Digestive and Liver Disease 48 (2016) 1503–1505

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Short Report

High-doses of proton pump inhibitors in refractory gastro-intestinal cancer: A case series and the state of art

Rosa Falcone [a,*], Michela Roberto [a], Chiara D'Antonio [a], Adriana Romiti [a], Annalisa Milano [a], Concetta Elisa Onesti [a], Paolo Marchetti [a], Stefano Fais [b]

[a] Department of Molecular and Clinical Medicine, "Sapienza" University of Rome, Italy
[b] National Institute of Health, Rome, Italy

ARTICLE INFO

Article history:
Received 10 June 2016
Accepted 9 August 2016
Available online 1 September 2016

Keywords:
Colorectal cancer
Metronomic chemotherapy
Proton-pump inhibitors
Refractory disease

ABSTRACT

Background: In recent years, proton pump inhibitors (PPIs) have been investigated at high-dose to modulate tumour microenvironment acidification thus restoring chemotherapeutic sensitivity. Moreover, several clinical data supports the role of cytotoxic drugs at low-dose continuously delivered as anticancer therapy.
Methods: Clinical records of three patients affected with gastrointestinal cancer refractory to standard treatments, who had received a combination of high-dose rabeprazole and metronomic chemotherapy were reviewed.
Results: The first case, a 78-year-old man was treated for lung metastasis from colon adenocarcinoma. The second case, a 73-year-old man was treated for metastatic rectal cancer to the liver. The third one, a 68-year-old man, underwent the combination regimen for colon cancer with lung, liver and peritoneal metastases.
Conclusions: Despite the failure of previous standard chemotherapy for metastatic disease, good clinical outcome was shown in these patients treated with an unconventional association of high-dose PPIs and metronomic chemotherapy.

1. Introduction

Extracellular acidity in cancer microenvironment has a pivotal role in the invasion, metastasis and drug resistance [1]. Vacuolar H^+-ATPases (V-ATPases) are proton exchangers that generate the pH gradient across both the plasma and intracellular organelles membranes by a net consumption of ATP. Enhanced V-ATPase activity is shown in tumour cells compared with their non-transformed counterparts [2]. Moreover, the expression of V-ATPases in chemo-resistant cancer cells is increased, and induced by chemotherapeutic agents [3]. High-doses of proton pump inhibitors (PPIs) have been demonstrated, both in vitro and in vivo experiments, to inhibit V-ATPase activity, modulate tumour acidification and restore chemotherapeutic sensitivity in drug-resistant cancer cells [4–6]. PPIs have already been tested in clinical studies to increase the sensitivity to chemotherapy [7–9] while several trials are presently ongoing (NCT02595372 and NCT01748500).

It has been reported that cytotoxic chemotherapeutic agents can be redirected to an endothelial cell target by changing their dose and frequency of administration [10]. This so termed 'metronomic' chemotherapy has lately been recognized as multitarget therapy [11]. Metronomic capecitabine (mCAP) has proved to be a moderately active, well-tolerated regimen as salvage chemotherapy in patients with metastatic gastro-intestinal cancer [12,13].

2. Patients and methods

Clinical records of three patients affected by gastrointestinal cancer refractory to standard chemotherapy and target therapy, treated at our Institute between 2013 and 2015 with a combination of high-dose PPIs and metronomic chemotherapy were reviewed. According to an experimental protocol (EudraCT Number: 2013-001096-20), all patients provided a written informed consent to participate and protocol approval of the Sant'Andrea Hospital Ethics Committee was obtained. Treatment consisted of rabeprazole 1.5 mg/kg bid, three days a week associated with capecitabine

* Corresponding author at: Department of Molecular and Clinical Medicine, "Sapienza" University of Rome – Sant' Andrea Hospital, Via di Grottarossa, 1035, 00189 Rome, Italy. Fax: +39 0633776663.
E-mail address: rsfalcone@libero.it (R. Falcone).

http://dx.doi.org/10.1016/j.dld.2016.08.126
1590-8658/

1500 mg/daily, continuously until disease progression or unacceptable toxicity. Tumour response was determined according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. The severity of adverse events was graded according to CTCAE v.4.03.

3. Results

3.1. Case report 1

The first case refers to a 78-years old man, who had undergone left colectomy for a large bowel adenocarcinoma of the sigma (AJCC 2010 classification: Stage I, pT2, N0 (0/13), G1). A whole-body CT scan, performed eight months after surgery (on March 2012), showed a nodule (diameter: 4 cm) in the VIII segment of the liver. The colic origin of the tumour was confirmed by biopsy. According to an integrated multidisciplinary approach a sequence of chemotherapy and surgery was decided. The patient underwent chemotherapy with leucovorin (400 mg/m^2 iv), 5-fluorouracil (400 mg/m^2 iv bolus plus 2400 mg/m^2 over 46 h by continuous infusion) and irinotecan (180 mg/m^2 iv) (mFOLFIRI) plus bevacizumab (5 mg/kg iv), repeated every 14 days, for 8 administrations. Although hepatic disease progression at the restaging CT scan occurred after four months of chemotherapy, liver surgery was performed according to segmentectomy. Histology confirmed the diagnosis of metastatic adenocarcinoma (k-RAS wild-type for codons 12, 13) while no signs of residual disease were recorded at a further postoperative CT scan. A complementary chemotherapy with a combination of leucovorin (400 mg/m^2 iv), 5-fluorouracil (400 mg/m^2 iv bolus plus 2400 mg/m^2 over 46 h by continuous infusion) and oxaliplatin (85 mg/m^2 iv) (mFOLFOX6), repeated every 14 days, for 12 administrations was delivered. A dose reduction was applied for the occurrence of severe hematologic (G4 neutropenia) and neurological toxicity (G3). A close follow-up was continued until the appearance of solid nodules at lungs a year later. Based on the previous kRAS evaluation, a target therapy with panitumumab (6 mg/kg iv, every two-weeks) was delivered. After 3-months therapy, a further disease progression, revealed by CT scan, occurred at lung with increased number and size of the multiple nodules. Patient was offered the participation to a no-profit randomized protocol with mCAP plus high-dose rabeprazole. Therapy was carried on for 19 months without radiologic signs of progressive disease but the growth of a pulmonary nodule (28 mm × 24 mm vs. 22 mm × 13 mm), which was successfully controlled by stereotactic radiation (total dose: 50 Gy in 5 fractions). The treatment was stopped for further progressive disease at the lung. Noteworthy, patient maintained a good performance status and quality of life over the whole treatment period. The maximum toxicity was G3 hand-foot syndrome (HFS), lasting 20 days and resolved with temporary drug discontinuation, application of topical urea (40%) cream and oral corticosteroid treatment. Presently, the patient is on treatment with regorafenib (160 mg/daily for 3 weeks every month). The duration of OS from the first diagnosis of metastatic disease to the last observation was 51 months.

3.2. Case report 2

The second case consists of a 73-years old man, suffering from peripheral arterial disease. On Jun 2008, after a prolonged period of constipation, he underwent recto-sigmoid resection with laparoscopic approach and a protective colostomy for adenocarcinoma (AJCC 2010 classification: Stage III, pT3 pN1(3/28) R0 V1, G3). Due to comorbidities including impaired renal function, he just underwent adjuvant radiotherapy (total dose 50.4 Gy) over 5 weeks associated with 5-fluorouracil (225 mg/m^2/day). Clinical monitoring was carried out for 3 years without signs of recurrent disease. On Nov 2011, radiological images revealed two lesions at the VIII segment of the liver, with increased glucose uptake at a PET scan. The diagnosis of wild-type k-RAS (codons 12 and 13) liver metastases was histologically confirmed. A first line chemotherapy with mFOLFIRI plus cetuximab (400 mg/m^2 iv loading dose followed by 250 mg/m^2 weekly) was performed for 3 months. Maximum toxicity was G2 diarrhoea. For progressive disease at liver previous regimen was replaced with mFOLFOX-6 plus bevacizumab. After 6-months therapy a partial response was achieved and maintenance therapy with bevacizumab alone continued for further 8 months. Treatment was interrupted because patient underwent resection of the femoral artery plus femoro-femoral bypass. Restaging of the disease by CT scan showed a new lesion (diameter: 18 mm) in the segment VIII of the liver, treated with stereotactic radiotherapy (total dose: 45 Gy). When further disease progression occurred at liver, patient was offered the inclusion in the experimental protocol with high-dose rabeprazole plus mCAP. Having signed the informed consent, he started the combination regimen on November 2014. After a 6-months treatment, the CT scan confirmed a stable disease. Toxicity was mild only consisting of G1 diarrhoea. The duration of OS from the first diagnosis of metastatic disease to the last observation was 55 months.

3.3. Case report 3

A 68-year-old male was diagnosed with colic adenocarcinoma (AJCC 2010 classification: stage IIB, pT4 pN0 G2) after having undergone right hemicolectomy in January 2011. Adjuvant oxaliplatin-based chemotherapy was delivered after surgery. On November 2012 a total body CT scan revealed relapse of disease at pelvis and lungs. A K-RAS mutation (codon 12) was identified in the primary tumour, thus the patient underwent first-line chemotherapy with mFOLFIRI-bevacizumab from January to July 2013. Because a partial response was achieved, a maintenance therapy with bevacizumab alone was carried on for an additional year. After a CT scan had revealed disease progression at lung, liver and peritoneum, the patient was proposed to entry in the experimental protocol with high-dose rabeprazole plus mCAP. After three months of therapy a CT scan showed marked regression of lung metastases and partial response of the abdominal disease. The patient kept treatment on for 13 months without signs of progressive disease, only suffering from G1 HFS. For the appearance of symptoms and signs of bowel occlusion, patient underwent rectal resection for recurrent adenocarcinoma, on October 2015. Postoperative CT scan also revealed liver disease progression, therefore patient was candidate to a treatment with regorafenib. The duration of OS from the first diagnosis of metastatic disease to the last observation was 36 months.

4. Discussion

Acidosis of the tumour microenvironment is a key factor for the development of multidrug-resistance and can promote tumour invasion through remodelling of the extracellular matrix [1]. Several preclinical and clinical studies have shown that PPIs can modulate the tumour acidification and restore the sensitivity to chemotherapy in drug-resistant cancer cells [4,6] (Table 1). Moreover, it has been reported that to gain anti-tumour effects, they need to be delivered discontinuously and at high dosages because acidic microenvironment is necessary for their transformation into active molecules [5]. Rabeprazole, which displayed a preeminent non-enzymatic metabolism, has both low potential for drug interactions and a pharmacokinetics that is rather independent from inter-individual variations linked to polymorphisms of CYP2C19

Table 1
Preclinical and clinical studies investigating high-dose PPIs in anticancer therapy.

Trial code/Ref.	Study design	Tumour type	Patients (*N*)	Chemotherapy	Proton pump inhibitors
Ferrari et al., 2013 [7]	Phase II	Osteosarcoma	98	Metrotrexate (12 mg/m^2 iv) Cisplatin (120 mg/m^2 iv) Doxorubicin (75 mg/m^2 iv)	Esomeprazole (60 mg/day p.o.) in two days prior to chemotherapy
Brana et al., 2014 [8]	Phase I	Solid tumours	24	Doxorubicin (60 mg/m^2 iv on d1, every 3 weeks)	Escalating doses of pantoprazole (80,160, 240 and 360 mg iv) prior to chemotherapy
Wang et al., 2015 [9]	R Phase II	Breast cancer	94	Docetaxel (75 mg/m^2 iv on d1) followed by cisplatin (75 mg/m^2 iv on d4), every 21 days	Weekly intermittent (3 days on, 4 days off) esomeprazole (80 mg p.o. bid vs. 100 mg p.o. bid) beginning on d1, maintained up to maximum 66 weeks
NCT02595372	Phase II	TNBC		Anthracycline and taxane containing chemotherapy	Omeprazole (80 mg p.o. bid) beginning 4–7 days prior to chemotherapy and continuing until surgery
NCT01748500	Phase II	CRPC		Docetaxel with prednisone	Pantoprazole (240 mg iv)

TNBC: triple negative breast cancer; CRPC: castration refractory prostate cancer; R: randomized.

and CYP3A4. On the basis of this rationale an experimental protocol has been set up. In this phase II study about 60 consecutive patients are randomly assigned 1:1 to mCAP with or without high-dose rabeprazole [14]. In order to detect possible interactions between rabeprazole and capecitabine, the evaluation of capecitabine pharmacokinetics will also be provided. Indeed, the knowledge of pharmacokinetics parameters of MCT is thought to be fundamental for the development of better computational model for future clinical studies [15].

Here we have reported 3 cases of patients treated with the combination of high-dose rabeprazole and mCAP for metastatic colorectal cancer, refractory to standard chemotherapy and target therapy. One out 3 patients showed a partial response, the remainders stable disease; PFS was 19, 7 and 13 months in case 1, 2 and 3 respectively. This was a remarkable clinical outcome if we considered that far lower PFS values are reported in clinical trial including comparable patients' setting [16,17]. Another interesting remark in such reported cases was the good tolerability of the combination, which is a fundamental requisite for putative palliative regimens.

In conclusion, despite the failure of previous standard regimens for colorectal cancer, a prolonged PFS was shown in these patients treated with the unconventional association of high-dose PPIs and mCAP.

Conflict of interest
None declared.

References

[1] Fais S, Venturi G, Gatenby B. Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. Cancer and Metastasis Reviews 2014;33:1095–108.

[2] Sennoune SR, Luo D, Martínez-Zaguilán R. Plasmalemmal vacuolar-type H+-ATPase in cancer biology. Cell Biochemistry and Biophysics 2004;40:185–206.

[3] Torigoe T, Izumi H, Ishiguchi H, et al. Enhanced expression of the human vacuolar H+-ATPase c subunit gene (ATP6L) in response to anticancer agents. Journal of Biological Chemistry 2002;277:36534–43.

[4] Luciani F, Spada M, De Milito A, et al. Effect of proton pump inhibitor pretreatment on resistance of solid tumors to cytotoxic drugs. Journal of the National Cancer Institute 2004;96:1702–13.

[5] De Milito A, Canese R, Marino ML, et al. pH-dependent antitumor activity of proton pump inhibitors against human melanoma is mediated by inhibition of tumor acidity. International Journal of Cancer 2010;127:207–19.

[6] Spugnini EP, Baldi A, Buglioni S, et al. Lansoprazole as a rescue agent in chemoresistant tumors: a phase I/II study in companion animals with spontaneously occurring tumors. Journal of Translational Medicine 2011;9:221.

[7] Ferrari S, Perut F, Fagioli F, et al. Proton pump inhibitor chemosensitization in human osteosarcoma: from the bench to the patients' bed. Journal of Translational Medicine 2013;11:268.

[8] Brana I, Ocana A, Chen EX, et al. A phase I trial of pantoprazole in combination with doxorubicin in patients with advanced solid tumors: evaluation of pharmacokinetics of both drugs and tissue penetration of doxorubicin. Investigational New Drugs 2014;32:1269–77.

[9] Wang BY, Zhang J, Wang JL, et al. Intermittent high dose proton pump inhibitor enhances the antitumor effects of chemotherapy in metastatic breast cancer. Journal of Experimental and Clinical Cancer Research 2015;34:85.

[10] Browder T, Butterfield CE, Kräling BM, et al. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Research 2000;60:1878–86.

[11] Romiti A, Cox MC, Sarcina I, et al. Metronomic chemotherapy for cancer treatment: a decade of clinical studies. Cancer Chemotherapy and Pharmacology 2013;72:13–33.

[12] Roberto M, Romiti A, Onesti CE, et al. A metronomic schedule as salvage chemotherapy for upper gastrointestinal tract cancer. Anti-Cancer Drugs 2016;27:106–11.

[13] Romiti A, Onesti CE, Roberto M, et al. Continuous, low-dose capecitabine for patients with recurrent colorectal cancer. Medical Oncology 2015;32:54.

[14] Marchetti P, Milano A, D'Antonio C, et al. Association between proton pump inhibitors and metronomic capecitabine as salvage treatment for patients with advanced gastrointestinal tumors: a randomized phase II trial. Clinical Colorectal Cancer 2016, http://dx.doi.org/10.1016/j.clcc.2016.06.005.

[15] Bocci G1, Kerbel RS. Pharmacokinetics of metronomic chemotherapy: a neglected but crucial aspect. Nature Reviews Clinical Oncology 2016, http://dx.doi.org/10.1038/nrclinonc.2016.64.

[16] Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303–12.

[17] Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncology 2015;16:619–29.