High dose etretinate and interferon-alpha--a phase I study in squamous cell carcinomas and transitional cell carcinomas

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Abstract
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High Dose Etretinate and Interferon-alpha

A Phase I Study in Squamous Cell Carcinomas and Transitional Cell Carcinomas

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Simultaneous exposure to retinoids and interferons can result in enhanced antiproliferative and differentiating effects on malignant lesions. We studied the toxicity and the potential efficacy of an association of high dose etretinate and Interferon-alpha (IFN-α) in squamous cell carcinomas of the lung, head and neck, the esophagus, cervix and the penis, as well as in transitional carcinomas of the bladder. The treatment consisted of etretinate (Tigason®) 4 mg/kg/d on 2, 3, 4 and finally 5 consecutive days every other week and IFN-α (Roferon®) 6 Mio IU sc. q.d. for 5 days every week. Of 24 patients enrolled, 23 were assessable for toxicity and 20 for response. With two occurrences of grade 3 cutaneous toxicity, the administration of etretinate (Tigason®) 4 mg/kg/d on 5 consecutive days every other week and IFN-α (Roferon®) 6 Mio IU sc. q.d. for 5 days every week was considered to be the MTD. Toxicity was mild otherwise, mostly at grades 1 and 2 level, causing fatigue, skin peeling and erythema, mucositis and cheilitis; 3 PR (partial response) and 8 SD (stable disease) were recorded. Of the responders, one patient had become resistant to cisplatin-based chemotherapy and the other two had at no time ever received systemic therapy. We conclude that the association of high doses of etretinate and IFN-α has moderate activity in squamous cell carcinomas, is well tolerated, and that IFN-α plays a role in the improved tolerance of the retinoid.

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Retinoids constitute a large family of vitamin A derivatives that are well known for their differentiating and antiproliferative properties in a wide variety of tumor cell lines in vitro (1). In humans, all-trans-retinoic acid (ATRA) was shown to be active in the treatment of acute promyelocytic leukemia, and is presently considered as a standard component in the treatment of this disease (2). Premalignant lesions of the mucosa and the skin can respond to the administration of other retinoids such as isotretinoin (Roaccutan®) (3). In overt solid tumors, however, the activity of retinoids is poor when administered alone. Isotretinoin has a modest anti-tumor activity as single agent in squamous cell cancers (SCCs) of the skin, head and neck and lung (4, 5). High doses of retinoid are required but are not suitable for continuous administration because of the development of intolerable mucocutaneous toxicity.

Etretinate (Tigason®) is another retinoid derivative known for its antiproliferative and differentiating properties in malignant lesions (6). At our institution etretinate was studied in a pilot phase II trial at two dose levels in patients with advanced SCC of the head and neck, lung, skin, vulva and transitional cell carcinoma of the bladder (P. Alberto and W. Bollag, unpublished data). Although the dose level of 150 mg/d was found ineffective (8 cases), 4 minor responses (< 50% decrease of tumor volume) were observed in 10 patients treated with 300 mg/d for 5 days, repeated every 2 to 7 weeks. At this dose level, however, there was grade 3 to 4 skin toxicity (painful skin peeling of the extremities) (7 patients), cheilitis and stomatitis (5 patients), conjunctivitis (7 patients) and sight impairment (3 patients). All of these side effects were completely reversible, but the patients had to be treated every 3 to 7 weeks instead of every other week as originally planned. It was concluded that high dose etretinate at 300 mg/d had some efficacy against SCCs but was too toxic to be given for 5 days every other week, and an administration scheme of 3 days every other week was proposed for any further investigation with etretinate at this dose level.

IFN-α is known to possess antiproliferative, differentiating and immunomodulatory properties, but probably exerts these effects through separate molecular mechanisms (7). A growing body of evidence from both laboratory and clinical research now supports the concept that simulta-
neous exposure to both retinoids and IFNs can result in enhanced antiproliferative and differentiating effects compared with results from exposure to either one or the other agent alone (8–11). The association of isotretinoin and IFN-\(\alpha\) has already been studied in several clinical trials, with very interesting results. Out of 28 evaluable patients with advanced SCC of the skin, 19 patients responded, with 7 complete responses (12). Response rates were 93% (13/14) in advanced local disease, 67% (4/6) in regional disease, and 25% (2/8) in distant metastatic disease. In locally advanced SCC of the cervix a 50% response rate was reported in 26 patients treated (13). Another important consideration in the simultaneous prescription of IFN-\(\alpha\) and retinoids is the lack of overlap between their major side effects. Retinoid toxicity is seen as desquama-
tive dermatitis, cheilitis, mucositis, pruritus, epistaxis, conjunctivitis with blurred vision and alopecia, whereas IFN-\(\alpha\) side effects are manifested mainly as fever, fatigue, headache, myalgia, loss of appetite and nausea (14–16).

Etretinate and IFN-\(\alpha\) were found to have a synergistic reaction to tumor cell lines in vitro (8). Furthermore, experiments with nude mice using xenografts of a human SCC of the tonsil have shown a synergistic effect of etretinate and IFN-\(\alpha\) (W. Bollag, unpublished data). So far, the combination of IFN-\(\alpha\) + etretinate was only tested in cutaneous T-cell lymphoma (17, 18). Because of our previous observation of marginal activity of etretinate in SCCs, we launched a phase I trial to explore the toxicity and the potential activity of the combination etretinate plus IFN-\(\alpha\) in patients with SCCs and transitional carcinomas of any origin for whom no other form of therapy was available.

**PATIENT SELECTION AND TREATMENT PLAN**

Patients had to have histopathologically proven squamous cell carcinoma of any origin or transitional carcinoma of the urogenital tract which was not amenable to curative therapy with measurable disease, a Zubrod performance status of \(\leq 2\), 20 to 75 years of age, no concomitant anticoagulation, bilirubin \(\leq 25\ \mu\text{mol/l}\), ASAT and ALAT \(\leq 2 \times \) the normal upper limit, serum creatinin \(\leq 120\ \mu\text{mol/l}\), normal cholesterol and triglyceride levels, granulocyte count \(\geq 1500/\text{mm}^3\) and platelets \(\geq 100000/\text{mm}^3\). Patients should neither have active CNS metastasis, nor have received IFN-\(\alpha\) or have been given any other retinoid previously. Written informed consent was also required.

The treatment consisted of IFN-\(\alpha\) (Roferon\(^\text{a}\)) given at 6 Mio IU sc. q.d. for 5 days each week and etretinate (Tigason\(^\text{a}\)) at 4 mg/kg/day given on 2–5 consecutive days every other week (see Table 1). Both IFN-\(\alpha\) and etretinate were provided by F. Hoffman-La Roche SA (Basel, Switzerland). Physical and blood count examinations were performed weekly, prothrombin time, liver function tests, serum creatinine, serum cholesterol and serum triglyceride were checked every other week, and responses were assessed monthly. Criteria of toxicity and response were those specified by WHO (19), apart from cutaneous toxicity which was assessed according to a modification of previously reported criteria (20). Patients were treated at the same dose level in groups of 6. If no more than one dose-limiting toxicity (DLT)—defined as any grade 3 toxicity occurring after one cycle of treatment and precluding treatment continuation as originally scheduled—occurred, the next 6 patients were treated at the next highest dose level. Patients were treated for at least 3 months unless progression occurred beforehand.

**RESULTS**

Twenty-four patients were enrolled in the study. One patient received one cycle of treatment but was lost to follow-up. Three patients were eligible for toxicity evaluation but not for tumor response; one because of refusal to continue treatment after the onset of acute diarrhea 2 days after the start of therapy, the second because of sudden death of unexplained cause during the third week on protocol, and the third patient because of protocol violation (concomitant irradiation of the measurable lesion). Therefore 23 patients were assessable for toxicity, and 20 for tumor response.

A total of 95 cycles of treatment was given. Toxicities are summarized in Table 2 and per treatment group in Table 3. Two cases of grade 3 skin toxicity were observed.
The responses by treatment group and tumor origin are presented in Tables 4 and 5: 3 partial responses (PR), 2 in lung tumors and 1 in a SCC of the esophagus. The two patients with lung tumors did not have any previous systemic therapy, whereas the patient with carcinoma of the esophagus had received cisplatin-based treatment and had become resistant to it. Of these three responders, one patient with lung carcinoma and the patient with carcinoma of the esophagus responded slowly with a time to objective response of 19 and 13 weeks, respectively. These responses lasted for 32 and 25 weeks, respectively. The other responding patient developed an objective response after 3 to 4 weeks of treatment, but this response lasted only 4 weeks. One patient with a transitional carcinoma of the bladder had a dramatic subjective response, with the disappearance of excruciating pain necessitating 270 mg morphine a day and resolution of left-leg edema caused by tumoral compression. However, this was not felt to be a sufficient response criterion to qualify as a PR and this patient was classified as stable disease. A stable disease classification was observed in other patients suffering from SCC of the lung, esophagus and cervix and lasted for 8 to 15 weeks.

**DISCUSSION**

The results of this study show that the combination of high dose etretinate and IFN-\(\alpha\) is tolerable and has a moderate reaction in squamous cell carcinomas. IFN-\(\alpha\) in group 4 and censored as DLTs. IFN-\(\alpha\) (Roferon\(^{\circledast}\)) given at 6 Mio IU sc. q.d. for 5 days every week and etretinate (Tigason\(^{\circledast}\)) at 4 mg/kg/d given on 5 consecutive days every other week was therefore considered to be the MTD. Only one patient in group 3 could not tolerate IFN-\(\alpha\) at 6 mio IU/d (fever grade 3 with general malaise and grade 3 fatigue occurring during the first cycle of treatment) and was treated with IFN-\(\alpha\) 3 mio IU/d only (3 cycles of treatment). One patient developed acute diarrhea accompanied by fever only 2 days after the start of therapy and refused to continue with the treatment. The relationship to investigational treatment was considered to be remote. One episode of grade 3 leukopenia was observed after 2 cycles of therapy in a patient with advanced head and neck disease suffering from chronically infected cutaneous metastases. The other occurrences of grade 3 toxicities (fatigue and anemia) were felt to be related to patient disease and poor performance status and were not censored as DLTs. Interestingly, cheilitis and mucositis were usually mild, and ocular symptoms occurred in only two cases.

<table>
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<th>Grade (Gd) 2 and 3 main toxicities per treatment group</th>
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<td>Treatment groups</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
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<td>Skin</td>
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<td>Cheilitis/mucositis</td>
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<td>WBC</td>
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might interfere with etretinate metabolism and could diminish its clinical toxicity.

The two occurrences of grade 3 cutaneous toxicities observed in group 4 developed 3 and 9 weeks after start of treatment, respectively. Since no skin toxicity ever occurred after a single cycle of treatment in any patient, it was felt posteriorly by the investigators that episodes of serious skin toxicity should be considered as DLTs whenever they occurred. Since many patients seemed to benefit from the continuous prescription of this drug combination over months, it was felt that further dose escalation above group 4 dose level would be incompatible with uninterrupted drug administration, and that IFN-α (Roferon®) given at 6 Mio IU sc. q.d. for 5 days every week along with etretinate (Tigason®) at 4 mg/kg/d given on 4 consecutive days every other week could be the recommended dose for regular administration of this drug combination.

Compared with the impressive toxicity observed in our previous study where etretinate was given alone at the same dose level, the toxicity observed in this study was unexpectedly mild. As reported previously, this suggests that IFN-α was interfering in some ways with the hypervitaminic effect of the retinoid, increasing its tolerability (20). It was hypothesized that alterations in retinoid pharmacology induced by IFN-α could explain this striking decrease in toxicity. Since acitretin is considered to be the active molecule whereas etretinate is a prodrug, a slower transformation of etretinate into acitretin or an accelerated metabolism of acitretin induced by IFN-α could be suspected (21). An intracellular interaction between IFN-α and the retinoids at cytoplasmic or nuclear level could be another possibility (9, 22, 23). Both a pharmacological and an intracellular hypothesis would be worth investigating.

Unlike our previous experience with high doses of etretinate alone (300 mg/d 5 days/week every other week) where only minor responses were observed, the combination of high dose etretinate with IFN-α allowed us to document three partial responses. The difference in the quality of responses in our three responders is of interest. One patient responded in less than a month but relapsed after only a few weeks. The other two patients needed 3 to 4 months of treatment to qualify as partial responders and stayed so for several months. This may suggest different mechanisms of response. The patient who failed to respond to retreatment with the cisplatin–vinblastine combination and was successfully put on etretinate and IFN-α (see Fig. 1A, B and C) illustrates the fact that the development of resistance to chemotherapy does not preclude response to retinoid-based therapy, which may operate through different apoptotic pathways.

Table 5

<table>
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<th>No. of patients</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
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<tr>
<td>H &amp; N</td>
<td>2</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Lung</td>
<td>9</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Bladder</td>
<td>2</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Cervix</td>
<td>3</td>
<td>–</td>
<td>2</td>
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<tr>
<td>Penis</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>3</td>
<td>8</td>
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In conclusion, we show that the combination of high dose etretinate and IFN-\(\alpha\) is tolerable and has a moderate anticancer reaction against advanced squamous cell carcinomas that are even resistant to chemotherapy. IFN-\(\alpha\) appears to increase the tolerance to the retinoid. Further phase II studies with this drug combination seem warranted.

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REFERENCES