Response to Chemotherapy, Reexposure to Crizotinib and Treatment with a Novel ALK Inhibitor in a Patient with Acquired Crizotinib Resistance

Kathrin Schrödl  Christoph von Schilling  Amanda Tufman  Rudolf Maria Huber  Fernando Gamarra

Department of Internal Medicine V, University of Munich, Comprehensive Pneumology Center, Member of the German Center for Lung Research, Munich, Germany

Established Facts
- Crizotinib treatment of ALK-positive patients with non-small cell lung cancer (NSCLC) leads to a median progression-free survival of 9.7 months.

Novel Insights
- Crizotinib retreatment of ALK-positive patients with secondary resistance to crizotinib after a drug holiday and conventional chemotherapy improves crizotinib sensitivity.
- A good response to the new ALK inhibitor LDK 378 was obtained in a case of NSCLC after two treatments with crizotinib.

Key Words
ALK inhibitor · Crizotinib · Crizotinib resistance · LDK 378 · Lung cancer

Abstract
The treatment of advanced non-small cell lung cancer (NSCLC) has dramatically changed over the last decade. It has developed from an unspecific approach based on platinum doublet chemotherapy to a personalized, molecularly targeted therapy. Crizotinib is a new tyrosine kinase inhibitor approved for the treatment of NSCLC with gene rearrangement of EML4 and ALK. Despite good initial responses, patients treated with crizotinib relapse after an average of 10 months. In this case report, we present a patient with acquired crizotinib resistance whose adenocarcinoma responded to a second course of crizotinib following a drug holiday and chemotherapy with pemetrexed. This is the second case report to suggest that retreatment with crizotinib is an option for patients with initial benefit from ALK inhibition.

Introduction
The treatment of advanced non-small cell lung cancer (NSCLC) has dramatically changed over the last decade and has developed from an unspecific approach based on platinum doublet chemotherapy to a personalized, mo-
lecularly targeted therapy [1–4]. Crizotinib is a new tyro-
sine kinase inhibitor (TKI) approved for the treatment of
NSCLC with gene rearrangement of EML4 and ALK [5].
Treatment with new TKIs, e.g. crizotinib, is often limited
by the development of secondary crizotinib resistance,
which ultimately limits the life expectancy of patients [4].
Therefore, in case of acquired crizotinib resistance, new
therapeutic strategies are needed. The following case re-
port describes successful management of crizotinib resis-
tance.

Case Report

A 70-year-old male patient (white, never-smoker) was diag-
nosed with adenocarcinoma [wild-type epidermal growth factor
receptor (EGFR), EML4/ALK translocation positive] of the right
upper lobe of the lung in February 2009.
The patient was initially diagnosed and treated at a com-
nunity hospital and was referred to our department following sec-
ond-line treatment for a second opinion. The stage at first diag-
nosis was cIIIA (cT2cN2cM0) and the patient was enrolled in a
clinical trial and received neoadjuvant chemotherapy with three
cycles of cisplatin and vinorelbine combined with cetuximab at
cycle two and three. PET-CT then showed a partial remission,
and resection was planned. Unfortunately, the thoracotomy re-
vealed inoperable mediastinal pleural infiltration and the proce-
dure was terminated. The patient was then treated with com-
bined radiochemotherapy with 54 Gy at the primary tumor site
as well as two further cycles of cisplatin and vinorelbine. Follow-
ing a 5-month period of progression-free survival, a follow-up
PET-CT showed recurrent tumor at the primary tumor site and
along the right inner thoracic wall. Second-line systemic therapy
with the EGFR-TKI erlotinib was initiated, but the tumor pro-
gressed after 4 months, causing clinically relevant multifocal cu-
taneous metastases, pleural carcinomatosis and total atelectasis
of the right lung. A third-line systemic therapy with pemetrexed
was initiated and the patient was referred to our center. Chemo-
therapy with pemetrexed was administered for two cycles. Prior
to chemotherapy with pemetrexed, the primary tumor occupied
most of the upper lobe with pleural and chest wall infiltration and
obstruction of the intermediate bronchus. In addition, involve-
ment of subcarinal and bilateral axillary lymph nodes was de-
dected. Pemetrexed treatment induced shrinkage of the contra-
lateral lymph nodes; however, no relevant change in the remain-
ing sites involved was noticed. Therefore, a clinically meaningful
response could not be established. Screening for the EML4-ALK
gene rearrangement assessed by ALK FISH break apart test was
positive, and therefore the patient was included in a clinical trial
with crizotinib dosed at 250 mg twice daily. Treatment with
crizotinib led to a partial remission with disappearance of the
cutaneous metastases, better ventilation of the right lung and a
reduction in exertional dyspnea. Following 6 months of crizo-
tinib, the primary tumor showed slight radiographic progres-
sion; however, the patient remained clinically stable on treat-
ment for an additional 3 months. Due to increasing cough and
thoracic pain, crizotinib was then discontinued and the treat-
ment had to be changed to a conventional chemotherapy. Ac-
cording to the clinical data, both pemetrexed and docetaxel have
a similar effect for second-line therapy of NSCLC. We consid-
ered both options, but the patient opted for pemetrexed instead
of docetaxel, because of the more favorable toxicity profile of the
former agent. Accordingly, the patient was treated with four cy-
cles of pemetrexed. This resulted in a partial response and im-
provement in symptoms.

Due to pemetrexed-associated neutropenia, pemetrexed was
then discontinued and the patient was monitored clinically and
radiologically. He remained stable for a period of 8 months before
tumor progression prompted us to retreat with crizotinib.
Retreatment with crizotinib led to a rapid and substantial im-
provement in the quality of life. CT confirmed significant remis-
sion of the intrathoracic tumor burden. Following 9 months of
retreatment with crizotinib, the patient developed brain meta-
stasis. Crizotinib was discontinued and the patient was included in a
study with LDK 378, a novel ALK inhibitor for crizotinib-resistant
ALK-positive NSCLC. At this time, the patient remains under
LDK 378 therapy and is in good general condition. Follow-up CT
scans have shown regression of the intrathoracic tumor masses as
well as the brain metastasis. Thus far, radiation of brain metastasis
has not been performed.

Discussion

EML4-ALK rearrangements result in an abnormal ex-
pression of ALK and subsequent activation of intracellu-
lar signaling pathways in a subset of NSCLC cells. Patients
with ALK-positive tumors respond well to treatment with
ALK inhibitors [4, 6]. Crizotinib is an orally available,
clinically well-tolerated TKI of ALK. Treatment of ALK-
positive NSCLC patients with crizotinib leads to a median
progression-free survival of 9.7 months [4, 7]. Unfortu-
nately, secondary resistance to crizotinib invariably de-
velops, limiting the life expectancy of these patients [7, 8].
Our patient developed secondary crizotinib resistance
with slow progression of his tumor after 9 months of
crizotinib. Previous publications regarding the retreat-
ment of patients with secondary resistance to EGFR-TKIs
suggest that a drug holiday and treatment with a conven-
tional chemotherapeutic may reestablish sensitivity to
TKIs [9, 10]. Although this strategy is well described for
EGFR-TKIs, there is to date only one case report indicat-
ing that crizotinib retreatment of ALK-positive patients
after a drug holiday and chemotherapy improves crizo-
tinib sensitivity [11]. This case report illustrates that pa-
ients with secondary resistance to crizotinib can benefit
from a range of therapeutic strategies, including drug hol-
day, chemotherapy, retreatment with crizotinib and
treatment with new ALK inhibitors in clinical trials. This
is the first case report describing a good response to the
new ALK inhibitor LDK 378 after two treatments with crizotinib. These observations illustrate the therapeutic options for crizotinib-resistant EML4-ALK-positive patients.

Financial Disclosure and Conflicts of Interest

All authors declare no conflict of interest.

References


