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Effects of sunitinib targeted chemotherapy on the osseointegration of titanium implants

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ABSTRACT

Targeted chemotherapies are novel therapeutic approaches for many malignancies. In contrast to conventional chemotherapies, which are given for a predetermined duration, treatment with targeted chemotherapies like sunitinib is routinely continuous over longer periods, sometimes years. During this prolonged treatment period, patients may need to restore their missing teeth with dental implants. The aim of this study was to examine the effect of the anti-angiogenic substance sunitinib targeted chemotherapy on the osseointegration of titanium implants in a rabbit model. Fourteen white New Zealand rabbits were randomly assigned to two groups of either oral sunitinib at 10 mg/kg twice per week dose for 4 weeks (n = 7) or placebo (n = 7). The first dose was given 2 days before the surgical intervention. Each rabbit received one titanium dental implant in the right distal femoral condyle. Four weeks following implant insertion, rabbits were sacrificed and bone specimens containing the implants were retrieved. Osseointegration of the implants was analyzed using micro-computed tomography and histomorphometric evaluation. Both micro-computed tomography and histomorphometric analysis showed that the osseointegration parameters, including the ratio of bone volume to total volume and bone-implant contact percent for the sunitinib group were significantly lower than those in the control group ($P \leq 0.05$). Sunitinib targeted chemotherapy had a negative effect on the osseointegration of titanium implants inserted in a rabbit model.

1. Introduction

Currently, the success and survival rates of dental implant therapy have reached more than 95% in a healthy population [1]. Nevertheless, ongoing perfection of the dental implant material, design, and surface treatment as well as advances in surgical techniques has led to an increased population of patients who can be considered candidates for implant therapy. Therefore, increasing interest is now focused on patients with disease-related variables that may influence implant integration and success [2].

The prevalence of edentulism and malignancies is continuously increasing. This may be explained by the gradually increasing life-expectancy of the population; therefore, it is expected that these age-related conditions will be seen more frequently in medical oncology and dental clinics. Therefore, more patients with cancer treated by systemic chemotherapy may need dental implants to replace missing teeth and improve quality of life [3]. Conventional anticancer medications are associated with several adverse effects, mainly due to chemotherapy's cytotoxic impacts on the bone marrow, kidneys, and oral mucosa. In addition, impaired vascular cells may result in lack of nutrition to the bones and influence the healing capacity of the alveolar bone, which is an essential prerequisite for successful implant osseointegration [3,4]. In two previous studies that addressed the effect of cisplatin, a conventional chemotherapeutic agent, on the osseointegration of titanium implants, the authors of both studies reported that cisplatin markedly inhibited the osseointegration of titanium implants [5,6].

Despite advances in multimodality treatments for oncogenic diseases, the survival rates and decreasing the toxicities of chemotherapy have remained less than optimal. Hence, new therapeutic approaches such as targeted chemotherapies have been introduced [7]. Targeted chemotherapies, which represent a marked improvement in cancer treatments, offer numerous advantages over conventional chemotherapy, including diminished toxicities and increasing selectivity [4,7,8]. These novel anticancer agents exert their actions via interfering

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selectively with specific molecular pathways involved in tumor growth, progression, and metastasis. Moreover, these targeted medications are regularly cytostatic (square tumor cell proliferation), while the standard chemotherapies are cytotoxic (kill tumor cells) [4,9]. Tyrosine kinase receptors (TKRs) are one of the molecular signaling cascades targeted by the recent chemotherapies. TKRs such as platelet-derived growth factor receptors (PDGFRs), fibroblast growth factor receptors (FGFRs), and vascular endothelial growth factor receptors (VEGFRs) play a vital role in tumor growth and angiogenesis [7,8].

Sunitinib is a novel orally administrated antitumor agent that was introduced as a monotherapy for several malignancies, including gastrointestinal stromal tumors and advanced renal cell carcinoma. In addition, sunitinib demonstrated promising therapeutic activity against several types of tumors such as advanced non-small cell lung, breast, colorectal, and neuroendocrine tumors [10]. Sunitinib exerts its action via inhibition of different groups of TKRs, such as VEGFR-1, VEGFR-2, VEGFR-3, fetal liver TKR type 3, stem-cell factor receptor, PDGFR-α, and PDGFR-β [11,12]. Targeting VEGF signaling pathways has a very efficient antitumor action, as it inhibits tumor angiogenesis and normalizes tumor vessels. Furthermore, antagonism of VEGF signaling can decrease the tumor tortuosity, diameter, and vascular permeability [13]. Sunitinib has fewer side effects than standard chemotherapies, and most of them can be reversed by dose adjustment or interruption of therapy without the need to discontinue therapy [14]. Reported side effects include fatigue, diarrhea, skin abnormalities, and hypertension, as well as oral adverse effects, such as mucositis, dry mouth, and altered taste [14,15].

Interestingly, several studies reported dose- and time-dependent antitumor efficacy of sunitinib [11,12,16]. Moreover, in contradiction to the conventional chemotherapeutics, which are given for a predetermined duration, treatment with sunitinib is routinely continuous over longer periods, sometimes years. Moreover, if sunitinib treatment is interupted or terminated, the disease may worsen and progress quickly [14]. During this prolonged treatment period, the patients may need to restore their missing teeth with dental implants.

Recently, the increases in cases reported with osteonecrosis of the jaw (ONJ) in patients taking medications other than bisphosphonate, such as the antiresorptive agents (e.g. denosumab) and the noval antiangiogenic therapies [17], have led the Special Committee of the American Association of Oral and Maxillofacial Surgeons (AAOMS), in 2014, to suggest the terminology of medication-related osteonecrosis of the jaw (MRONJ) instead of bisphosphonate-related osteonecrosis of the jaw (BRONJ) [17]. Several studies have documented the link between the incidence of ONJ and these novel antiangiogenic therapies [18–20]. However, another study conducted on a three large prospective trials has demonstrated little association between them [21].

Two previous studies evaluated the effects of antiangiogenic therapy on the osseointegration of titanium implants. One study investigated the effects of a potent inhibitor of angiogenesis, TNP-470, in a rabbit model and reported reduction in the amount of newly formed bone around the implants, whereas the quantity of bone-implant contact was not affected [22]. A recent study by Al Subaie et al. assessed ranibizumab, anti-VEGF, effects on bone healing and implant osseointegration and concluded that ranibizumab may negatively influence bone healing and the process of implant osseointegration [23].

Currently, the antiangiogenic effects of sunitinib targeted chemotherapy on the osseointegration process of titanium implants have not been reported. Therefore, in the present study, we investigated the influence of sunitinib targeted chemotherapy on the osseointegration of titanium implants in a rabbit model using micro-computed tomographic (CT) and histomorphometric analysis. The study independent variable is the administration of sunitinib, while the dependent variables are the bone implant contact (BIC %) and bone volume to tissue volume at 500 μm from the implant surface.

2. Materials and methods

2.1. Experimental animals and ethical approval

The ethical review board for experimental animal research approved the protocol of this study (Approval No. IRB-2016-02-073). All experimental procedures were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23; 1996) as well as the regulations of the Standing Committee for Research Ethics on Living Creature at our institute (SCRELC). The study design followed ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines.

2.2. Study design

The study was conducted on a group of 14 adult male, 6–8 months-old, white New Zealand rabbits, weighing 3.5–4.2 kg. Each rabbit was accommodated in a separate stainless-steel cage and provided with a standard rabbit pellet diet and water ad libitum. Standard environmental conditions (25 °C, 50%–55% relative humidity, and 12-h light/dark cycles) were maintained during the whole study.

Animals were allowed to acclimatize for 2 weeks before any intervention, and then the rabbits were randomly assigned to two groups of either oral sunitinib (LC laboratories, Woburn, MA, USA) at 10 mg/kg twice per week dose for 4 weeks (n = 7) or placebo (n = 7). The first sunitinib dose was given 2 days before the surgical intervention. The dose was chosen based on a previous work [24]. Sunitinib was given as an oral suspension in 0.5% carboxymethyl cellulose (CMC) using a ratio of 1 ml per kg via gastric gavage. The placebo group received a similar volume of CMC solution in the same ratio.

Sample size was estimated by (http://powerandsamplesize.com/Calculators/Compare-2-Means/2-Sample-Equality) using the following assumptions: alpha error = 5%, power = 80%, means in the 2 groups based on previous similar study [22] = 46.1 and 58.4, standard deviation = 7 and sampling ratio = 1:1. The minimum required sample size was 6 with an additional 10% increased to compensate for potential dropouts. Also, taking the 3Rs (reduction, refinement and replacement) guiding principles of laboratory use of animals into consideration. The sample size per group was thus planned to be 7 animals.

2.3. Surgical procedure

Animals were anaesthetized by ketamine and xylazine anesthesia (30 and 5 mg/kg, respectively). After surgical site preparations, a 2 cm length skin incision was placed on the lateral surface of the right hind leg after injection of 1 ml of 2% Lidocaine with 1:100:000 epinephrine (Novocol Pharmaceutical of Canada, Inc., Cambridge, Canada), then muscles were gently dissected and the periosteum was reflected to expose the flat bone surface on the lateral aspect of the distal condyle. Each rabbit received one cylindrical screw-type titanium dental implant (SICmax® invent AG, Birmannsgasse 3, CH-4055 Basel, Switzerland), 3.7 mm diameter, 7.5 mm length. The implant sites were prepared at the middle of the lateral surface of the head of the femurs. All implants were inserted unicortically (perpendicular to the flat bone surface), threaded to the bone level, and covered by cover screws. Lastly, the wound edges were sutured with Vicryl 3-0 (Ethicon GmbH, Norderstedt, Germany). Following surgery, animals were carried to the recovery room and observed for any complications until complete recovery, then 1.5 mg/kg of diclofenac sodium and 15 mg/kg of oxytetracycline were injected immediately after surgery, then every 24 h for 3 days.

Four weeks following implant insertion, animals were sacrificed with an overdose of pentobarbital (Narkorens, Meral GmbH, Hallbergmoos, Germany). Next, femoral specimens containing the implants were retrieved, cleaned, and sectioned with a circular saw 1 cm proximal and 1 cm distal to the implant. Samples were then preserved