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Novel iontophoretic administration method for local therapy of breast cancer☆

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ABSTRACT

Ductal drug therapy is a novel therapeutic approach for primary breast cancers, particularly those involving ductal carcinoma in situ lesions. Total or partial mastectomy with or without radiotherapy is the standard local therapy for primary breast cancer. Here, we propose a novel drug administration method for ductal drug therapy based on a drug delivery system (DDS) for primary breast cancer. This DDS was designed to deliver miproxifen phosphate (TAT-59), an antiestrogen drug, to ductal lesions via the milk duct, where carcinomas originate, more efficiently than systemic administration, using an iontophoretic technique applied to the nipple (IP administration). Autoradiography imaging confirmed that TAT-59 was directly delivered to the milk duct using IP administration. The plasma concentrations of TAT-59 and its active metabolite DP-TAT-59 were quite low with IP administration. The area under the curve value of DP-TAT-59 in the mammary tissue was approximately 3 times higher with IP administration than with oral administration, at a 6-fold lower dose, indicating higher availability of the drug delivered via DDS than via systemic administration. The low plasma concentrations would limit adverse effects to minor ones. These characteristics show that this DDS is suitable for the delivery of active DP-TAT-59 to ductal lesions.

1. Introduction

Breast cancer is by far the most common cancer in women worldwide, and its incidence is increasing in most countries, including in Asian nations [1]. Primary breast cancer occurs within the milk ducts and progresses to malignant breast cancer [2,3]. The natural history of primary breast cancer remains poorly understood [2,3], and the treatment strategies differ remarkably between invasive and noninvasive carcinomas. Local therapy currently consists of surgery and radiation therapy for noninvasive lesions and systemic drug therapy such as hormone therapy, chemotherapy, and anti-HER2 therapy for invasive lesions [4]. During systemic administration, diffusion of the drug to the ductal lesions from the blood vessels is considered to be obstructed by the basement membrane of the milk duct [5] and because of the distance from the capillary vessels [2]. In fact, ductal lesions often persist after preoperative neoadjuvant systemic therapy despite invasive lesions disappearing after treatment [5,6].

Therefore, it would be reasonable to investigate local drug therapy that targets the ductal lesions, both noninvasive cancers such as ductal carcinoma in situ (DCIS) and lesions that are resistant to systemic treatments. Local ductal drug therapy would hypothetically be able to reduce the surgical burden and enhance systemic drug therapy. Several investigators have suggested the possibility of intraductal therapy such as intraductal administration of an anti-tumor drug via a cannulated needle for primary breast cancers [7–10].

In this study, we considered mechanisms for delivering high concentrations of drug directly into the mammary ducts. Methods for injecting drug solutions into the mammary duct have been reported [7–10]. We developed the drug delivery system (DDS) for introducing drugs into the mammary duct using an iontophoretic technique that is applied to the nipple. Iontophoresis is a physical method that

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facilitates the percutaneous absorption of compounds that penetrate the skin in a manner dependent on the electrical potential difference; despite the fact that this technique has been investigated for half a century [11], it remains under investigation today [12,13]. Iontophoresis helps the transport of charged and high-molecular-weight compounds that cannot normally be delivered by passive transport and proportionally increases the rate of drug delivery according to the applied current [11]. We attempted to deliver the drug directly into the mammary duct from the nipple, the opening site of the milk duct orifices, by applying an electrical potential difference between the nipple and the breast skin using an iontophoretic technique (IP administration).

We applied miproxifen phosphate (TAT-59, Fig. 1-A), which has potent antiestrogenic activity, as the therapy drug [14]. Antiestrogen is the proper candidate drug for the treatment of ductal lesions because ductal lesions are known to often express estrogen receptors (ER) [15]. TAT-59 has a negative charge at the phosphorus group under physiological conditions. Response to iontophoresis is attributable to the negative charge of TAT-59. TAT-59 is rapidly biotransformed by alkaline phosphatase to the dephosphorylated metabolite miproxifen (DP-TAT-59), the main active metabolite of TAT-59 (Fig. 1-A) [16]. DP-TAT-59 is an analog of 4-hydroxy-tamoxifen (4OH-TAM), an active metabolite of tamoxifen (TAM), and has cytostatic activity similar to 4OH-TAM *in vitro* [17]. When administered orally, TAT-59 is completely metabolized to DP-TAT-59 during intestinal absorption [16], and TAT-59 is not detected in plasma or tissues [18]. The clinical efficacy and adverse effects of oral doses of TAT-59 have been reported to be similar to those of TAM in Phase II clinical trials of patients with advanced metastatic breast cancer [19,20].

In this article, we elucidate the characteristics and benefits of IP administration of TAT-59 and DP-TAT-59 into the mammary duct using a DDS and present proof of concept of IP administration for drug therapy for ductal lesions, based on pharmacokinetic data of TAT-59 and DP-TAT-59, obtained by administering TAT-59 via IP administration to dogs.

2. Materials and methods

2.1. Materials

2.1.1. Chemicals

TAT-59 and DP-TAT-59 were obtained from Siegfried Ltd. (Zofingen, Switzerland). ^{14}C-labeled TAT-59 (^{14}C-TAT-59), ^{13}C-labeled TAT-59 (^{13}C-TAT-59), and DP-TAT-59 (^{13}C-DP-TAT-59) were obtained from Sekisui Medical Co., Ltd. (Tokyo, Japan).

Indocyanine green (ICG) was purchased from Daiichi Sankyo Co., Ltd. (Tokyo, Japan) as Diagnogreen, a medical diagnostic product.

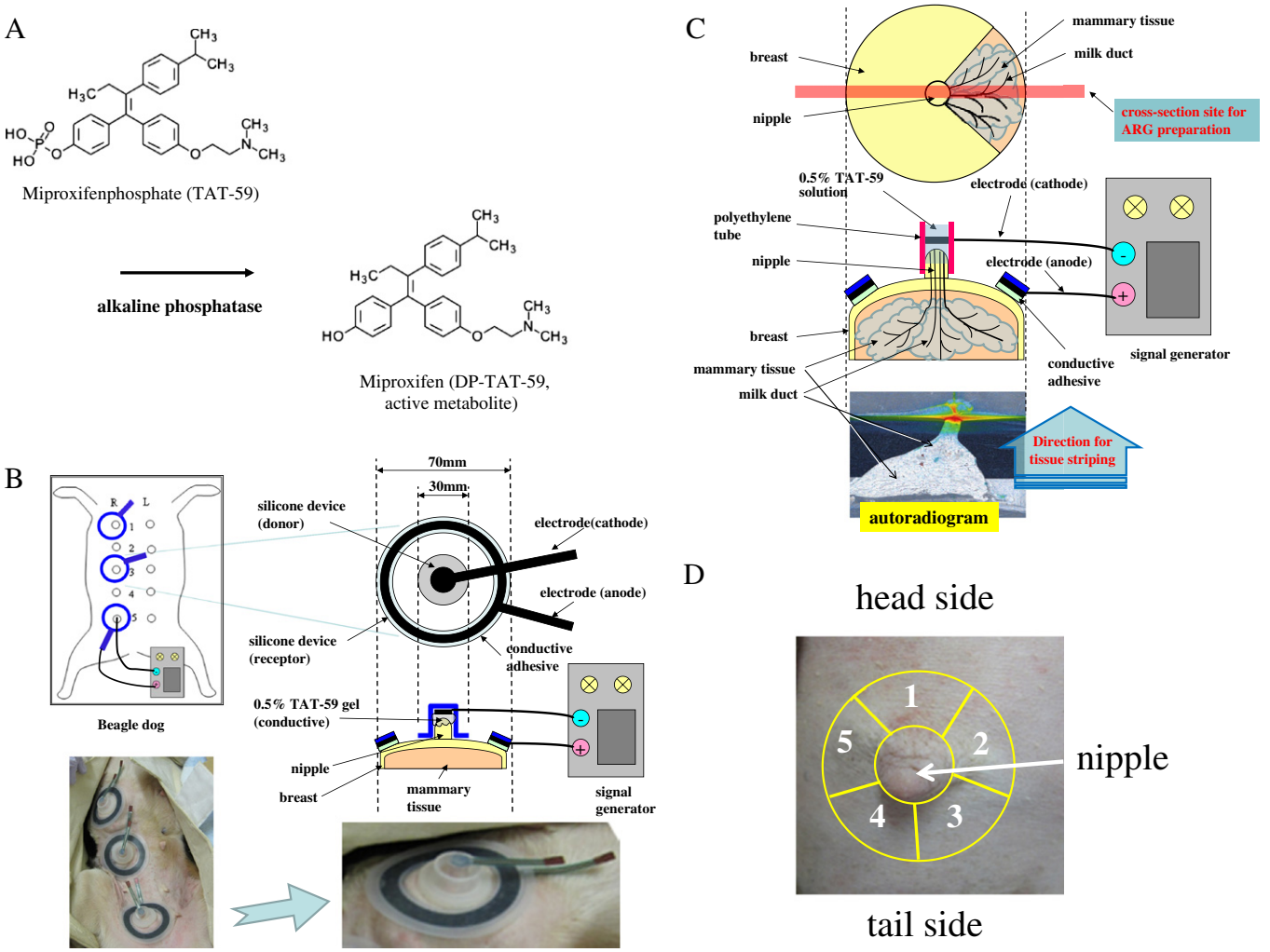

Fig. 1. A: Chemical structural formula of miproxifen (TAT-59) and its metabolic pathway to DP-TAT-59, an active metabolite. B: Diagrammatic illustration of the iontophoretic administration method and device. C: Diagrammatic illustration of iontophoretic administration for autoradiography imaging. D: Diagrammatic illustration of the collection site for the determination of DP-TAT-59 concentration homogeneity in mammary tissue after IP administration. The numbers in the illustration refer to the site numbers in Table 2.