REVIEW ARTICLE

ISSN 2508-190X

CLL 2(2):31-35, 2017

www.kslymph.or.kr

Pharmacological Management of Lymphedema

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Current clinically available pharmacotherapy of lymphedema is limited to symptomatic management and conventional nonspecific use of benzopyrones or venotonics. Diuretic use with purpose of reduction of fluid stasis has limited role and potential adverse effect. Prophylactic antibiotics can be used for the patients with recurrent cellulitis and skin preparation agents can be applied to reduce keratinization of hardened skin. Stimulating phagocytosis and lymphatic vessels drainage are the proposed effects of benzopyrone but their clinical effectiveness is inconclusive and coumarin is withdrawn due to hepatotoxicity. Flavonoids originally developed as phlebotonics and selenium are widely used but their benefits are unclear. Hyaluronidase directly administered to the affected tissue facilitates breaking down hyaluronan in the interstitium and lymphangiogenesis. With small benefits of current pharmacotherapy options, growing interest in searching for targeted therapy has led to significant numbers of studies on lymphatic regeneration in molecular biology level. Vascular endothelial growth factor-C (VEGF-C) through vascular endothelial growth factor receptor-3 (VEGFR3) is main target in promoting lymphangiogenesis, and the application of VEGF-C proven to be effective in lymphedema management in animal model. Combination therapy of VEGF-C with stem cells, lymph node transfer or ESWT has shown potential benefits. Lymphangiogenesis is possibly promoted by other agents like hepatocyte growth factor (HGF), interleukin 8 (IL-8), G-protein-coupled receptors, cilostazol and matrix metalloproteinase (MMP)-9.

Key Words: Lymphedema · Pharmacological management · Pharmacotherapy · Lymphatic regeneration

INTRODUCTION

Pharmacological treatment of lymphedema has limited role at present time. Agents used conventionally have the lack of conclusive evidence for their effectiveness [1]. Many other targeted agents still have limitation in application for clinical use as well as potential side effects.

However, pharmacotherapy is still the interesting management options because it is rather simple to use with less inconvenience compared to the compressive management. It is welcome to have an extra treatment option adjunctive to decongestive therapy especially in chronic or severe lymphedema patients.

▸ Received: November 1, 2017, ▸ Accepted: November 7, 2017

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Pharmacological management targets the different steps of lymphedema pathogenesis including congestion of lymphatic vessel passages, extravasation of lymph through endothelial layer, damage and deterioration of the lymphatic vessels, protein and debris trapped in interstitial tissue, frequent inflammation and infection of the tissue, and fibrotic change and hyper-keratinization of skin.

Variety of medication is proposed to prevent or improve lymphedema, including diuretics, antibiotics, benzopyrones, flavonoids, venotonics, hyaluronidase, retinoids, topical cream, and agents promoting lymphatic regeneration.

Reviewing these medications used for lymphedema management and their mechanism of action will help to expand our horizon in management options as well as research interest.

MAIN

1. Diuretics

Diuretics might help lymphedema control in early stage

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by extracting whole-body fluid to reduce fluid load, but do not have role in chronic stage of lymphedema with fibrotic change as diuretics are not effective in removing interstitial lymphatic fluid.

Patients particularity with medical co-morbidity causing fluid overload or who have high hydrostatic pressure due to mechanical obstruction like malignant lymphatic blockage or post-phlebitic syndrome may benefit from diuretics [2].

Diuretics rather induce protein concentration and increased osmolarity in the interstitial tissue and lymphedema might become even worse [3].

Electrolyte balance needed be closely monitored and dehydration over long time could disturb skin integrity leading to easy break down.

2. Antibiotics

Tissue with lymphedema is prone to infection because the protein rich lymph and tissue debris accumulates and immune response is reduced. Prevention and early management of infection is critical in lymphedema patients [4].

Penicillin, 1st generation cephalosporin, erythromycin and clindamycin targeting staphylococcus aureus and streptococci are the first line of treatment.

In patients with recurrent cellulitis, prophylactic antibiotic use can be considered in addition to the attentive skin care.

Patients experiencing recurrent lymphangitis or cellulitis may require long-term, prophylactic treatment with antimicrobial agents [5,6].

3. Benzopyrones

Benzopyrone is a ketone derivate of benzopyran, which can be derived from natural substance, or prepared synthetically.

1) Coumarin

Coumarin, 5, 6-benzo-α-pyrone, is thought to act on the tissue macrophages. It stimulates macrophages to release lysosomal enzyme to degrade tissue proteins to smaller molecules which can be easily removed from the tissue resulting in lower osmolarity. Coumarin also binds to the interstitial protein to induce phagocytosis by macrophages [7]. Vasoconstriction by direct stimulation of smooth vessels promoting lymphatic flow is another proposed action of coumarin. A few studies showed improvement in edema volume and symptoms control by coumarin [8-10] but the systemic review on clinical trials of coumarin could not draw concrete conclusion about its efficacy [11,12].

Critical hepatotoxicity made the coumarin withdrawn from clinical use. Idiosyncratic hepatotoxicity is proposed that genetic polymorphism in CYP2A6 causes coumarin metabolized to cytotoxic metabolite which is excreted in bile [7]. The role of pharmacogenetic study to identify individuals of the hepatotoxicity risk in reconsideration of coumarin as lymphedema treatment tool is still questionable.

2) Flavonoids

Flavonoids, benzo-γ-pyrone, are widely found in plants and fruits, and have been used for traditional medicine because of their claimed anti-oxidant and anti-inflammatory actions. Commercially used flavonoids are grape seed extract (entelon), micronized purified flavonoid fraction (daflon, venitol), troxerutin (paroven), and naftazone (mediaven).

Originally developed as venotonics, flavonoids are believed to improve endothelial function to reduce permeability of vessels. Their role in lymphedema is to reduce fluid and macro-molecules extravasated into interstitial fluid. As the main lymphedema pathology is the failure of drainage of lymph rather than the production of interstitial fluid, the impact of flavonoids in lymphedema control appears to be small and higher dose is required to give enough benefits. Increased venous tone and lymphatic contraction introduced as another function of flavonoids but flavonoids are studied mainly for vascular insufficiency [13] and few clinical trials on lymphedema have been reported with inconclusive benefit [11,14].

Benzopyrones cannot be a primary treatment for the lymphedema and should be used as adjunctive management tool to complex decongestive therapy especially in cases of superimposed venous system failure [2].

4. Selenium

Selenium is an essential element in the body with antioxidant activity and often used as remedy to reduce side effects of chemotherapy or radiotherapy in cancer patients [15]. It reduces reactive oxygen species (ROS) through glutathione peroxidase activation and inhibits

nuclear factor-κB therefore suppresses inflammatory responses. Tissue fibrosis is also reduced as selenium inhibits expression of adhesion molecules. Oral administration or injection to the affected tissue results in reduction of lymphedema volume and infection risk [16].

5. Hyaluronidase

Hyaluronan is glycosaminoglycan forming extracellular matrix that it contributes trapping extravascular fluid. Direct injection of hyaluronidase, cleaving hyaluronan in the interstitium, to the limb affected by lymphedema is proven to be effective in inhibiting fibrogenesis and inflammation, and stimulating lymphangiogenesis in animal model [17]. In hyaluronidase treated tissue, tumor necrosis factor (TNF)-alpha and transforming growth factor (TGF)-beta1 expression is reduced but the level of endothelial hyaluronan receptor (LYVE)-1, vascular endothelial growth factor receptor-3 (VEGFR3), interferon-γ, podoplanin, and CD 44 increased [17,18].

6. Topical agents

Retinoid like agents, applied orally or topical preparation such as topical tazarotene (topical gel 0.1%), can be used in chronic lymphedema to reduce keratinization, inflammation, or fibrosis of the skin [19].

Ammonium lactate, urea and salicylic acid in topical form keep skin hydrated and remove excessive keratin.

7. Lymphatic regeneration

As understanding of lymphatic system in molecular biology aspect and the specific markers affecting lymphatic generation has been expanding for the last two decades, many researches about halting or reversing the lymphatic system failure in vivo or animal model have been emerging. The molecular level manipulation inducing lymphangiogenesis is the main focus of these target therapy studies [20].

1) Vascular endothelial growth factor-C and D (VEGF-C , VEGF-D)

Vascular endothelial growth factor-C and D (VEGF-C, VEGF-D) through vascular endothelial growth factor receptor-2 and 3 (VEGFR-2, VEGFR-3) is known to be the core pathway for lymphatic epithelial cell (LEC) proliferation and lymphatic vessel differentiation [21]. Subcutaneous or parental injection of VEGF-C in many animal models demonstrated edema reduction and lymphatic vessel remodeling in distal level [22]. However, functional networking involving collecting vessels and effective lymphedema control for clinical use in human are still unwarranted.

Lymphangiogenesis stimulated by VEGF can reinforce the effect of other therapy tools.

VEFG improves lymph node transplant viability and function by promoting connection of the lymph node into the existing lymphatic vessels. In the animal study of lymph node transfer, VEFG-C injected perinodally facilitated lymphatic vessel growth and secured the transferred lymph node, whereas untreated nodes as control degenerated [23].

Combined therapy of stems cells and VEGF-C has synergic effect. In a rabbit model, bone marrow stromal cells with VEGF-C protein injected resulted in better outcome than both single treatments in volume reduction, VEGF-C expression and the numbers of VEGF-R3 positive vessels [24]. Stem cells applied with VEFG-C hydrogel, control release form, showed augmented results of reduced dermal depth and increased lymphatic vessel endothelial hyaluronan receptor-1 (LYVE1) positive vessels in mouse model [25].

Low-energy extracorporeal shock wave therapy (ESWT) promoted lymphangiogenesis by VEGF-C up-regulation [26] that ESWT application to VEGF-C treated tissue showed positive results [27].

Animal models of lymphedema studies have limitation due to the difference from human in terms of progression and sustainability of lymphedema as well as distance of expected lymphatic regeneration.

VEGF-C and VEGF-D is known to contribute to cancer metastasis of lymph nodes that the safety of clinical use of VEGF for the patients with cancer related lymphedema is significant concern and should be further studied.

2) Others

Beside VEGF-C, several other agents acting on lymphatic generation and function have been introduced.

Hepatocyte growth factor (HGF) and HGF receptors promotes lymphatic vessel formation and mutations in HGF and HGF receptors are considered to have connection with primary and secondary lymphedema [28]. Interleukin 8 (IL-8), G-protein-coupled receptors, cilostazol and matrix metalloproteinase (MMP)-9 are found to have association with lymphangiogenesis [29].

CONCLUSION

Heterogeneous groups of medicines have been proposed to prevent or improve lymphedema targeting different aspect of pathophysiology of lymphedema. Besides symptomatic treatments like antibiotics or topical emollient, nonspecific treatment including benzopyrones and selenium has been used conventionally but studies have failed to prove their therapeutic efficacy. Targeted therapy aiming lymphatic regeneration, especially focusing on VEGF-C expression, has been vigorously studied in animal model and shown promising results. However, feasible clinical methods of application should be developed and effectiveness and safety in human to be researched significantly before clinical use.

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