Haemangiomas are benign angiomatous hamartoma occurring in about 1% of infants. They usually appear soon after birth, proliferate for 8 to 18 months and then slowly involute over the next 5 to 8 years. The majority of haemangiomas do not require treatment and are nothing more than a cosmetic inconvenience. However in a small percentage of cases, they can be life-threatening because of situations such as blockage or pressure on vital structures like the airway from subglottic haemangiomas, consumptive coagulopathy (Kasabach-Merritt syndrome) with severe thrombocytopenia and consumptive coagulopathy and congestive heart failure from hepatic haemangiomatosis.

Treatment options include corticosteroids, antifibrinolytics, embolisation, or local therapy such as surgery, laser cauterly and intralesional injections of corticosteroids. Chemotherapy has been tried with some success. However response to treatment is not always consistent, sustained or effective. In the 1980s, alpha-interferon was found to have specific anti-angiogenic activity. Since 1990, it has been used to treat life-threatening haemangiomas in selected children with remarkable success.

INTERFERONS

Interferons are a family of endogenous glycoproteins produced by cells such as human leukocytes and fibroblasts in response to viral infections or other stimuli. They are broadly active physiological regulators enhancing expression of specific genes inhibiting cell proliferation and augmenting immune effector cells. The interferon family is heterogeneous. Interferon-alpha and interferon-beta are the predominant forms produced by monocytes and fibroblasts, respectively. Immune interferon or interferon-gamma is the predominant form produced by stimulated lymphocytes. Recombinant interferons are now available.

Early studies concentrated on the antiviral effects of interferons. However, in 1980 it was observed that they also inhibited capillary endothelial cell locomotion. In 1987, interferons were reported to inhibit endothelial cell proliferation in vitro and angiogenesis in experimental models. Studies with interferon-alpha-2a revealed specific angiogenesis inhibitory activity. Although interferon-alpha-2a was originally developed as an antiviral agent, it was serendipitously noted to modulate Kaposi's sarcoma, a cutaneous vascular tumour, in a clinical trial to treat patients with acquired immuno-deficiency syndrome. This was followed by anecdotal case reports of efficacy in other haemangiomatous diseases eg. pulmonary angiomatosis, haemangoendothelioma and haemangiomas causing the Kasabach-Merritt syndrome.

In 1992, Ezekowitz et al reported on a series of 20 patients treated with interferon-alpha-2a with remarkable.
success. This became the landmark paper on which the use of interferon-alpha in haemangiomas is based. However, the paper was subsequently the focus of some controversy when allegations of irregularities and inaccuracies were made.\textsuperscript{21-24} A later series by other authors,\textsuperscript{9-14} however, bore out the results reported by Ezekowitz. Despite this, the number of patients involved in most studies has remained small and more worrying is the recent emergence of reports of long term side effects of interferon-alpha such as spastic diplegia,\textsuperscript{25} retinopathy,\textsuperscript{26} acute interstitial nephritis and several autoimmune diseases.\textsuperscript{27}

**EXPERIENCE WITH INTERFERON-ALPHA IN SINGAPORE**

In our institution, 11 children (8 females, 3 males) with haemangiomas have been treated with recombinant interferon-alpha. The reasons for treatment were airway compromise (5), Kasabach-Merritt syndrome (4), visual impairment (1) and other (1). The dose of interferon-alpha was 3 million units/m\textsuperscript{2}/day given subcutaneously, alone or in combination with other drugs. Response to treatment was assessed by a combination of subjective and objective methods: full blood count and liver function tests were taken at least every 3 months. Patients were maintained on epsilon amino-caproic acid (EACA) or tranexamic acid, if necessary after cessation of therapy with interferon-alpha.

The age when patients were first seen or referred to us ranged from day 3 of life to 16 months with a mean of 5 months. The age when treatment began ranged from day 4 of life to 2.5 years with a mean of 9.3 months. Duration of treatment ranged from 1.5 months to 3 years with a mean of 9.9 months. One child was lost to follow up when she left the country 2 months after starting treatment, leaving 10 children for evaluation. The follow up ranged from 5 months to 8.6 years with a mean of 3 years.

**RESPONDERS**

Out of 10 children, 6 (60\%) showed a response. Two children received only interferon-alpha treatment whilst the rest were given a combination of steroids, anti-fibrinolytics or local therapy before or together with interferon-alpha. Four children, including the two that only received interferon-alpha, had complete resolution of their haemangiomas and remain symptom-free. The other two children are described in more detail in cases 1 and 5.

**Case 1**

SH presented at birth in a private hospital, with a giant haemangioma covering the left side of his trunk and promptly developed Kasabach-Merritt syndrome on day one of life. Despite copious amounts of blood products, his coagulopathy could not be corrected and he deteriorated rapidly. Ultrasound and MRI of the abdomen confirmed the lesion to be confined to the left abdominal wall. Ultrasound of the head was normal. He was transferred to us on day 3 of life and we decided to use steroids, tranexamic acid together with interferon-alpha to give him the best chance of recovery. The Kasabach-Merritt syndrome began to resolve after about a week of treatment and this was followed by the haemangioma slowly involuting though not completely resolving. At 13 months of age the child had a short episode of jerky movements in his right upper limb. A CT of the head excluded a bleed and cranial haemangioma. At 22 months of age, he was still unable to stand or walk because of spasticity of his lower limbs with bilateral sustained ankle clonus and had to be supported while standing on tiptoe. His speech at 2 years was confined to a few words with no sentence formation.

An MRI of the head at 2 years was unsuccessful. A repeat scan at 2
years 7 months showed normal signal intensities except for the central white matter of the parietal lobes which were of intermediate brightness on T2 weighted scans and slightly dark on the T1 images. The findings suggested a slight delay in the process of myelination. After 33 months of treatment, he was taken off interferon-alpha.

Unfortunately, 5 months later, he again developed Kasabach-Merritt syndrome with low platelets and prolonged coagulation. He was put back on interferon-alpha for another 8 months and subsequently went on every-other-day doses for another year. He still has a sizeable haemangioma although it is much smaller than at presentation and appears to be involuting. He also has spastic diplegia and walks with the aid of a frame or walking sticks. For his age, 6 years, his functioning is in the range of the intellectually deficient. A recent IQ assessment recorded a performance score of 69 and a verbal score of 68. It is uncertain if his spastic diplegia and delayed development are a result of his stormy perinatal period or his prolonged treatment with interferon-alpha.

**Case 5**

This child was born 2 months premature with dysmorphic facies, congenital heart disease, a huge cystic hygroma almost encircling the neck, multiple haemangiomas in the axillae, under the tongue, in the trunk and thighs. She developed Kasabach-Merritt syndrome at one month of age. She was treated with steroids and interferon-alpha. The Kasabach-Merritt syndrome resolved after 3 months of treatment. The haemangiomas on the trunk and thighs became smaller and the ones under the tongue and in the axillae resolved. When her coagulopathy resolved, she underwent excision of the cystic hygroma because of respiratory compromise. Due to increasing transaminitis, deteriorating liver function and ultrasound-proven biliary sludging, interferon-alpha was stopped after 105 days of treatment. However, it was uncertain if interferon-alpha was the cause of the transaminitis because the child was also on long-term parenteral nutrition. Unfortunatley she died 6 weeks later due to an unrelated cause.

**NON-RESPONDERS**

Four children (40%) did not show any appreciable response.

**Case 7**

The histology of this child’s periorbital lesion turned out to be haemangioendothelioma which was extremely resistant to treatment. Despite two resections, local radiotherapy (at a total of 800 rads in divided doses of 100 rads three times a week), intralesional dexamethasone as well as one year’s treatment with interferon-alpha, there was no response.

**Case 8**

This child died on the table when surgery was attempted as a final effort to relieve her respiratory distress, after failure of steroids and interferon-alpha.

**Case 9**

This girl also had severe tracheobronchomalacia and died of aspiration pneumonia.

**Case 10**

In this 16 month old girl, interferon alpha was started for cosmetic reasons with no evidence of Kasabach-Merritt syndrome. The multiple lesions on her left upper limb were unsightly and bluish, especially the lesions on her hand and ring and little fingers. There was no objective response to her 1 year course of interferon-alpha except for significant lightening of her bluish skin lesions.

**DISCUSSION**

The use of anti-angiogenic agents such as interferon ushers in a
promising new era in the treatment of angiogenic diseases. It appears to be effective in inducing regression in haemangiomas although the effect is neither universal nor predictable. It is also well tolerated in the majority of cases and can be a life-saving measure in patients with the Kasabach-Merritt syndrome. However, there are still some unanswered questions.

Who Should Receive Interferon?
It is important to remember that the majority of haemangiomas are only of concern cosmetically and are self-limiting. Thus for the majority of cutaneous haemangiomas, no treatment is necessary except to reassure the parents that spontaneous resolution should occur with time.

It is only in life-threatening situations such as airway obstruction, Kasabach-Merritt syndrome and high output congestive cardiac failure that the use of interferon should not be delayed. In other situations, the role of interferon therapy is not clearly defined.

The pathological classification of vascular lesions in children is complicated. A biological classification proposed in 1982 suggests that there are two major categories:

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<td>Side Effects of Interferon-alpha</td>
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a) haemangioma, which has a history of rapid neonatal growth and slow involution and is characterised by endothelial proliferation followed by diminishing hyperplasia and progressive fibrosis.

b) vascular malformation, which is present at birth, grows commensurately with the child, and is characterised by a normal rate of endothelial cell turnover.

Bartlett et al. also emphasised the difference in pathology between haemangiomas and vascular malformations, stating that haemangiomas are made up of thin-walled, immature vessels of capillary size, lined by one layer of capillary cells whereas vascular malformations are composed of mature blood vessels.

While haemangiomas may respond to interferon, a vascular malformation does not. Similarly, haemangioendotheliomas may not respond as well to interferon as haemangiomas. The known differences in the characteristics and behaviour between haemangiomas and vascular malformations should help reduce the need for a biopsy before the initiation of interferon therapy.

At this point in time, interferon should perhaps be reserved for life-threatening haemangiomas. It is controversial whether it should be used as first line treatment in other situations.

What Dose and How Long?
While the optimal dose of interferon-alpha in the treatment of haemangiomas has not been objectively determined, practically all reports quote a daily subcutaneous dose of 3 million units/m² of body surface area. It appears unlikely that non-responsive patients would benefit from a higher dose.

The optimal duration of interferon therapy is hard to define. It must be based on each patient’s response and it has to be emphasised that too early withdrawal of interferon therapy during the proliferative phase of haemangioma development can result in rapid rebound growth of the haemangioma and associated complications. Case 1 is a case in point.
It must be emphasised that interferon-alpha is a slow-acting drug, and it is difficult to measure response. Based on our rather limited experience, we recommend using it for at least 3 months before considering it ineffective.

Is any Regression due to Interferon Treatment and not the Natural History of the Haemangioma?

While the answer has to be no, it is unusual for any haemangioma to show signs of spontaneous resolution during infancy. The 4 infants in our small series who responded to interferon therapy did so in a convincing fashion. In 3 of these infants who presented with subglottic haemangiomas and stridor, interferon alpha was the only drug used. The fourth infant (case 6) with a truncal haemangioma needed the addition of epsilon amino-caproic acid (EACA) to reverse the development of Kasabach-Merritt syndrome.

How Can Response to Interferon be Measured Objectively?

While the coagulation profile and platelet count can be considered helpful early objective measurements of the response to interferon in patients with the Kasabach-Merritt syndrome, the measurement of size reduction of a haemangioma can only confirm response to treatment after several weeks or even months of therapy. Sometimes the site or the shape of the haemangioma can make objective measurement very difficult, and response has to be judged by subjective means, like the disappearance of stridor in a patient with subglottic haemangiomas. Serial photographs, computed tomography (CT) and magnetic resonance imaging (MRI) have their drawbacks. Basic fibroblast growth factor (bFGF) can be detected in the urine during the proliferating and involuting phases of haemangiomas and may
provide an objective method for monitoring response.  

Long Term Side-effects of Interferon

When interferon was first used, the acute side-effects were largely predictable and reversible with cessation of therapy. Mild flu-like symptoms and the occasional fever are well-known. Other side-effects include neutropenia, anaemia and hair loss. However, after almost a decade of use in haemangioma in children, disturbing reports of long-term side effects are now surfacing.  

CONCLUSION

Although interferon-alpha shows promise in the treatment of life-threatening haemangiomas, great care should be exercised in the choice of patients. Interferon is not an innocuous drug and is now associated with a number of long-term side effects. Therefore close monitoring of patients during its use is mandatory. We would recommend its early use in all patients with life-threatening haemangiomas. An algorithm of the management of haemangiomas is presented in the figure.

REFERENCES


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