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A review of contemporary options for medical management of hemangiomas, other vascular tumors, and vascular malformations

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ABSTRACT

Vascular anomalies include vascular tumors and vascular malformations. With growing pharmacologic options and parallels to cancer treatment and biology, the hematologist–oncologist has assumed a more prominent role in clinical care and research relating to these diagnoses. This also is a growing area for targeted therapies and drug repositioning. We performed a review of contemporary options for medical management of these lesions. PubMed was searched for "vascular anomaly", "hemangioma", "vascular malformation", "arteriovenous malformation", "capillary malformation", "cerebral cavernous malformation", "lymphatic malformation", and "venous malformation", each with "drug treatment" as a modifier. Manuscripts were reviewed to verify diagnoses, indications for treatment, dose-schedules, evidence of effectiveness, toxicities, and mechanisms of action. ClinicalTrials.gov also was reviewed for relevant trials. More than 20 agents were identified which have been used to treat vascular anomalies. Rigorous studies are lacking for many of these. The rarity of these tumors has limited development of medical approaches to treatment. Cooperative group trials will be needed to prove the effectiveness of drugs which have shown promise in cases and small series. The observant clinician remains a powerful tool for identifying potential new treatments for vascular tumors and malformations.

Contents

1. Introduction

Vascular anomalies are a heterogeneous group of diseases which include hemangiomas and other vascular tumors, intermediate and more aggressive malignancies, and vascular malformations of veins, arteries, capillaries and lymphatics (Enjolras & Mulliken, 1997; Blei, 2013). Hemangiomas are the most common of these lesions, with an incidence of 10% in white infants; vascular malformations as a group occur in 1–5% of children and adults (Hochman et al., 2011). Many centers have organized multidisciplinary clinics to manage patients with hemangiomas and vascular malformations (Mathes et al., 2004), inviting expertise in anesthesia, dermatology, dermatopathology, surgical, medical and pediatric subspecialties, diagnostic and vascular interventional radiology, rehabilitation medicine, cancer and vascular biology. With growing pharmacologic options and obvious parallels to cancer treatment and biology, there has been a paradigm shift in the pharmacologic approach to these lesions in the past decade. The

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hematologist–oncologist has assumed a more prominent role in clinical care and research. To provide an overview of growing options for management, we searched the literature for drugs which have been effective in the treatment of vascular anomalies.

2. Methods

2.1. Literature search procedure

PubMed was searched for "vascular anomaly", "hemangioma", "vascular malformation", "arteriovenous malformation" (AVM), "capillary malformation" (CM) (previously called "port wine stain"), "cerebral cavernous malformation" (CCM), "lymphatic malformation" (LM) (previously called "cystic hygroma"), and "venous malformation" (VM), each with "drug treatment" as a modifier. Where available online, abstracts of manuscripts whose titles indicated human experience with one or more specific medications were further screened for specifics of diagnoses and treatment. Relevant manuscripts were reviewed in an attempt to verify diagnoses, indications for treatment, responses, toxicities, and mechanisms of action. Only citations in English for which a manuscript was available on-line were included. For each drug, the strength of evidence for its effectiveness was reviewed: whether a drug had been used in one or more randomized or single arm clinical trials, in multiple case reports, or whether experience was limited to single case reports. Only representative citations are referenced but the body of literature was taken into account to determine quality of evidence. Drugs such as bleomycin which are used for sclerotherapy, or aminocaproic acid and tranexamic acid which have been reported as supportive care to treat bleeding but which have no effect on the vascular anomaly itself were not included.

2.2. Review of ongoing clinical trials

ClinicalTrials.gov was reviewed for trials which were recruiting as of February 1, 2013. Additional studies on that website which were ongoing but not recruiting or which had been completed but not yet published were not included. Both PubMed and ClinicalTrials.gov were used to look for mechanisms of action. Most of the agents are thought to work through inhibition of one or more angiogenic pathways.

3. Results

3.1. Historical treatment — an overview

Prior to 2008, corticosteroids, gamma or alpha interferon, and traditional chemotherapies (such as vincristine and cyclophosphamide) were typical medical therapies for vascular tumors (mostly hemangiomas and hemangioendotheliomas) that required treatment. Use of the most common agents has been reviewed elsewhere (Gottschling et al., 2006; Blei, 2013). These were used, as single agents or in combination, as adjuncts to excisional surgery, intralesional injection, pulse dye laser therapy, or sclerotherapy (Buckmiller, 2004; Gottschling et al., 2006). No randomized clinical trials ever compared these agents to each other or to placebo. However, they were used empirically and are considered to be effective in some patients with hemangiomas or hemangioendotheliomas with or without consumption coagulopathy (Kasabach–Merritt syndrome (KMS)). Newer conventional chemotherapies also have been applied to refractory vascular tumors (Pintoffl et al., 2009; Grenader et al., 2011).

3.2. Contemporary options for treatment

Other, mostly newer, pharmacologic options are listed in Table 1. Because most of the agents we identified have been used to treat multiple different vascular anomalies, the table is arranged by drug rather than by diagnosis. Using our search criteria, PubMed identified several thousands of manuscripts, of which a number appeared in multiple searches (e.g., in searches of both "hemangioma" and "vascular anomaly"). However, fewer than 600 met criteria for inclusion (under "vascular anomaly" (n = 83), "hemangioma" (n = 274), "vascular malformation" (n = 94), AVM (n = 26), CM (n = 4), CCM (n = 2), LM (n = 14), VM (n = 46)). In many cases, the literature searches incorrectly identified the type of vascular anomaly (e.g., "hemangioma/drug treatment" pulled up many articles relevant to the telangiectasias of hereditary hemorrhagic telangiectasia (HHT, Osler Weber Rendu syndrome)). Although not specifically searched for, treatments for primary lymphedema are included in these results since they were identified in searches for LM.

Propranolol, a non-selective beta adrenergic blocker used for many years to treat hypertension, arrhythmias, and other cardiovascular abnormalities in children, is recently the most widely recognized agent for hemangiomas of infancy (IH). It has become first line therapy for IH in the proliferating phase in many centers (Blatt et al., 2011; Hogeling et al., 2011; Drolet et al., 2013) since the publication in 2008 of a series of 11 patients (Leaute-Labreze et al., 2008). The first patient had been given propranolol for treatment of obstructive hypertrophic myocardiopathy and dramatic improvement of her facial hemangioma was noted. This coincidental observation was duplicated in the other 10 children. Responses to propranolol since have been confirmed in over a thousand children with hemangiomas (Drolet et al., 2013). A single prospective randomized trial comparing propranolol to placebo proved efficacy and safety (Hogeling et al., 2011). Oral propranolol typically is started at doses of ≤1 mg/kg/day and escalated to 2 mg/kg/day divided in two or three doses. Responses can be noted within several days to two months of starting, and corticosteroids sometimes are continued as a bridge to achieving target dosing and initial responses. Side effects of propranolol generally are negligible, but rarely can be life-threatening. The overall frequency of complications has ranged from 0.1 to 10% (Blatt et al., 2011; Drolet et al., 2013). These include hypoglycemia, bradycardia and hypotension, hyperkalemia, somnolence or other sleep disturbances, respiratory embarrassment, and cool or mottled extremities — each of which can occur anytime during the course of treatment. Guidelines for treating and monitoring infants and children and hemangiomas with propranolol have been suggested (Drolet et al., 2013). Timolol maleate (0.5% gel forming solution), a topical beta-blocker, is an alternative in children with superficial lesions (Pope & Chakkittakandiyii, 2010; Blatt et al., 2011). Propranolol has been used anecdotally for related lesions including epithelioid hemangioma of the retina (Moss et al., 2012) and cavernoma (abnormal collections of vascular sinusoids that are lined by a single endothelial layer and lack intervening brain parenchyma) of the brain (Moschovi et al., 2010). It has been used with variable success for the treatment of tufted angiomas or Kaposiform hemangioendotheliomatosis with or without KMS (Chiu et al., 2012), and lymphangiomas (Ozekl et al., 2011; Annabel et al., 2012). In vitro studies have suggested that it might have application to patients with HHT (Albiñana et al., 2012). Randomized trials of patients with hemangiomas or CM in Sturge–Weber syndrome comparing beta-blockers with corticosteroids or placebo are in progress (ClinicalTrials.gov; Table 2). Other beta-blockers with greater specificity (atenolol (Raphaël et al., 2011); acebutolol (Blanchet et al., 2010)) have been offered as alternatives to propranolol, but have been used much less commonly in this setting. In a recently published small prospective series, nadolol (which like propranolol is a non-selective beta-blocker) was found to be as effective as propranolol for hemangiomas in young children (Pope et al., 2013). Its favorable safety profile and longer half-life make this drug an attractive candidate for prospective head to head comparisons with propranolol. The mechanism by which beta-blockers work is multi-factorial, including vasoconstriction through beta blockade, anti-angiogenesis via decreased expression of vascular endothelial growth factor (VEGF) and β fibroblast growth factor (FGF), and apoptosis of capillary endothelial cells (Greenberger & Bischoff, 2011) (Fig. 1). Several small series indicate that captopril, an antihypertensive which is an ACE inhibitor, also may have anti-angiogenic activity (Tan et al., 2012).