Hemangiomas:
Current therapeutic strategies

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Abbreviations used in this paper: IH, infantile hemangioma; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; MMP, matrix metalloproteinase

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Abstract

Hemangiomas are benign neoplasms of the vasculature frequently encountered in children. Several studies have shown that these tumors are characterized by excessive angiogenesis. Although benign, the lesions can present with complications, and may thus require treatment. There are multiple therapeutic options available for patients with problematic or life threatening hemangiomas, some of which have serious side effects. Randomized clinical trials and evidence-based studies on the efficacy of these treatments is still lacking.

The recognition that excessive angiogenesis underlies hemangiogenesis offers an opportunity for the development of safer therapeutic strategies that are based on the inhibition of angiogenesis. We review medical therapies currently employed in the management of hemangiomas and the role of angiogenesis inhibition in hemangioma therapy.

Introduction

Hemangiomas are benign neoplasms of the vasculature (Mulliken *et al.*, 1982; North *et al.*, 2002). These lesions, often referred to as infantile hemangiomas (IH), are considered to be the most common tumors of infancy (Mulliken and Glowacki, 1982; Sarihan *et al.*, 1997). The incidence of hemangiomas has not been well documented, but it is estimated that one in every ten children develops a hemangioma, most of which are on the head or neck (Mulliken and Glowacki, 1982). The frequency of hemangioma development is increased to 22.9 % for premature infants with a birth weight below 1 Kg (Blei, 2005). The clinical appearance of hemangiomas varies with the degree of dermal involvement and the depth of the lesions (Mulliken and Glowacki, 1982). They can have deep, superficial, or mixed components (Bruckner and Frieden, 2003). When the superficial dermis is involved, the skin is usually raised and firm. When the lesion is limited to the deep dermis, subcutaneous tissue or muscle, the overlying skin is raised slightly (Pandey *et al.*, 2009). The degree of dermal involvement has treatment implications in that certain modalities are effective in the treatment of superficial lesions. For instance, in a study involving more than two thousand patients conducted over a period of twenty years, Pandey and co-workers observed that steroid therapy was much more effective in the treatment of superficial hemangiomas (Pandey *et al.*, 2009).

Various vascular tumors have been described in the pediatric population (Table 1), and it appears that IH differ from these tumors in that they express the glucose transporter GLUT1 (North *et al.*, 2000). Most IH begin their growth in the first few weeks of life (Mulliken and Enjolras, 2004). The lesions have a unique natural history which is divided into three phases, the proliferative phase, the involuting phase and the involuted phase (Mulliken and Glowacki, 1982). The proliferative phase is characterized by rapid growth of the lesion, while during the involuting phase there is a decline in growth, which is followed by the involuted phase or complete regression of the lesion with or without residual sequelae (Mulliken and Glowacki, 1982; Mulliken *et al.*, 1982).

In this paper, we review the current medical therapies that are used in the treatment of hemangiomas. We also discuss the effects of these therapies on the

vasculature, and address the future application of antiangiogenic agents in the management of paediatric hemangiomas.

Pathogenesis

The pathogenesis of infantile hemangiomas is not well understood although both intrinsic and extrinsic theories have been proposed. The intrinsic theory suggests that the underlying factor in the development of the tumor is a mutation in a critical gene in a precursor stem cell and that the clonal expansion of this single cell carrying a somatic mutation leads to hemangiomagenesis (North, *et al.*, 2002; Regnier *et al.*, 2007).

According to the extrinsic theory, growth factors, an abnormal hormonal milieu, such as increased oestrogen levels, or tissue hypoxia, which leads to increased expression of hypoxia inducible factor (HIF1 α) and ultimately the stimulation of angiogenesis via vascular endothelial growth factor (VEGF), underlie hemangioma development (Zhang *et al.*, 2008). It is believed that a nascent hemangioma may result from endothelial proliferation secondary to increased levels of growth stimulating factors or decreased levels of growth-inhibitory factors normally present in the tissue (Mulliken and Glowacki, 1982).

Given the fact that hemangiomas are clinically heterogeneous, it is plausible that the tumors are not all due to the same underlying defect; it is also possible that a hemangioma in a single patient may arise due to a combination of mechanisms explained by both theories.

Role of angiogenesis

Hemangioma growth has been described as an example of an angiogenic disease in which an imbalance in normal vascular tissue turnover occurs, and that the increased endothelial proliferation may be caused by abnormal levels of angiogenic stimulators (increased) or inhibitors (reduced) (Mulliken and Enjolras, 2004; Pepper 1997). Light microscopic studies undertaken by Mulliken and

Glowacki on hemangioma tissue have demonstrated that the hallmark of the growing hemangioma is endothelial cell proliferation (Mulliken and Glowacki 1982).

In addition, some of the growth factors which mediate the complex stages of angiogenesis, namely VEGF and basic fibroblast growth factor (bFGF), were found to be over expressed in proliferating hemangiomas (Takahashi *et al.*, 1994). In a separate study, VEGF and high molecular weight matrix metalloproteinases (MMPs) were found to be elevated in urine samples of patients with proliferative hemangiomas (Zhang *et al.*, 2008). Matrix metalloproteinases are involved in the degradation of extracellular matrix components during the angiogenic process (Pepper, 1997). These markers of angiogenesis diminish to normal levels during hemangioma regression (Takahashi *et al.*, 1994). There is also an increase in endothelial cell apoptosis and a decrease in endothelial cell proliferation during the involution of IH (Hasan *et al.*, 2000; Razon *et al.*, 1998). Therefore, therapeutic strategies focused on specific cellular events that occur during angiogenesis may be effective in the treatment of these tumors.

Complications

Not all hemangiomas require treatment since most are asymptomatic. However, a subset of patients experience serious complications due to the location of the lesion or interference of the lesion with a physiological function (Blei, 2005). For instance, facial hemangiomas can result in disfigurement and feeding difficulties, while subglottic hemangiomas can lead to airway obstruction (Haik *et al.*, 1994).

Other complications include pain, infection, ulceration, and bleeding (Blei, 2005; Cordoro *et al.*, 2009), the latter of which, although rare, can lead to severe anaemia (Blei, 2005). In patients with large hemangiomas, moderate thrombocytopenia is a common occurrence (Martins 1970). According to Martins, the trapping of platelets and other coagulation factors within the hemangioma leads to thrombocytopenia (Martins 1970).

The development of congestive heart failure is another complication that is encountered in infants with hepatic hemangiomas (Boon *et al.*, 1996), and these patients require treatment. It has been reported that without treatment, the mortality for hepatic hemangiomas is as high as 80%, and that early and aggressive treatment can lower mortality to approximately 20% (Boon *et al.*, 1996).

Treatment

There have been several reports on the management of both symptomatic and asymptomatic hemangiomas. Thus while there is consensus that problematic hemangiomas require intervention, the management of asymptomatic lesions remains controversial, partly because of the lack of randomized clinical trials that prove the efficacy of commonly used therapies (Barlow *et al.*, 1998). Various therapeutic modalities ranging from surgery to radiation therapy were originally employed in the treatment and management of hemangiomas (Enjolras and Mulliken 1993).

Decompression surgery and radiation therapy were the traditional means for treating lesions causing spinal pain or compression. Surgery is often associated with massive haemorrhage from these highly vascular tumors and is not commonly employed.

Medical therapies have become the mainstay in the management and treatment of hemangiomas (Enjolras and Mulliken 1993; Pandey *et al.*, 2009). The major goals of management of IH have recently been outlined in the Guidelines of Care for Hemangiomas of Infancy by the American Academy of Dermatology (Frieden *et al.*, 1997) and these include: (i) the prevention of life-threatening complications or those complications that interfere with physiological function, and the treatment of such complications if they arise; (ii) the prevention of disfigurement due to residual skin changes after the involuted phase; (iii) the minimizing of psychological distress; (iv) avoidance of aggressive potential scarring procedures; (v) the minimizing of scarring, infection and pain. The effects of the commonly used drugs in the management of hemangiomas are shown in Table 2.

Steroid Therapy

The efficacy of steroids in the treatment of IH was initially observed by Zarem and Edgerton, who noted that hemangiomas decreased in size when steroids were used to treat paediatric patients for thrombocytopenia (Zarem and Edgerton 1967). A number of studies have since been published on the efficacy of steroid therapy in the treatment of hemangiomas (Enjolras and Mulliken 1993; Martins 1970; Pandey *et al.*, 2009). One study reported on the use of steroid therapy in 39 hemangioma patients, with an unpredictable outcome (Martins 1970). Growth retardation was a reported side effect; however, there was recurrence of growth after interruption of therapy (Martins 1970). Despite this side effect, steroid therapy has at times proven to be very effective in reducing the size of the lesion and in increasing the number of platelets in patients presenting with thrombocytopenia.

At present, complicated hemangiomas are treated initially with corticosteroids, systemically, topically or intralesionally. Overall, steroids dramatically regresses hemangiomas in a third of the patients, and has little or no effect in the remaining two thirds, with some of the patients showing signs of worsening while still on treatment (Enjolras and Mulliken 1993).

The mechanism of steroid treatment in accelerating hemangioma regression remains unclear; however, a study undertaken by Hasan and coworkers showed that triamcinolone acetonide (TA) inhibits neovessel growth in an *in vitro* human hemangioma model. Similarly, dexamethasone, another glucocorticoid used in the treatment of hemangiomas, has been shown to inhibit neovessel growth in cultured human hemangioma biopsies; neither VEGF nor bFGF appeared to play a vital role in steroid induced inhibition of capillary growth based on observations in studies undertaken using the human hemangioma model (Hasan *et al.*, 2003).

The effects of both triamcinolone acetonide and dexamethasone appeared to be directly on hemangioma endothelial cells. Triamcinolone acetonide has previously been shown to inhibit VEGF-induced angiogenesis in the rat corneal micropocket assay, and to block interleukin-6 (IL-6) mediated neovascularization in the same

assay (Ebrahem *et al.*, 2006). An independent study demonstrated that TA also inhibits angiogenesis in the chorioallantoic membrane (CAM) assay (McKay *et al.*, 2008).

Other glucocorticoids commonly used in the treatment of hemangiomas, such as betamethasone, methylprednisolone and hydrocortisone, had a negligible effect on capillary growth *in vitro* in the same hemangioma model (Hasan *et al.*, 2003).

The inhibition of neovessel growth in dexamethasone-treated hemangioma biopsy cultures was associated with an increase in the transcription of clusterin/apolipoprotein J (clust/apo J) and increased transcription of the apoptotic gene, mitochondrial cytochrome b (Hasan *et al.*, 2000). Clusterin/apolipoprotein J is a secreted glycoprotein involved in a number of biological processes and is a marker of apoptosis; it is also associated with hemangioma involution (Hasan *et al.*, 2000). Therefore, induction of endothelial cell apoptosis may play a role in dexamethasone-induced hemangioma regression. The mechanisms underlying the effects of betamethasone, methylprednisolone and hydrocortisone are yet to be elucidated, although prednisolone has been shown to inhibit angiogenesis in a mouse model (Banciu *et al.*, 2006).

Even though corticosteroid therapy is undoubtedly a useful form of treatment for proliferative infantile hemangioma, it can lead to complications such as Cushingoid appearance, hypertension, decreased growth rate and weight gain (Enjolras and Mulliken 1993; Pandey *et al.* 2008; Pandey *et al.*, 2009). However, in most cases the symptoms tend to resolve following cessation of treatment.

Interferon

Potentially life-threatening hemangiomas that do not respond to corticosteroids have been treated with interferon α (Barlow *et al.*, 1998). Ezekowitz *and co-workers* evaluated the effectiveness of interferon α in the treatment of hemangiomas in twenty patients, with a successful outcome. (Ezekowitz *et al.*, 1998). Transient side effects that included fever and neutropenia were observed in this group of patients (Ezekowitz *et al.*, 1998). In another study undertaken more recently, an 85% success rate in twenty hemangioma patients treated with

interferon α 2b was reported. No major side effects were reported (Jimenez-Hernandez *et al.*, 2008). Interferon's therapeutic effectiveness in the treatment of IH has been attributed to its antiangiogenic activity (Fotsis *et al.*, 1994; Sgonc *et al.*, 1998). The analysis of skin sections from a hemangioma patient treated with interferon α revealed apoptotic endothelial cells (Sgonc *et al.*, 1998).

The major side effect of interferon is spastic diplegia (Barlow *et al.*, 1998; Enjolras and Mulliken 1993; Grimal *et al.*, 2000). As a result, even though high success rates have been reported with this drug, concerns remain about the risk of developing irreversible neurotoxicity in hemangioma patients treated with interferon.

Vincristine

Vincristine, a microtubule-disrupting plant alkaloid used in cancer chemotherapy, has been advocated by some authors to be an effective second-line treatment for hemangiomas (Enjolras *et al.*, 2004). Reports on the use of vincristine for the treatment of life-threatening hemangiomas characterised by the Kassabach-Merritt Syndrome (KMS) are anecdotal (Enjolras *et al.*, 2004). These 'hemangiomas' associated with KMS, although closely related to IH based on the basis of their biological behaviour, have been found to be histologically different from IH, and so the tumors are referred to as kaposiform haemangioendothelioma (KHE) (Enjolras *et al.*, 2008; Fernández *et al.*, 2009).

Concerning 'true' hemangiomas of infancy, only a few case studies have reported on the effectiveness of vincristine in the treatment of such lesions (Perez *et al.*, 1995). Side effects observed in patients following treatment with vincristine were transient (Perez *et al.*, 1995).

Vincristine has antiangiogenic properties that may underlie its effectiveness in the treatment of infantile hemangiomas. In a study using the CAM assay, vincristine had an inhibitory effect on vascularisation. The drug is also a potent inhibitor of endothelial cell growth, migration and *in vitro* capillary-like tube formation, and induces endothelial cell apoptosis (Mabeta and Pepper, 2009). Only a few studies have reported on the use of vincristine for the treatment of IH. Thus Phase II

clinical studies, which are underway and which are aimed at comparing the efficacy of corticosteroids and vincristine in the treatment of hemangiomas, will be useful in providing the necessary data to determine the drug's potential as a second-line treatment.

Bleomycin

Bleomycin is an antineoplastic antibiotic which is effective against a variety of human neoplasms, particularly head and neck squamous carcinoma, Hodgkin's and non-Hodgkin's lymphomas, and testicular carcinoma (Sarihan *et al.*, 1997). The drug was initially reported by Kullendorf to be an effective form of treatment for complicated cutaneous and massive symptomatic inoperable hemangiomas (Kullendorff, 1997).

Subsequent studies revealed that intralesional bleomycin induces accelerated resolution in hemangioma patients, without severe complications (Muir *et al.*, 2004; Pienaar *et al.*, 2006; Sarihan *et al.*, 1997). Low dose intralesional Bleomycin is commonly used as a sclerosing agent for the treatment of vascular anomalies in China, and has been cited as an effective treatment option for IH, with a good safety record (Yang *et al.*, 2009).

In a prospective study undertaken by the Pretoria Vascular Malformation Study Group, intralesional bleomycin was shown to have a curative effect on IH (Muir *et al.*, 2004) The study also showed an extremely low side effect profile, with reported complications mainly including local pain and transient flu-like symptoms (Muir *et al.*, 2004).

Ulceration and hyper-pigmentation were also observed in a small percentage of patients (unpublished data). Another study conducted by the Red Cross Children's Hospital in South Africa showed that bleomycin was effective in accelerating hemangioma regression in infants, with a success rate of more than 70% in the 30 patients who were treated. The only reported side-effect was hyper-pigmentation (Pienaar *et al.*, 2006).

Bleomycin was also reported to be effective in treating hemangiomas when administered in combination with dexamethasone (Yang *et al.*, 2009) In twenty-one hemangioma patients treated with the drug combination, a more than 90% reduction in tumor size in more than 80% of the patients was reported (Yang *et al.*, 2009). Although the effectiveness of the treatment was largely attributed to bleomycin, given the fact that both drugs were administered at the same time, and given the fact that the two drugs were previously shown to inhibit angiogenesis in human hemangioma biopsies, the degree to which each drug contributed to the induction of tumor regression is not clear.

The findings from studies on the effects of bleomycin on human hemangioma biopsies *in vitro* suggest that bleomycin may inhibit hemangioma growth in human patients in part by inhibiting neovascularization (Mabeta and Davis, 2008).

This is corroborated by the observation that bleomycin inhibits growth factor-induced endothelial cell invasion, endothelial cell growth and migration, and also induces endothelial cell apoptosis (Mabeta and Pepper, 2009).

Furthermore, increased apoptosis has been shown to coincide with hemangioma regression (Razon *et al.*, 1998). Thus, the induction of endothelial cell apoptosis by bleomycin, and its inhibitory effect on angiogenesis, may underlie its therapeutic effect in IH.

Propranolol

Propranolol is a non-selective beta-blocker used in the treatment of cardiovascular diseases such as heart failure and hypertension. The effectiveness of propranolol in the treatment of hemangiomas was reported in 2008 by Léauté-Labrèze and coworkers following the successful treatment of a steroid resistant potentially life-threatening hemangioma with propranolol (Léauté-Labrèze *et al.*, 2008). The favorable outcome led to the treatment of nine hemangioma patients with the drug, with excellent results. Excellent results were also obtained following the treatment of thirty-two hemangioma patients with propranolol (Sans *et al.*, 2009). The drug was well-tolerated and no side effects were reported.

The successful therapeutic effects of propranolol on IH have been attributed to its inhibitory effects on aspects of the angiogenic process (Léauté-Labrèz *et al.*, 2008). Previous studies have also revealed that propranolol induces apoptosis in microvascular endothelial cells *in vitro* (Sommers *et al.*, 2002).

The excellent clinical outcome and apparent lack of side-effects of this form of treatment has prompted its recommendation as a first line treatment for hemangiomas. Another beta-blocker with similar effects to propranolol, namely nadolol, is currently in phase II clinical trials for the treatment of IH.

Cyclophosphamide

Cyclophosphamide is a chemotherapeutic drug used to treat certain autoimmune disorders and, together with other chemotherapeutic agents, to treat lymphomas, some forms of leukemia and certain solid tumors. Cyclophosphamide has been employed infrequently to treat hemangiomas (Zvulunov and Metzker, 2002). One study has reported on the effectiveness of the drug in the treatment of life threatening multiple hemangiomas after failure with corticosteroids, and no side effects were observed (Gottschling *et al.*, 2006). In a more recent study, the successful use of cyclophosphamide to treat steroid-resistant hepatic hemangioma was reported (Vlahovic *et al.*, 2009). No serious side effects were observed during three years following treatment. The drug's mechanism of action is not well understood, although its effect on hemangioma may be partly attributed to its antiangiogenic effect (Zhang *et al.*, 2006; Zvulunov and Metzker 2002).

Continuous low-dose cyclophosphamide has been shown to have an antiangiogenic effect, and this effect was enhanced when it was administered in combination with another antiangiogenic agent, ginsenoside Rg3 (Zhang *et al.*, 2006). Cyclophosphamide has been used successfully, in combination with interferon α, to treat a complicated hemangioma of the orbit (Wilson *et al.*, 2007).

Thalidomide

Thalidomide is an inhibitor of angiogenesis that was recently reported to be effective in the treatment of a life-threatening unresectable intracranial

hemangioma (Frei-Jones *et al.*, 2008). The main symptoms of toxicity were sleeplessness and constipation. The latter side effect was so severe that treatment had to be discontinued (Frei-Jones *et al.*, 2008). *In vitro*, thalidomide inhibits VEGF secretion and microvessel formation. It has also been shown to induce the migration of human endothelial cells (Komorowski, 2006). Concerns about the debilitating side effects ensue, and it is not readily employed in the management of IH. However, thalidomide, in combination with cyclophosphamide, is in phase II trials for the treatment of recurrent pediatric malignancies. A combination of these two drugs, which have been employed singly to treat complicated hemangiomas, may hold promise in the treatment of the lesions.

Conclusion

Although there is at present no universally-agreed upon treatment for hemangiomas of infancy, pharmacological therapy remains the first line of treatment for complicated tumors. Steroids produce variable results, and are largely effective in treating hemangiomas in the proliferative phase. While interferon produces a success rate of 80-90% in the treatment of these lesions, its debilitating side-effect, namely the development of spastic diplegia, precludes its use on a routine basis. Propranolol has been used infrequently and the reported cases on the effectiveness of the drug are few. Cytotoxic chemotherapy, which is generally reserved for malignant disease, has also been used for the treatment of infantile hemangiomas with serious complications. Drugs used in this category include cyclophosphamide, vincristine, bleomycin and pingyangymycin. There is concern about the use of cytotoxic chemotherapy to treat juvenile benign lesions. There is therefore a need to find effective and less toxic therapeutic therapies for problematic IH.

In addition, such treatments will have to be studied systematically or be proven to be efficacious in the treatment of hemangiomas through randomised clinical studies.

Drugs that are currently used to treat hemangiomas have been shown in various independent studies to have antiangiogenic properties. This provides the basis for rational drug design based on the mechanistic pathways that occur in hemangiomas, in order to provide therapies that are targeted and specific. A multi-targeted drug approach may broaden the efficacy of hemangioma therapies, and may perhaps carry a reduced side effect profile if the drugs can be administered at lower doses. Dexamethasone and bleomycin have been used in combination for hemangioma therapy, with excellent outcomes. Therefore the application of these and other angiogenesis inhibitors warrants further investigation, with a special focus on dose response and drug combinations.

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Infantile hemangioma (IH)

Rapidly involuting congenital hemangioma (RICH)

Noninvoluting congenital hemangioma (NICH)

Tufted angioma

Kaposiform haemangioendothelioma

Pyogenic granuloma (lobular capillary tumors)

Other rare tumors

Drug	Model	Antiangiogenic effects	References
Triamcinolone	**Rat corneal micropocket**	**Inhibits VEGF mediated angiogenesis Inhibits IL-6 mediated angiogenesis**	**Ebrahem *et al.*, 2006**
	CAM assay	**Inhibits angiogenesis**	**McKay *et al.*, 2008**
	Cultured human hemangioma biopsies	**Inhibits neovessel formation**	**Hasan *et al.*, 2003**
Dexamethasone	**Cultured human hemangioma biopsies**	**Inhibits neovessel formation Increases Clust/Apo J expression Increases expression of mitochondrial cyt b**	**Hasan *et al.*, 2003**
Prednisolone	**B16 melanoma in mice**	**Inhibits angiogenesis**	**Banciu *et al.*, 2006**
Bleomycin	**Bovine microvascular endothelial (BME) cells**	**Inhibits endothelial cell growth & migration Inhibits in vitro angiogenesis Induces endothelial cell apoptosis**	**Mabeta and Pepper 2009**
	Cultured human hemangioma biopsies	**Inhibits neovessel formation**	**Mabeta and Davis, 2008**
	CAM assay	**Inhibits neovessel formation**	**Oikawa *et al.*, 1990**
Interferon α	**Skin sections from hemangioma patients**	**Induces apoptosis**	**Sgonc *et al.*, 1998**
	Nude mice - hepatocellular carcinoma	**Inhibits angiogenesis**	**Wang *et al.*, 2003**
	Human brain endothelial cells	**Inhibits capillary-tube formation Inhibits VEGF secretion**	**Annabi *et al.*, 2009**
Thalidomide	**EA.hy 926 cells**	**Inhibits endothelial cell tube formation**	**Komorowski *et al.*, 2006**
	Rat aorta	**Inhibits neovessel formation Inhibits VEGF secretion**	**Bauer *et al.*, 1998**
Vincristine	**HUVEC**	**Inhibits capillary network formation**	**(Hayot *et al.*, 2002)**
	BME cells	**Inhibits endothelial cell growth and migration Inhibits in vitro angiogenesis Induces endothelial cell apoptosis**	**(Mabeta and Pepper, 2009)**
	Human leukaemia T cells	**Inhibits VEGF secretion**	**Avramis *et al.*, 2001)**
Propranolol	**PMA-activated human leukaemia cells**	**Decreases VEGF expression Inhibits angiogenesis**	Hajighasemi *et al.,* 2009
	Bovine Brain endothelial cells	**Down-regulates VEGF and bFGF**	D'Angelo et al., 1997
Cyclophosphamide	Lewis lung carcinoma in	Inhibits angiogenesis Decreases VEGF expression	Zhang *et al.,* 2006

	C57BL6 mice		

Table 1

Vascular tumors of infancy

Table 2

Antiangiogenic effects of drugs commonly used in the treatment of infantile hemangiomas.