizuoka Cancer Center, Nagoya University school of medicine, Osaka Prefectural Hospital Organization Osaka International Cancer Institute, School of Medicine, Fukuoka University, Kyushu University Hospital, Kumamoto University Medical School, National Hospital Organization Kagoshima Medical Center

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

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Conflict of interest statement

None declared.

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