

LETTER TO THE EDITOR



The CDK 4/6 inhibitor ribociclib has activity in the treatment of inoperable desmoid tumor. A case report

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Introduction

Desmoid tumors (DT) are nonmalignant mesenchymal neoplasms with a high recurrence rate. Tumors concentrate into the small bowel mesentery and the abdominal wall when associated with familial adenomatous polyposis (FAP) [1]. FAP patients are managed with prophylactic colon surgery to prevent the development of colorectal cancer from premalignant polyps. For these patients, DTs are an important cause of mortality accounting for approximately 10% of death causes [2].

The optimal combination and sequence of different treatment strategies for DTs including surgery, radiotherapy (RT), variable medical therapies and watchful waiting remains unsolved [3,4]. Especially patients with progressive multiple and/or intra-abdominal DTs may benefit from systemic treatment. Medical therapy includes hormonal therapy, nonsteroidal anti-inflammatory drugs, tyrosine kinase inhibitors, and chemotherapy.

The pathophysiology of DTs involve characteristic β -catenin accumulation in tumor cells. The abundant β -catenin in the nucleus acts as a co-regulator for transcription factors controlling target genes such as cyclin D1 *CCND1*. Cyclin D1 in complex with cyclin-dependent kinases (cdk) 4 and 6 convey cell-cycle progression from G1 to S phase. Uncontrolled proliferation leads to tumorigenesis. Palbociclib, ribociclib, and abemaciclib are European Medicines Agency and U.S. Food and Drug Administration approved cdk 4/6 inhibitors for advanced breast cancer used in combination with hormonal therapy [5]. In phase-II study of palbociclib in well differentiated or dedifferentiated liposarcoma, the median progression free survival (PFS) was 17.9 weeks with one complete response noted [6].

The effect of systemic treatments in DTs is inconsistent, calling for novel approaches. We report here a prolonged disease stabilization with ribociclib combined with goserelin and letrozole in a patient with multiple aggressive DTs resistant to endocrine treatment alone.

Case report

A 19-year-old otherwise healthy female was diagnosed with multifocal DTs. She had a familial history of FAP and a

colectomy was performed previously. During the long treatment of this patient, management guidelines of DTs have changed toward a more conservative approach. In this patient, six DTs were operated in eight operations, one recurrent tumor was resected six times. Due to rapid growth, three DTs were treated with four separate RT courses and one tumor was irradiated twice. Fractionation schemes were 50 Gy, 60 Gy, 40 Gy and 60 Gy, all in 2 Gy fractions. The patient was treated with tamoxifen, oral vinorelbine, pegylated liposomal doxorubicin, toremifene, toremifene combined with goserelin, and letrozole combined with goserelin. The DTs did not respond to cytotoxic drugs nor tamoxifen. Partial response (toremifene) or prolonged stable disease was achieved by the other endocrine treatments (Supplementary Table 1).

Upon progression during goserelin and letrozole therapy in January 2017 ribociclib 600 mg was added. During this treatment, pain was relieved and the total dose of opioids was diminished. The best response according to World Health Organization (WHO) criteria was stable disease with maximal size reduction of 18% in the sum of the product of bi-dimensional measurements (Figure 1). WHO criteria were used instead of RECIST 1.1. criteria due to the irregular tumor shape of most lesions. Ribociclib caused grade 1 fatigue, a tickling sensation in the tumors, grade 1 oral mucositis, acne-like rash in the neck, and vesicular hand rash. Due to grade 4 neutropenia, the dose was reduced to 400 mg and then further to 200 mg. In October, grade 4 neutropenia recurred, the pain was increased and one lesion enlarged significantly, and ribociclib was discontinued though formal criteria for progressive disease were not reached. In November, a growing pleural tumor was irradiated with 30 Gy in 3 Gy fractions.

In December 2017, blood tests revealed deep leucopenia $0.8 \times 10^9/l$ and trombocytopenia $64 \times 10^9/l$. A bone marrow aspirate revealed promyelocytic leukemia. Fluorescent *in situ* hybridization confirmed the diagnostic PML-RARA fusion gene. At the time of writing this report (October 2018), maintenance leukemia treatment was finished with morphological

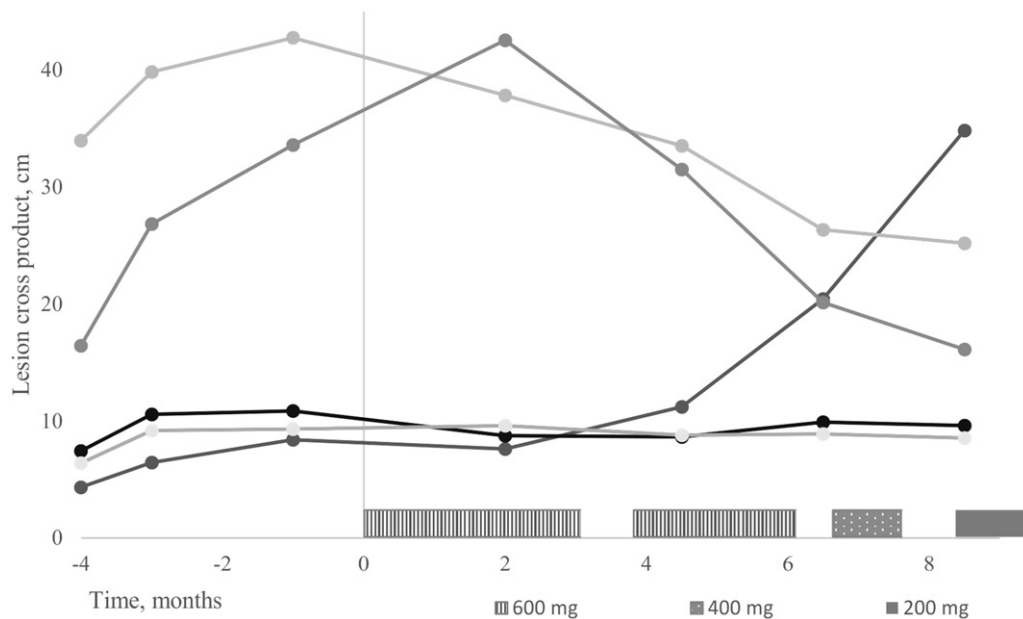


Figure 1. Ribociclib dose and desmoid tumor perpendicular diameters according to WHO criteria before and after the initiation of medication.

and molecular remission in the bone marrow. The DTs continued to grow slowly except for earlier irradiated tumors which were shrinking. Fulvestrant was initiated.

A radiologist (A.B.) with oncologist (K.S.) assessed the responses according to WHO and RECIST 1.1 criteria [7]. Non-irradiated DTs and irradiated tumors progressing after radiotherapy were considered evaluable. The patient gave informed consent for the experimental therapy with ribociclib and publication of this report.

Discussion

We report here a patient with multiple DTs not amenable to surgery treated with ribociclib combined with goserelin and letrozole. The therapy continued for 9 months with stable disease, decrease in size of several tumor lesions and symptomatic relief. To our knowledge, this is the first report of ribociclib therapy for DTs.

Several facts indicate that sex hormones influence the growth of DTs. The incidence of DTs is higher in women at childbearing age. Pregnancy and sex steroids may promote the development of DTs [8]. Estrogen receptor (ER) β is positive in up to 100% of DTs; however, the expression has not been associated with treatment response [9,10]. Tamoxifen is the most commonly used selective estrogen-receptor modulator and toremifene has also shown activity as first- and second-line endocrine therapy of DTs [11,12]. A systematic review of hormonal therapy reported a response rate (RR) of 51% at a median treatment duration of 9 months. The review was based on case reports and small series and therefore publication bias cannot be excluded [13]. In a prospective phase-II study of 59 patients, the Children's Oncology Group only 8% responded and 36% were progression free at 2 years [14]. Goserelin and aromatase inhibitors have reported to have activity in DTs in a few case reports [15–17]. Furthermore, endocrine treatments have a favorable toxicity profile.

In ER-positive breast cancer cyclin D1 protein overexpression has been associated with poor prognosis [18,19]. This may be mediated by the connection of cyclin D1 expression and hormone therapy resistance [20]. Ribociclib is a highly specific cdk 4/6 inhibitor that binds to the complex of cyclin D1 and cdk 4 or 6 and thereby induces cell cycle arrest. Cdk 4/6 inhibitors have exhibited high efficacy in advanced ER positive breast cancer by substantial PFS prolongation [5,21]. In DTs, β -catenin accumulation has been associated with cyclin D1 overexpression [22]. Cyclin D1 expression has varied in different series from 44% to 71% [22–24]. In breast cancer, cdk 4/6 inhibitors act synergistically with antiestrogen treatment [5]. Moreover, several lines of evidence indicate estrogen dependence of DTs. These considerations motivated the experimental use of ribociclib combined with endocrine treatment in this treatment resistant DT patient.

Ribociclib combined with goserelin and letrozole led to symptomatic relief and stabilization of multiple DTs. Although the patient experienced a brief objective response previously on toremifene, none of the previous six systemic treatments stabilized the disease for as long as 10 months. The disease had previously progressed during treatment with goserelin and letrozole, indicating that addition of ribociclib was responsive for pain relief and a prolonged disease stabilization. Although spontaneous regression cannot be excluded, this remains unlikely as none of the patient's multiple DTs had previously spontaneously regressed. Moreover, only lesions progressing at start of treatment were included in the response evaluation. Bi-dimensional measurements of five evaluable lesions indicated mixed response, with the largest decreasing in size and others remaining stable. Different clonal origin of the tumors may be responsible for the heterogeneous treatment response. Measurement of the DT size even from high-quality MRI images is often difficult due to the irregular shapes of the tumors and their poorly circumscribed border. For this reason, we chose to use WHO response criteria instead of the more commonly used RECIST

criteria. Ribociclib dose had to be reduced repeatedly and the treatment was eventually discontinued due to cytopenia and fatigue, which were interpreted as side effects of the drug. The most common adverse events of cdk 4/6 inhibitors are hematologic and require interruption and dose modifications [25]. In this patient, leukopenia and thrombocytopenia increased soon after the treatment discontinuation and the patient was diagnosed with acute promyelocytic leukemia (APL). In retrospect, APL may have contributed to the increasing myelosuppression during ribociclib treatment even earlier. APL occurring after cancer treatments is a rare event representing approximately 11% of new APL patients [26]. We have found no evidence indicating that ALP might be complication of ribociclib or any other cdk 4/6 inhibitor [25,27]. Therapy-related APL may be associated with previous radiation or cytotoxic therapy, particularly topoisomerase II inhibitors. The patient had received three courses of liposomal doxorubicin and received several radiotherapies. Of these radiotherapy is possibly the primary contributing factor to the development of leukemia. Therapy-related APL is managed like de novo leukemia and the prognosis is fairly good [26]. Especially when treating young DT patients with cytotoxic agents or radiotherapy the risk for a secondary cancer should be taken into account.

Conclusion

In conclusion, ribociclib in combination with endocrine treatment may have activity in DTs. Our experience prompts for further investigation of ribociclib in DTs.

Disclosure of interest

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