Interferon α-2a Therapy in 18 Hemangioblastomas

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ABSTRACT

Multiple hemangioblastomas (HBs) of the central nervous system (CNS) and retina are associated with von Hippel-Lindau disease (VHL) and also predispense individuals to renal cell carcinomas and visceral cysts. In VHL, microsurgery or radiosurgery cannot prevent new HBs from arising in the CNS or coagulation of retinal HBs. Multiple but thus far asymptomatic HBs pose a therapeutic problem. IFN-α-2a has antiangiogenic activity with an especially favorable effect on life-threatening hemangiomas of the liver in children. This is the first study to assess the efficacy of IFN-α-2a in treatment of asymptomatic HBs of the CNS and retina. Four patients (three with VHL) with a combined total of 15 HBs of the CNS, 3 HBs of the retina, and 14 renal and 2 pancreatic cysts were treated with s.c. IFN-α-2a for 12 months at 3 × 10^6 IU, 3 times/week. Baseline workup consisted of detailed neurological, ophthalmological, and radiological examinations. Follow-up studies at 3, 13, and 21 months were used to monitor the response. No de novo HBs were detected during the therapy, but one appeared 9 months after cessation of IFN-α-2a therapy. HBs of the CNS did not shrink markedly during the therapy. IFN-α-2a may decrease blood flow in HBs as suggested by shrinkage and diminished leakage of two retinal HBs. However, the therapy did not prevent visceral cysts from growing. The systemic response was also monitored by measurement of serum levels of vascular endothelial growth factor and erythropoietin, which remained essentially unchanged during the treatment. No serious side effects were recorded.

INTRODUCTION

VHL3 VHL (1) is a rare (1/36,000 live births) dominantly inherited cancer syndrome that predisposes individuals to multiple HBs of the CNS and retina, RCCs, pheochromocytomas, pancreatic carcinoma, and cysts in the kidneys, liver, and pancreas (1–4). VHL is caused by a defect in the VHL tumor suppressor gene in chromosome 3p25-p26 (5). The function of the VHL gene is not fully understood, but loss of the gene product function in normoxic conditions may lead to an inappropriate expression of hypoxia-inducible proteins such as VEGF (6, 7), which may account for the hypervascular nature of VHL-associated neoplasms (8–10). The average age at death in VHL is 40–50 years (11, 12), and RCC is the leading cause of death, followed by HBs of the CNS (11).

HBs of the CNS and Retina. HB is a highly vascular, benign and well-circumscribed, slowly growing neoplasm (12, 13) composed of stromal cells, endothelial cells, pericytes, and mast cells (4, 14). The origin of the stromal cells, believed to be the true neoplastic cells of HB tissue, is still undefined (14). HBs may cause polycytemia by secreting EPO from stromal or mast cells (15). HB of the CNS is sporadic in 60–90% of cases (12, 16–19), and in these cases, it is typically a single cystic lesion of the cerebellum, presenting at the average age of >40 years (17). In VHL, HBs of the CNS are multiple, occur about 10 years earlier (20, 21), and are more often located in the brain stem and medulla than their sporadic counterparts (4, 12). HBs of the retina originate from the inner, midperipheral retina and usually grow, causing visual impairment due to leakage leading to secondary changes in the vitreous and retina resulting in retinal detachment (22). About half of retinal HBs seem to be related to VHL (23).

Treatment of HBs in VHL. Microsurgery is the treatment of choice in HBs of the CNS (4, 12), aided, if necessary, by preoperative embolization to reduce intraoperative bleeding (24). Radiosurgery offers a noninvasive means to treat small intracranial HBs in eloquent areas, but it may not prevent cyst formation (25). Retinal HBs, even when small and asymptomatic, should be treated with laser or cryocoagulation to prevent progression with loss of vision (22). In VHL, the problem is the appearance of new and multiple HBs in the CNS and retina. There is increased morbidity related to repeated microsurgery and radiosurgery of HBs of the CNS, as well as laser or cryocoagulation of retinal HBs. Therefore, it is justifiable to seek other approaches to treat multiple HBs.

IFN-α in Antiangiogenic Tumor Therapy. IFN-α has an established role in cancer therapy in some cancer types such
as hairy cell leukemia and melanoma (26-28). In life-threatening hemangiomas of the liver and facial areas in children, the response to long-term IFN-α treatment at a high dosage is often favorable, with most lesions shrinking markedly by 12 months when treated with $3 \times 10^6$ IU/m$^2$/day (29). Side effects of IFN-α are dose dependent and usually consist of transient, mild flu-like symptoms, but central nervous toxicity, such as depression, memory loss, and lethargy, has been described in long-term use of IFN-α (30, 31). Hematological adverse effects include leukopenia, and, less commonly, thrombocytopenia and anemia (28, 32).

**Present Study.** In VHL, HBs could be ideal targets for systemic antiangiogenic therapy because they are highly vascular and often multiple and located in eloquent areas, and VEGF may have a role in their pathogenesis. To our knowledge, this is the first study to assess the efficacy of IFN-α, an agent with weak antiangiogenic properties, in treatment of HBs of the CNS and retina.

**PATIENTS AND METHODS**

**Patients and Manifestations.** Three VHL patients with 14 small, solid, asymptomatic HBs of the CNS and 3 asymptomatic retinal HBs and one non-VHL patient with 1 HB of the CNS were included in the study. Informed consent was required, and the study was approved by institutional review boards. The study was conducted according to the Declaration of Helsinki.

**IFN-α-2a Administration.** Recombinant human IFN-α-2a (Roceron-A; Roche) was injected s.c. into the patients at a dose of $3 \times 10^6$ IU, 3 times/week for 12 months. When necessary, anti-inflammatory drugs were administered to prevent shivering and other flu-like symptoms. The authors have no financial interest in the drugs used.

**Assessment of Response.** A baseline workup consisted of a physical and neurological examination, obtaining a family history for VHL, an ophthalmological examination including indirect ophthalmoscopy and Goldmann three-mirror contact lens fundus examination and FA in patients with retinal HBs, enhanced high-resolution MRI of the head and the spine, and enhanced CT of the kidneys, adrenal glands, liver, and pancreas. The response of tumors and cysts to treatment was judged by comparing lesion sizes (maximal diameter in millimeters) at 3, 13, and 21–22 months after the start of therapy. The diameters of the retinal HBs were measured from retinal photographs and FAs.

To monitor the systemic effects of treatment, serum levels of hemoglobin, VEGF, and EPO were measured at baseline and at 3 and 9 months after initiation of the therapy. S-VEGF concentrations were determined as S-VEGF immunoreactivity, using a quantitative sandwich enzyme immunoassay technique essentially as described previously (Quantikine R; R&D Systems, Minneapolis, MN; Ref. 33). Serum levels of EPO were measured as S-EPO immunoreactivity (Human EPO IVD; R&D Systems) essentially as described for S-VEGF measurement.

**Assessment of Toxicity.** Side effects were recorded at follow-up examinations performed at 2-month intervals in a hospital outpatient department. To further assess toxicity, the blood cell counts and liver transaminases were monitored. The WHO classification (34) was used in grading of toxicity.

**RESULTS**

**Patients and Manifestations**

At the beginning of the IFN-α-2a treatment, the three VHL patients (patients 1–3) had a combined total of 14 small untreated HBs of the CNS (Figs. 1–5), 2 previously treated retinal HBs, and 1 untreated retinal HB. Two VHL patients had a
combined total of 16 renal and 2 pancreatic cysts (patients 1 and 3), but the third VHL patient had none (patient 2). The single non-VHL patient (patient 4) had a slowly growing HB remnant in the jugular foramen. All patients were asymptomatic in relation to these tumors. After the 12-month IFN therapy, the patients were followed-up for an additional 9–10 months.

Patient 1. This male VHL patient has no family history of VHL. At the age of 21 years, he had two intramedullary HBs removed, and a small cerebellar HB (Fig. 1) and visceral cysts were detected. By the time he was 24 years old, another cerebellar and three new spinal HBs had appeared, but no retinal HBs were present. Thus, at the beginning of the IFN-α-2a treatment, he had two small cerebellar and three small spinal HBs together with one pancreatic cyst and two renal cysts. At 21 months, 9 months after the cessation of IFN therapy, the sizes of both cerebellar HBs had increased, and two of the three spinal HBs had doubled in diameter (Fig. 5). The visceral cysts had also enlarged, and new renal cysts had appeared; however RCC had not appeared. The patient had mild flu-like symptoms for the first 2 weeks of therapy and developed transient mild leukopenia (WHO grade 1; 3.0–3.9 × 10^9/liter), neutropenia (WHO grade 1; 1.5–1.9 × 10^9/liter), and a slight increase in the levels of liver transaminases (WHO grade 1; 1.25–2.6 × normal values). No de novo HBs of the CNS or retina developed during the IFN-α-2a treatment or during the subsequent follow-up.

Patient 2. This female VHL patient with a positive family history for VHL was operated on for a cerebellar HB at the age of 49 years. Twelve years later, five small retinal HBs were detected and treated with laser coagulations. The patient had full vision in both eyes. Two of the five retinal HBs developed a small jelly-like recurrence with some open capillaries and were recoagulated (the last recoagulation was at 11 months before initiation of IFN-α-2a therapy). By the beginning of the IFN-α-2a treatment at the age of 71 years, five spinal HBs (Fig. 2) and one cerebellar HB had been detected. There were two small [one-fifth of the optic DD (DD ≈ 1.5 mm)] jelly-like HBs in the middle of retinal scars in the left eye and one HB with some capillaries. In the right eye, there were only retinal scars. No visceral cysts had appeared. At 21 months after the initiation of the IFN-α-2a therapy, three of the six HBs of the CNS were smaller, two were unchanged, and one had increased in size (Fig. 5). The size of the two retinal HBs had not changed at 12 months, but the appearance of one of the lesions resembled that of an “empty pocket” without the jelly-like formation. Nine months later, the empty pocket was still unchanged, but FA showed slight leakage. The patient’s vision remained unchanged. The patient had transient mild anemia (WHO grade 1; 95–109 g/liter) and leuko- and neutropenia. Nine months after the discontinuation of the IFN therapy, a small asymptomatic de novo HB in the thoracic medulla was detected.
Patient 3. This female VHL patient had a positive family history for VHL. At the age of 44 years, the right eye lost vision due to total exudative retinal detachment caused by a large HB, and visceral cysts were also detected. At the age of 54 years, after having miotics for 3 months due to open-angle glaucoma, she experienced floaters, and a small left-sided HB with posterior vitreous detachment and a retinal break was found. The retinal break was surrounded by laser coagulations. When the patient was 59 years old, one cerebellar HB was removed, and two incidental cerebellar HBs were detected; later, one more appeared. By the beginning of the IFN-α-2a treatment at age 62 years, there were 3 small cerebellar HBs (Fig. 5) and 1 retinal HB (two-thirds DD) together with 1 pancreatic cyst (Fig. 4) and 12 renal cysts. The patient had full vision in the left eye. At the end of IFN-α-2a treatment, the HB of the retina had slightly diminished in size, and its appearance had changed from a typical “vascular raspberry” to a less vascular “shrunken raspberry” (Fig. 3). The patient’s vision remained unchanged. Nine months after the cessation of IFN-α-2a therapy, two of the three cerebellar HBs had become slightly enlarged. The retinal HB again seemed to be more vascular and slightly enlarged (Fig. 3). The pancreatic cyst increased in size during and after the therapy (Fig. 4), and the renal cysts in both kidneys fused to form larger cysts. The patient developed transient mild leuko- and neutropenia during therapy and experienced a transient mild weight loss (5 kg). No de novo HBs of the CNS or retina developed during therapy or the subsequent follow-up.

Patient 4. This 43-year-old non-VHL female patient was asymptomatic when the HB remnant in the jugular foramen started to grow 20 years after primary surgery at the age of 22 years. The size of the HB did not change during IFN therapy or during the 9-month follow-up (Fig. 5). The patient had fatigue during therapy, but she remained able to work and did not develop abnormal laboratory findings.

Overall Response

During the 12-month IFN therapy, 2 of the 15 HBs of the CNS diminished slightly, 9 remained unchanged, and 4 became enlarged. During the subsequent follow-up of 9 months, 4 tumors decreased slightly in diameter, 6 remained unchanged, and 5 increased slightly in diameter (Fig. 5). These HBs were small, and some of the changes (±1 mm) may be due to measurement errors from the MRI scans. On the other hand, small but real changes in diameter mean considerable volume changes. HBs of the retina were easier to monitor because they were accessible to direct visual observation of appearance and size. Two of the three HBs of the retina decreased slightly during the treatment, but one of them increased again after the therapy, suggesting that IFN-α-2a diminished their blood flow. No de novo HBs of the CNS or retina appeared during the IFN therapy, but one new lesion was detected 9 months after discontinuation of the therapy. The treatment did not prevent visceral cysts from enlarging and fusing. Two VHL patients had a combined total of eight HBs in the spinal cord, but they did not develop marked peritumoral edema or medullary symptoms during IFN-α-2a treatment. No unusual toxicity was observed, and the mild adverse effects did not necessitate a reduction of the IFN dosage or discontinuation of the treatment.

None of the patients had erythrocytosis before or during the therapy. No significant changes were observed in the serum levels of VEGF and EPO during the therapy (Fig. 6). This was consistent with the stable size of the HBs during the IFN-α therapy.
DISCUSSION

Response to IFN-α2a Treatment. No de novo HBs were detected during IFN-α2a therapy given at 3 × 10^6 IU s.c. 3 times/week for 12 months, but one HB appeared 9 months after discontinuation of the therapy. However, none of the HBs of the CNS decreased markedly in size during the therapy. The pathogenic mechanisms of VEGF (35, 36) in retinal pathology are thought to be mediated by mitogenic activity on endothelial cells and the permeability effect on the vascular wall (37). Furthermore, VEGF has been shown in animal studies to be associated with increased blood flow in the retina (38), which is thought to be an important element in the pathogenesis of early diabetic retinopathy (38). Thus, IFN-α2a may have counteracted this effect of VEGF and decreased blood flow in HBs as suggested by shrinkage of two retinal HBs, which has been shown to occur in response to another VEGF antagonist, protein kinase C β inhibitor (39). However, the effect of IFN-α may be much more complex than an anti-VEGF effect alone, and the precise mechanisms remain to be explored. In our series, IFN-α2 did not prevent the growth of visceral cysts, which is their natural course in VHL (40). The treatment was generally well tolerated.

There are no published data on the effect of IFN-α on S-VEGF in cancer patients. However, S-VEGF levels are increased in patients with disseminated cancer (41). VEGF plays a role in VHL, promoting angiogenesis of HBs of the CNS and retina (8). In our three VHL patients, however, there was no obvious association between the number of HBs and the S-VEGF or S-EPO levels. The S-VEGF and S-EPO levels were consistent with the stable size of the HBs and the effect of IFN therapy, but the number of patients is too small to draw firm conclusions. The patients were not polycytemic, and their S-EPO levels were within a normal range and remained so during the therapy.

Dosage of IFN. The dosage in our Phase II study was rather low (9 × 10^6 IU/week for 12 months). Higher IFN doses are often poorly tolerated in long-term use, which is needed to treat slowly growing tumors. Hypothetically, the effect on HBs might have been more pronounced at the expense of more severe side effects if a higher or more frequent dosage had been
used, such as $3 \times 10^6$ IU/m$^2$/day for up to 13 months, a dose regimen used successfully to shrink large hemangiomas in children (29). However, there was no statistically significant correlation between dose intensity and the response rate in a review of 525 RCC patients treated with IFN-$\alpha$ (26). In HBs of the CNS, it is difficult to estimate the treatment effect because the growth pattern is slow (12, 13) and unpredictable, with some tumors in VHL patients growing and others remaining dormant. Spontaneous regression of retinal HBs has also been reported (42), but usually, these lesions grow, and they eventually cause loss of vision if left untreated. If IFN-$\alpha$-2a treatment will prevent some HBs of the CNS and retina from growing, the problem will be how to identify the potential responders. Moreover, because of the lifelong tendency of VHL patients to develop HBs, IFN therapy should be long-lasting and continued for several years, possibly intermittently, to reduce adverse effects.

**Future Trends.** More potent antiangiogenic drugs such as angiostatin and endostatin derivates (43, 44) may offer means to prevent the appearance of new lesions or to shrink or stabilize established ones. These drugs may be successfully combined with radiotherapy, chemotherapy, or immunotherapy.

**Conclusions.** Our conclusions are as follows: (a) no de novo HBs were detected during 12-month IFN-$\alpha$-2a therapy at a dose of $3 \times 10^6$ IU s.c. 3 times/week for 12 months was well tolerated in treatment of HBs; and (f) a larger Phase II study, possibly with different IFN-$\alpha$ doses and treatment times and/or IFN-$\alpha$ in combination with other antiangiogenic agents, is warranted in treatment of HBs of the CNS and retina.

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