Best Practice & Research Clinical Gastroenterology 25 (2011) 495–506

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Gastroenterology

5

DFMO: Targeted risk reduction therapy for colorectal neoplasia

Christina M. Laukaitis, MD, PhD, FACP, Assistant Professor [a,*], Eugene W. Gerner, PhD, Professor Emeritus [b,1]

[a] Department of Medicine, University of Arizona, 1515 N. Campbell Ave., PO Box 245036, Tucson, AZ 85724, USA
[b] Department of Cellular and Molecular Medicine, BIO5 Oro Valley, 1580 E. Hanley Blvd., University of Arizona, Tucson, AZ 85737, USA

Keywords:
DFMO
Chemoprevention
Colorectal cancer
Polyamines

Strategies to decrease intracellular polyamine levels have been studied for their efficacy in reducing colorectal cancer (CRC) risk. A successful strategy combined agents that decreased polyamine synthesis by inhibiting ornithine decarboxylase with difluoromethylornithine (DFMO), and increased cellular export of polyamines by activating the spermidine/spermine acetyl transferase with non-steroidal anti-inflammatory drugs (NSAIDs). A Phase III trial treating resected adenoma patients with DFMO plus sulindac demonstrated marked reduction of metachronous adenomas, advanced adenomas and multiple adenomas compared to placebo. This combination regimen was well-tolerated, however there was a non-significant excess of cardiovascular events in the treatment arm compared to placebo as well as modest ototoxicity. Targeting this therapy to people at elevated risk of CRC, and employing clinical and genetic predictors, should improve patient benefit and reduce the risk of side effects to improve the acceptability of this strategy.

Introduction

Eflornithine (difluoromethylornithine or DFMO) was synthesized by scientists at the Merrell Dow Research Institute as an enzyme-activated irreversible inhibitor of ornithine decarboxylase (ODC), the first and rate-limiting enzyme in polyamine synthesis [1]. DFMO was ineffective as a single agent for cancer treatment [2], but was subsequently shown to be effective in other pathologies. Since then

* Corresponding author. Tel.: +1 520 626 5845.
E-mail addresses: claukaitis@azcc.arizona.edu (C.M. Laukaitis), egerner@azcc.arizona.edu (E.W. Gerner).
[1] Tel: +1 520 626 2197.

1521-6918/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bpg.2011.09.007

DFMO in combination with a non-steroidal anti-inflammatory drug (NSAID) has been shown to be safe and effective in chemoprevention of colorectal adenomas in people with prior colon polyps [3].

FDA-approved uses of DFMO

DFMO is a potent, enzyme-activated irreversible inhibitor of ODC [4], an essential enzyme in the polyamine synthesis pathway. DFMO is generally cytostatic in mammalian cells, causing a reduction in the rate of cell proliferation in the absence of cell death. However, in certain protozoans, DFMO is cytotoxic, possibly due to the combined inhibitory effect both on polyamine synthesis and on the production of an essential antioxidant, trypanothione.

DFMO (Ornidyl®) was developed as a treatment for forms of African sleeping sickness and an intravenously dosed form of this agent was approved by the US Food and Drug Administration under an orphan drug indication in 1990. The combination of DFMO (intravenous 400 mg/kg per day; every 12 h for seven days) and oral Nifurtimox was shown to be non-inferior to DFMO monotherapy (intravenous 400 mg/kg per day; every six h for 14 days) and judged to be suitable for first-line treatment of human African trypanosomiasis [4].

Topical DFMO (Vaniqa®) was developed as a depilatory agent and received FDA approval for treatment of hirsutism in 2001 [5–7].

DFMO as a chemopreventive agent

DFMO inhibits the promotion and proliferation/progression stages of initiated cancer cells [8,9] suggesting its use as a cancer chemotherapy. Treatment of carcinogen-exposed animals with DFMO has been reported to reduce tumour incidence in bladder, colon, oesophagus, small and large intestine, liver, mammary gland, glandular stomach, skin and pancreas [10–15]. DFMO has also been shown to have an inhibitory effect on specific markers of cell proliferation and neoplasia in animal models of carcinogenesis and efficacy has been reported in a variety of target organs, including bladder, colon, small intestine, mammary gland, and skin [4,12,16–24]. Although DFMO inhibits the growth of tumour cells *in vitro*, in many animal models *in vivo*, prohibitively high doses of DFMO were required to inhibit malignant tumour growth in early chemotherapeutic trials [25–27].

When used as a single agent in patients with a variety of malignancies, DFMO did not significantly slow tumour growth or disease progression [28]. When DFMO was used to prevent recurrent gliomas, however, 45% of patients improved and suffered only modest toxicity [29]. It has been proposed that the lack of efficacy DFMO has demonstrated against established tumours is due to the availability of extracellular polyamines derived from the diet, the retroconversion pathway and gastrointestinal microbial flora [30]. A growing body of evidence suggests that proliferation only needs to return to normal, not be completely blocked, to inhibit the process of carcinogenesis. Very low, non-toxic doses of DFMO may slow growth to normal and/or inhibit stimulation of proliferation by various carcinogens [31] and has led to interest in DFMO as a cancer chemopreventive agent [2].

Human trials of DFMO alone have shown mixed results in cancer chemoprevention. Topical DFMO reduced by one-quarter the number of pre-malignant actinic keratoses as compared to placebo [32]. Treatment with oral DFMO (0.5 g/m^2/day) for 4–years showed a trend towards protection against all non-melanoma skin cancers, and significantly decreased the number of basal cell carcinomas [33]. One year of 0.5 g/m^2/day DFMO decreased prostate putrescine levels and the rate of prostate growth [34]. Oral DFMO at 0.125 and 0.5 g/m^2 for 28 days did not cause regression of CIN 2–3 cervical lesions in affected women [35] nor did 1 g daily prevent recurrence of low-risk superficial bladder cancer [36]. Six months of 0.5 g/m^2/day oral DFMO did not improve cytological measurements of hyperplasia or atypia found in random breast periareolar fine-needle aspirations compared to placebo [37]. A non-placebo-controlled trial showed that after six months of 0.5 g/m^2/day of DFMO, expression of proliferation genes was decreased in samples from patients with Barrett's oesophagus [38].

Therapeutic and prevention clinical trials of DFMO in colorectal cancer (CRC) have been conducted including pilot Phase IIa and IIb studies of DFMO in reducing polyamine content in colorectal tissue. These trials have been used to determine the dose of DFMO necessary to consistently lower polyamine