Radiotherapy and Oncology 131 (2019) 240–241

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Letter to the Editor

Severe acute radiation-induced enterocolitis after combined palbociclib and palliative radiotherapy treatment

Dear Editor,

We read with great interest the article by Hans et al., titled 'Preliminary results of the association of palbociclib and radiotherapy in metastatic breast cancer patients' [1]. This is the only published data on tolerance of combined palbociclib and radiotherapy (Palbo-RT) treatment, which reported no instances of increased toxicity including gastrointestinal acute radiation syndrome (GI-ARS) [1].

Palbociclib is the standard treatment for hormone-receptor–positive advanced breast cancer [2]. As a selective cyclin-dependent kinases 4/6 (CDK4/6) inhibitor, palbociclib controls G1/S cell cycle checkpoint, which may be a promising approach for ameliorating GI-ARS [3]. However, we experienced a case of severe acute radiation-induced enterocolitis after Palbo-RT. Here, we report the case of a 58-year-old female who underwent Palbo-RT for bone metastases resulting from breast cancer.

She had a medical history of asthma but not of digestive tract diseases. She received total mastectomy for left breast cancer, left axillary lymph node dissection and partial mastectomy for right breast cancer in September 2013. Subsequently, she received chemotherapy: four cycles of 5-fluorouracil, 500 mg/m^2; epirubicin, 75 mg/m^2 and cyclophosphamide, 500 mg/m^2, followed by four cycles of docetaxel, 75 mg/m^2. Next, she received endocrine therapy with tamoxifen (20 mg, daily) and radiotherapy delivered to the left chest wall, left supraclavicular lymph nodal area and right breast (50 Gy in 25 fractions). She presented with multiple bone metastases and started palbociclib (100 mg/day, orally, 3 weeks, followed by 1 week off) and fulvestrant (500 mg, intramuscularly, every 14 days for the first three injections and then

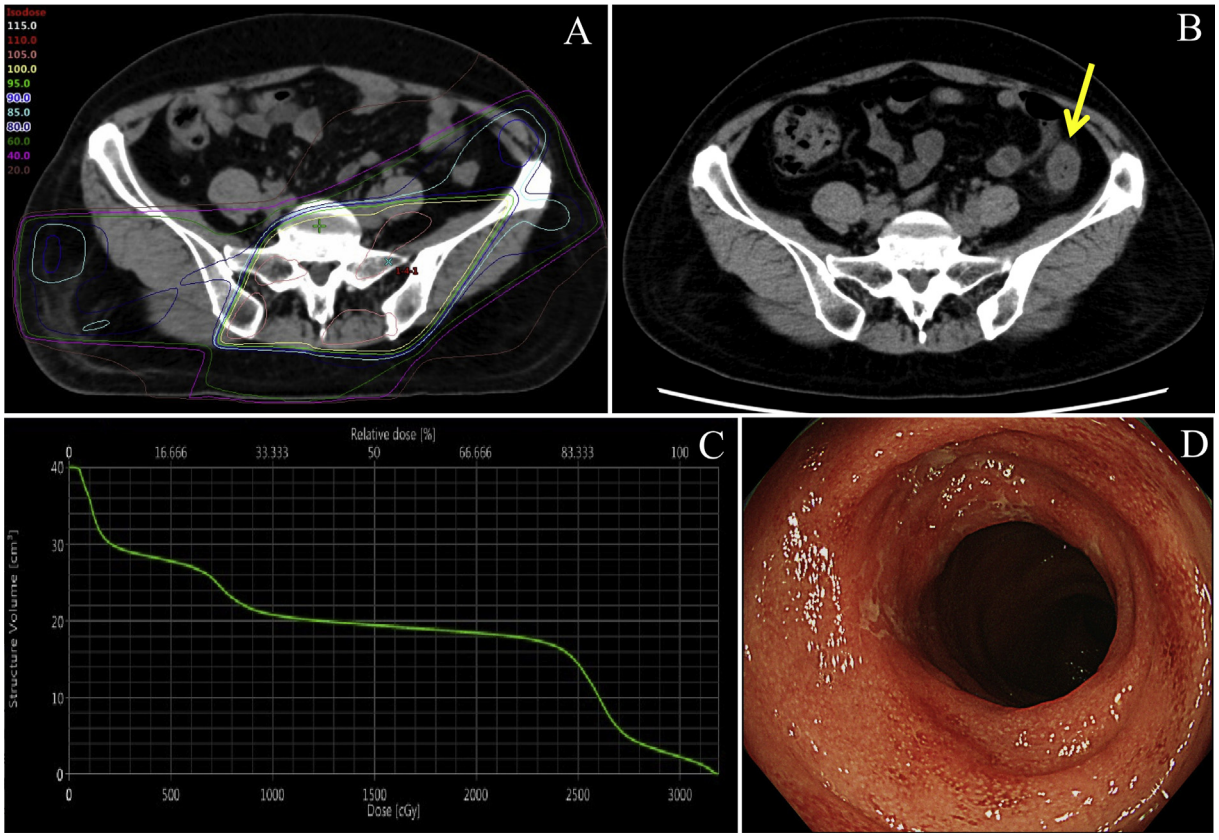

Fig. 1. (A) Radiotherapy to sclerotic bone metastases at the left iliac bone and first sacral vertebrae and dose distribution. (B) Thickening of the descending colon wall (arrow). (C) Dose–volume histogram depicting the dosimetric parameter analysed at the descending colon. (D) An erosion and angiogenesis in the mucosa of the descending colon.

https://doi.org/10.1016/j.radonc.2018.09.020

every 28 days) in April 2018. She experienced grade 1 diarrhoea during treatment with palbociclib and fulvestrant. She gradually developed severe lumbar pain and a computed tomography (CT) scan revealed sclerotic bone metastases at the left iliac bone and first sacral vertebrae. She underwent Palbo-RT in July 2018. We administered conformal radiotherapy of 30 Gy in 10 fractions, over 2 weeks. She experienced grade 1 diarrhoea during treatment with Palbo-RT. Three days after radiotherapy completion, she experienced left abdominal pain, bloating and bloody diarrhoea and was diagnosed with grade 3 colitis (CTCTE v4.0). A CT scan revealed descending colon wall thickening corresponding to the irradiation field (Fig. 1A, 1B). Within the descending colon, the max dose was 31.9 Gy, with 21 mL receiving 10 Gy or higher, and 18 mL receiving 20 Gy or higher (Fig. 1C). Colonoscopy revealed erosion and angiectasis of the descending colon (Fig. 1D); therefore, acute radiation-induced enterocolitis was diagnosed. Following 3 weeks of conservative treatment, her symptoms abated.

The normal bowel radiation tolerance dose is approximately 50 Gy in 25 fractions [4]. Biologically, 30 Gy in 10 fractions is well below the tolerance dose. For patients who receive 30 Gy radiotherapy in 10 fractions for bone metastases, the incidence of grade 1/2 diarrhoea is 7.1%, and of grade 3/4 is 0% [5]. For patients who receive palbociclib, the incidence of grade 1/2 diarrhoea is 19.1%, and of grade 3/4 is 0% [2]. Considering these results, palliative radiotherapy or palbociclib alone is unlikely to cause severe GI-ARS.

No previous studies have reported severe toxicities of Palbo-RT, whereas serious toxicity has been observed in palliative radiotherapy followed by antiangiogenic therapy. A German case series reported that a the patient who underwent palliative radiotherapy alone (28 Gy in 7 fractions) for a right ileum metastasis from renal cell cancer 4 months before starting bevacizumab (10 mg/kg every other week) experienced a caecal perforation within the radiation field and died [6].

Treatment with palbociclib before a single dose of irradiation reportedly protects mice from GI-ARS. Conversely, treatment with palbociclib before and during 5 daily fractions of irradiation exacerbates GI-ARS in mice [7]. Thus, combining palbociclib with fractionated radiotherapy may exacerbate acute gastrointestinal toxicity, as with our case.

This case provides evidence of normal tissue over-sensitisation secondary to palbociclib administration. Additional studies on combined CDK4/6 inhibitor and radiotherapy are needed to examine the efficacy and toxicity of combined Palbo-RT treatment.

Competing interests

The authors declare that they have no competing interests.

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Received 8 September 2018
Received in revised form 20 September 2018
Accepted 26 September 2018

Available online 15 October 2018