Interferon Therapy in the Field of Dermatology

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Abstract: Interferon therapies for dermatological diseases were clinically reviewed. This article will mainly focus on interferon therapy for malignant melanoma and cutaneous lymphoma in Japan. The cutaneous adverse symptoms that accompany interferon therapies are also discussed in this review.

Key words: Interferon; Malignant melanoma; Cutaneous malignant lymphoma; Adverse reactions

Introduction

Interferon (IFN) is used in treating various dermatological diseases. This paper focuses on the IFN therapy for malignant melanoma and cutaneous malignant lymphoma because many patients suffer from them and Japanese medical insurance covers the IFN therapy for them. The paper goes on to summarize the IFN therapies clinically studied for other diseases in Japan and foreign countries. Cutaneous adverse reactions to IFN therapies are also discussed.

Treatment for Malignant Melanoma and IFN

Malignant melanoma (Fig. 1) is a malignant tumor of melanocytes. The annual development rate of malignant melanoma in Japan is about 1.5 to 2 per 100,000 persons, and the rate tends to increase. Malignant melanoma is known to easily metastasize and be resistant to chemotherapy. It is also known to regress spontaneously. Therefore, investigators have considered it as a tumor with antigenicity to be treated with immune therapy. Although various therapies have been examined, including the use of BCG (Bacille bilié de Calmette-Guérin), adoptive immune therapy, vaccine therapy, and gene therapy, most of them remain at the level of basic research. IFN-β was found effective for cutaneous metastatic foci of melanoma and has been widely used as a postoperative adjuvant therapy for malignant melanoma in Japan.

Malignant melanoma is classified into several disease stages by the thickness of the tumor, presence/absence of lymph node metastasis, and presence/absence of distant metastasis.

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and is treated according to the stage of the disease. The American Joint Committee on Cancer (AJCC) revised the disease stage classification of malignant melanoma in 2001 (Tables 1 and 2). Malignant melanoma is mainly treated with surgical excision. IFN-β is used alone or in combination with chemotherapy as a postoperative adjuvant or maintenance therapy for the disease in the IIB to III stages. Unfortunately, no prospective study with an adequate population has been performed due to associated ethical problems and the small number of patients. However, IFN-β has been widely used as a postoperative adjuvant therapy in Japan because a basic study

Table 1 Melanoma TNM Classification

<table>
<thead>
<tr>
<th>T classification</th>
<th>Thickness</th>
<th>Ulceration Status</th>
</tr>
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</table>
| T1               | ≤1.0 mm   | a: without ulceration and level II/III  
b: with ulceration or level IV/V |
| T2               | 1.01–2.0 mm | a: without ulceration  
b: with ulceration |
| T3               | 2.01–4.0 mm | a: without ulceration  
b: with ulceration |
| T4               | >4.0 mm   | a: without ulceration  
b: with ulceration |

<table>
<thead>
<tr>
<th>N classification</th>
<th>No. of Metastatic Nodes</th>
<th>Nodal Metastatic Mass</th>
</tr>
</thead>
</table>
| N1               | 1 node                  | a: micrometastasis†  
b: macrometastasis† |
| N2               | 2–3 nodes               | a: micrometastasis†  
b: macrometastasis†  
c: in transit met(s)/satellite(s) without metastatic nodes |
| N3               | 4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s) |

<table>
<thead>
<tr>
<th>M classification</th>
<th>Site</th>
<th>Serum Lactate Dehydrogenase</th>
</tr>
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<tbody>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal mets</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
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<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

†: Micrometastases are diagnosed after sentinel or elective lymphadenectomy.
††: Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.
showed IFN-β locally administered to a tumor migrated through lymph ducts into the tumor-affected lymph nodes at a high concentration\(^7\) and because a retrospective study showed a significantly higher 5-year survival rate with DAV (DTIC [dacarbazine], ACNU [nimustine], and VCR [vincristine]) therapy plus IFN-β than with DAV therapy alone in patients with Stage III malignant melanoma.\(^8\)

DAV plus IFN-β therapy has been performed with the following protocol.\(^9,10\) DTIC is administered by intravenous drip infusion at a dose of 80 to 140 mg/m\(^2\) for 5 days continuously. ACNU at 50 to 80 mg/m\(^2\) and VCR at 0.5 to 0.8 mg/m\(^2\) are intravenously administered with a side tube on Day 1. In parallel with these treatments, IFN-β is locally injected for 5 to 10 days at several intracutaneous sites around the primary surgical site at a total dose of 3,000,000 IU/body. This is considered as a single course, and repeated after withdrawal intervals of 4 to 6 weeks. This therapy is repeated for 2 to 3 courses for the IIA and IIB stages, and for 5 to 6 courses for the IIC and III stages. The maintenance therapy with IFN-β is performed, if possible, by locally injecting it to several intracutaneous sites around the primary surgical site at a total dose of 3,000,000 IU/body every 2 to 4 weeks for 2 to 3 years. Although the local injection of IFN-β

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### Table 2 Proposed Stage Groupings for Cutaneous Melanoma\(^4\)

<table>
<thead>
<tr>
<th>Clinical Staging</th>
<th>Pathologic Staging</th>
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<tbody>
<tr>
<td><strong>T</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>O</td>
<td>Tis</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
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<tr>
<td></td>
<td>T2a</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
</tr>
<tr>
<td>IIB</td>
<td>T3b</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b</td>
</tr>
<tr>
<td>III(^5)</td>
<td>Any T</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-4a</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1-4b</td>
</tr>
<tr>
<td></td>
<td>T1-4a</td>
</tr>
<tr>
<td></td>
<td>T1-4a/b</td>
</tr>
<tr>
<td>IICC</td>
<td>T1-4b</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
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</tbody>
</table>

\(^*\): Clinical staging includes microstaging of the primary melanoma and radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

\(^†\): Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage 1A patients are the exception; they do not require pathologic evaluation of their lymph nodes.

\(^\dagger\): There are no stage III subgroups for clinical staging.
is painful, the pain can be relieved by dissolving it in 1 to 3 ml of a 1% procaine injection solution. No lidocaine injection solution can be used because IFN-β changes its formulation to cause clouding. Fever that may occur after the local injection of IFN-β can be relieved by administering an anti-inflammatory analgesic.

It should be noted that several cases with secondary cancer suspected to derive from DTIC or ACNU (acute myeloid leukemia and myelodysplastic syndrome) were recently reported in patients treated with the postoperative adjuvant therapy. It is necessary to decide whether the DAV plus IFN-α therapy should be performed or not for patients in the II stage, and if applicable in the III stage as well, by carefully considering the patient’s age, physical status, complications, and tumor thickness. Patients choose their therapy under the informed consent. Postoperative adjuvant therapy with only a local injection of IFN-β has also been examined. That is, IFN-β is intracutaneously injected once daily at several sites around the surgical site at a total dose of 3,000,000 IU/body, and a course consisting of 10 injections is repeated after withdrawal intervals of 4 to 6 weeks. It is considered appropriate to perform 2 to 3 courses for the II stage disease and 5 to 6 courses for the III stage disease. The decision to choose an optimal postoperative adjuvant therapy should be made carefully, in accordance with the patient’s condition.

The IV stage disease should be treated by a combination of surgical excision of localized metastatic foci, chemotherapy, BRM therapy, radiotherapy, immunotherapy, and thermotherapy. Known regimens of the BRM therapy include the CDDP + IFN-α + IL-2 therapy in which chemotherapy, IFN-α, and interleukin-2 (IL-2) are combined, DTIC + BCNU + CDDP + TAM + IFN-α + IL-2 therapy, and DTIC + CDDP + VBL + IFN-α + IL-2 therapy. Although some investigators have reported high response rates for these regimens, the regimen most effective for life prognosis (chemotherapy alone, chemotherapy + BRM therapy, or BRM therapy alone) has not been determined. Since none of the above regimens are covered by Japanese medical insurance, the VI stage disease is often treated with DAC-TAM therapy.

**IFN Therapy for Cutaneous Malignant Lymphoma**

Several types of lymphoma cause cutaneous lesions; among these, IFN therapy is used for mycosis fungoides and adult T cell lymphoma. IFN therapy is known to be effective for skin lesions to some degree. However, IFN therapy has not been strictly evaluated for life prognosis in relation to any type of cutaneous malignant lymphoma.

1. **Mycosis fungoides**

Mycosis fungoides (Fig. 2) is the most frequent type of cutaneous malignant lymphoma. It is T cell lymphoma in which erythematous stage and plaque stages last for a long time, and

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**List of abbreviations**

occasionally progress to a tumor stage. Patients with mycosis fungoides often die when the disease progresses to the tumor stage. It does not respond well to treatments. However, the disease progresses slowly before the tumor stage without causing visceral erosion. Therefore, during the erythematous stage and plaque stage, treatment is performed to prevent the disease from progressing to the tumor stage. The disease is managed by reducing tumor cells and minimizing the demerits associated with adverse reactions. So far, the disease during the erythematous stage and plaque stages has been treated with phototherapy (psoraren ultraviolet A therapy: PUVA). Although actinotherapy remains important, the use of IFN alone or in combination with phototherapy has been increased since the early 1990’s. When the lesions of the disease extend to the whole skin, recombinant IFN-γ (rIFN-γ) is administered by intravenous drip infusion at 2,000,000 to 4,000,000 IU once daily, 3 to 5 times a week. When it is locally administered, it is administered to several sites in and around the lesion at a total dose of 200,000 to 2,000,000 IU/lesion, or 1,000,000 to 2,000,000 IU/cm². Natural IFN-γ (nIFN-γ) is intramuscularly injected once daily 2 to 3 times a week at a dose of 1,000,000 IU. In any case, the effectiveness of the therapy is determined at 4 weeks from the start. However, there was a patient in whom skin lesions of cutaneous malignant lymphoma were successfully relieved with nIFN-γ, but subsequently extended to other organs, leading to death. Although it is unknown whether the patient experienced exacerbation of the disease through its natural course or nIFN-γ changed the characteristics of tumor cells, extreme care should be exercised in using IFN, as with other therapeutic techniques. There is a protocol of IFN-α in which 3,000,000 IU/m² of IFN-α is subcutaneously injected 3 times weekly in combination with the oral administration of etretinate, although it is not covered by Japanese medical insurance.

2. Adult T cell leukemia/lymphoma

Adult T cell leukemia/lymphoma is leukemia and lymphoma caused by HTLV-1. It is classified into 4 types, namely, acute, lymphoma, chronic, and smoldering types, and the smoldering type is further divided into cutaneous and narrow sense smoldering subtypes. It has been reported that the intramuscular injection of 1,000,000 IU of nIFN-γ once daily was effective for eruptions in patients with the cutaneous type characterized by the cutaneous infiltration of tumor cells without leukemia, tumor-induced lymph node swelling, or tumor cell infiltration to other organs. nIFN-γ has been reported effective to some degree even in patients with cutaneous tumor or leukemia, while there have been many patients including patients during acute exacerbation or with acutely progressing disease, who have not responded to IFN-γ. Therefore, one should refrain from using IFN-γ in such patients.

Attempts at IFN Therapy for Other Diseases

Other diseases for which the therapeutic effect of IFN has been reported include viral verruca, porphyria cutanea tarda, cryoglobulinemia associated with type C hepatitis, Kaposi’s sarcoma associated with AIDS, intraepidermal carcinoma, such as Bowen’s disease, actinic keratosis, and Paget’s disease.

Cutaneous Lesions Associated with IFN Therapy

As the use of therapies involving various cytokines has advanced, it has become known that such therapies may cause cutaneous lesions. The cutaneous lesions that can be caused by IFN are summarized below.

1) Erythema and skin itching: Urticaria, edematous erythema, and erythematous papula may occur in the initial stage of IFN therapy, often in a few weeks. However, IFN
therapy can often be continued with symptomatic therapy or by adjusting the dose or administration intervals.

2) Psoriasis: IFN may exacerbate concurrent psoriasis vulgaris or induce psoriasis.\(^{32-34}\) Psoriasis may worsen so severely that the treatment of the primary disease has to be discontinued.

3) Alopecia: Alopecia frequently occurs with IFN therapy.\(^{35}\) The incidence of alopecia ranges from 10 to 30%, depending on reports. It has been particularly frequently reported with the use of IFN-\(\alpha\). It often occurs 2 to 3 months after the start of IFN therapy and resolves in several months even when the therapy is continued.

4) Pigmentation and depigmentation: Several cases with pigmentation or depigmentation have been reported.\(^{36-37}\)

5) Pemphigus: Pemphigus is an autoimmune disease characterized by blisters on the whole body surface. A small number of cases with the disease have been reported with the use of IFN-\(\alpha\) or \(\beta.\)\(^{38,39}\) The disease requires immediate treatment because it can be lethal.

6) Skin ulcers at injection site: The subcutaneous or intramuscular injection of IFN-\(\alpha\) or \(\beta\) may cause ulcers at the injection site.\(^{40-43}\) They may occur a while after the start of the IFN therapy, often after 6 months or later. It is inferred that IFN may exacerbate the skin ulcers. It is desirable to inject IFN intramuscularly, instead of subcutaneously, to prevent them. It is necessary to change injection sites regularly to avoid injecting IFN at the same site continuously. Although the ulcers may resolve with conservative external therapy, they may require surgical treatment when they are associated with extensive skin necrosis.

7) Others: The use of IFN has been reported to cause contact dermatitis,\(^{44}\) sarcoidosis,\(^{45}\) and erythema nodosum.\(^{46}\)

Conclusions

IFN therapy in the field of dermatology is mainly performed for treating malignant melanoma and cutaneous malignant lymphoma. The former is treated with IFN-\(\beta\) used for postoperative adjuvant therapy, while the latter is treated with IFN-\(\gamma\) in patients in whom lesions remain at the cutaneous level and progress slowly. The DAV + IFN-\(\beta\) regimen is included in the standard therapies for malignant melanoma. However, IFN therapy causes various cutaneous adverse reactions. Since IFN therapy is generally used for intractable or malignant primary diseases, efforts should be made to continue it as long as skin symptoms can be controlled with symptomatic therapies or by adjusting the dose of IFN. However, extreme care should be exercised regarding cutaneous symptoms during IFN therapy, because they may threaten the patient’s life.

REFERENCES


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