CASE REPORT

Successful treatment by prednisolone for interstitial pneumonia associated with anagrelide in a patient with essential thrombocythemia

Satoshi Tamaru^{1,2} · Yasutaka Tono¹ · Takeshi Matsumoto^{1,3} · Hiroyasu Oda¹ · Yuka Sugimoto¹ · Toshiro Mizuno¹ · Naoyuki Katayama¹ · Masakatsu Nishikawa^{1,2}

Received: 7 July 2016 / Accepted: 20 September 2016 / Published online: 27 September 2016
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Abstract Anagrelide is a cytoreductive agent for essential thrombocythemia and its common side effects are anemia, headache, palpitation, diarrhea, and fluid retention. However, severe pulmonary adverse effects are rare. A 66-year-old Japanese man with essential thrombocythemia presented with hemoptysis 2 months after starting anagrelide treatment. Interstitial pneumonia was diagnosed based on physical and radiographic findings. Discontinuation of anagrelide and institution of corticosteroids resulted in the improvement of interstitial pneumonia. Severe lung injury associated with anagrelide is a rare but an important adverse event that must be addressed when treating interstitial pneumonia.

Keywords Anagrelide · Essential thrombocythemia · Interstitial pneumonia · Hypersensitivity pneumonitis · Corticosteroids

Introduction

Anagrelide (Shire PLC. AGRYLIN[®]) is one of the cytoreductive agents for essential thrombocythemia (ET). Study SPD422-308 (NCT01214915), which was sponsored by Shire PLC, was started for high-risk Japanese patients

with ET who were intolerant or refractory to their first-line cytoreductive therapies to evaluate the efficacy, safety, and tolerability of anagrelide as a second-line therapy [1]. One of the participants from our hospital had interstitial pneumonia associated with anagrelide.

In this study, we reported the case of a Japanese male with interstitial pneumonia associated with anagrelide and successfully treated with prednisolone.

Case

A 66-year-old Japanese male was diagnosed with *JAK2* V617F-mutated essential thrombocythemia in September 2009. He was administered with hydroxyurea, aspirin and rebamipide from that point on, but hydroxyurea was stopped because of alopecia. The patient provided informed consent and subscribed to participate in the SPD422-308 study. He was initiated on anagrelide at 1.0 mg/day on November 2010. Two months later, the patient visited our hospital because of hemoptysis, which had occurred for 4 days. Chest X-rays showed bilateral infiltration in the lower lung field. A computed tomography scan (CT) showed bilateral lower lobe dominant ground glass opacity. We diagnosed interstitial pneumonia from these findings and the patient was hospitalized. Laboratory findings are shown in Table 1. Leukocytosis, eosinophilia and elevation of LDH, C-reactive protein (CRP), and KL-6 were observed. Treatment for the patient with prednisolone was started. Azithromycin and levofloxacin were started empirically for atypical pneumonia. Administration of anagrelide was stopped the same day. The result of blood culture was negative and sputum culture revealed no evidence of any specific infection. On day seven, the hemoptysis disappeared and

✉ Satoshi Tamaru
tamaru3@clin.medic.mie-u.ac.jp

¹ Department of Hematology and Oncology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu City, Mie 514-8507, Japan

² Clinical Research Support Center, Mie University Hospital, 2-174 Edobashi, Tsu City, Mie 514-8507, Japan

³ Division of Blood Transfusion Service, Mie University Hospital, 2-174 Edobashi, Tsu City, Mie 514-8507, Japan

Table 1 Laboratory findings on admission

CBC		Blood chemistry		Serological exam	
<u>WBC</u>	<u>20510/μl</u>	TP	7.3 g/dl	<u>CRP</u>	<u>4.93 mg/dl</u>
Hb	12.6 g/dl	Alb	4.0 g/dl	<u>KL-6</u>	<u>585 U/ml</u>
Ht	37.2 %	BUN	15 mg/dl		
MCV	103.6 fl	Cre	1.01 mg/dl		
MCH	35.1 pg	Na	141 mEq/l		
MCHC	33.9 g/dl	K	4.8 mEq/l		
<u>PLT</u>	<u>$75.4 \times 10^4/\mu$l</u>	Cl	103 mEq/l		
<u>Neu</u>	<u>86.5 %</u>	Ca	9.3 mEq/l		
Lym	4.5 %	<u>LDH</u>	<u>325 IU/l</u>		
Mo	2.5 %	AST	20 IU/l		
<u>Eo</u>	<u>5.5 %</u>	ALT	11 IU/l		
Baso	1.0 %	T-Bil	0.9 mg/dl		

Underlined values indicate values above the normal range

interstitial pneumonia improved. On day 24, interstitial pneumonia improved, and the patient was discharged (Fig. 1). We assessed the hemoptysis and interstitial pneumonia as mild and moderate in intensity, respectively, and considered both events related to anagrelide. Prednisolone was reduced slowly and hydroxyurea was re-administrated for ET. Four months later, CT showed ground glass opacity was improved and fibrosis just under the pleura was occurred. He had no clinical symptom of deterioration of interstitial pneumonia, so prednisolone was stopped. Until now, interstitial pneumonia had not been worsen and he had no obvious immunocompetence.

Discussion

Common side effects of anagrelide are anemia, headache, palpitation, diarrhea, fluid retention, but severe pulmonary adverse effects are rare. A major anagrelide study (PT-1 [2], ANAHYDRET [3]) reported no severe lung injury. We searched PubMed using the keywords “anagrelide” and “pneumonia”, and found only two reports [4, 5]. The summary of these reports with our case are shown in Table 2 [4, 5]. The type of lung injury in all cases was hypersensitivity pneumonitis. Time from starting anagrelide to development of severe lung injury was within 8 weeks in two cases. Our case is an ex-smoker having quit 20 years previously. He had no rheumatic diseases such as vasculitis. All cases were treated with discontinuation of anagrelide and institution of corticosteroids, and recovered within 30 days. A rechallenge using anagrelide was not done in all cases.

There are many reports that show several drugs, especially anticancer drugs, cause interstitial pneumonia and sometimes result in poor outcomes. As hypersensitivity pneumonitis, which is in large part responsible for the immune system, is a type of interstitial pneumonia associated with anagrelide, treatment with corticosteroids and immunosuppressant agents are considered effective. In fact, these drugs were very effective and patients with interstitial pneumonia recovered within about 3 weeks in all cases.

Fig. 1 Clinical course

Table 2 Summary of severe lung injury associated with anagrelide

Case	Age	Disease	Present illness	Type of IP	Time from starting anagrelide to onset of IP	Risk factor	Treatment for IP	Recovery time	Rechallenge	Next treatment for disease	Authors
1	60	CML	Type 2 diabetes mellitus, essential hypertension, chronic renal insufficiency, and gout	Hypersensitivity pneumonitis	6 weeks	Non-smoker	Discontinuation of anagrelide and hydroxyurea Methylprednisolone iv	21 days	No	Imatinib	Raghavan Met al.
2	45	ET	None	Hypersensitivity pneumonitis	3.5 years	Streptococcus pneumoniae Ex-smoker of 3 years	Discontinuation of anagrelide Prednisolone 60 mg od	10 days	No	Hydroxyurea	Spencer EM et al.
3	66	ET	None	Hypersensitivity pneumonitis	8 weeks	Ex-smoker of 20 years	Discontinuation of anagrelide Prednisolone 60 mg od	24 days	No	Hydroxyurea	Tamaru S et al.

IP Interstitial pneumonia, *CML* chronic myeloid leukemia, *ET* essential thrombocythemia

In conclusion, severe lung injury associated with anagrelide is rare, but we have to consider the possibility of such an occurrence.

Acknowledgments We thank Dr. Kakuya Kitagawa, radiologist in Mie University Hospital, for CT interpretation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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