Lung Cancer 108 (2017) 217–221

Contents lists available at ScienceDirect

Lung Cancer

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

Development of psoriatic arthritis during nivolumab therapy for metastatic non-small cell lung cancer, clinical outcome analysis and review of the literature

Juan Ruiz-Bañobre[a,*], Eva Pérez-Pampín[b,d], Jorge García-González[a], Antonio Gómez-Caamaño[c], Francisco Javier Barón-Duarte[a], Rafael López-López[a], Francisca Vázquez-Rivera[a]

[a] Servizo de Oncoloxía Médica & Grupo de Oncoloxía Médica Traslacional, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complexo Hospitalario Universitario de Santiago de Compostela, Spain
[b] Servizo de Reumatoloxía, Complexo Hospitalario Universitario de Santiago de Compostela, Spain
[c] Servizo de Oncoloxía Radioterápica, Complexo Hospitalario Universitario de Santiago de Compostela, Spain
[d] Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complexo Hospitalario Universitario de Santiago de Compostela, Spain

ARTICLE INFO

Keywords:
Immune-related adverse event
Immunotherapy
Nivolumab
Non-small cell lung cancer
Psoriatic arthritis
Programmed cell death-1

ABSTRACT

Lung cancer is the leading cause of cancer-related death worldwide. The most common type, non-small cell lung cancer (NSCLC), is further divided into two main types, squamous cell and non-squamous cell (which includes adenocarcinoma). Nivolumab, a fully human IgG4 programmed death-1 immune checkpoint inhibitor antibody, has shown not only an overall survival advantage when compared to docetaxel, but also a relatively good side-effect profile among patients with previously treated advanced squamous and non-squamous NSCLC. Psoriatic arthritis (PsA), a heterogeneous chronic inflammatory disease, has a wide clinical spectrum and a variable clinical course that affects mainly musculoskeletal structures, skin and nails. Here we report the second case to the best of our knowledge of PsA development during nivolumab therapy. It is important to note that arthritis activity decreased without nivolumab discontinuation with the use of naproxen and a low dose of corticosteroid. Furthermore, a minimal disease activity was achieved adding methotrexate to the treatment and antitumor therapy efficacy was not influenced (a partial response was documented after eight and 39 cycles of nivolumab). Rheumatic immune-related adverse events management is a challenge and a coordinated multidisciplinary management by medical oncologists, rheumatologists and immunologists will be mandatory in the near future.

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. The most common type of lung cancer, non-small cell lung cancer (NSCLC), is further divided into two main types, squamous cell and non-squamous cell (which includes adenocarcinoma) [2]. Platinum-based chemotherapy, with or without maintenance therapy and subsequently followed by second-line cytotoxic chemotherapy, is a standard treatment for most patients with advanced NSCLC, with a median survival of approximately 1 year [3,4].

During 2015 nivolumab, a fully human IgG4 programmed cell death-1 (PD-1) immune-checkpoint–inhibitor antibody was approved to treat patients with advanced squamous NSCLC whose disease progressed during or after platinum-based chemotherapy. Then, approval expanded the use of nivolumab to also treat patients with non-squamous NSCLC. This was possible taking into account the results of two randomized, open-label, international phase 3 clinical trials, in which nivolumab showed an overall survival (OS) advantage with a favorable side-effect profile when compared to docetaxel in patients diagnosed with squamous (9.2 vs 6.0 months, respectively) and non-squamous NSCLC (12.2 vs 9.4 months, respectively) [5,6]. Also during 2015 pembrolizumab, a humanized monoclonal IgG4 kappa isotype anti-PD-1 antibody was approved to treat patients with advanced or metastatic NSCLC with programmed cell death ligand 1 (PD-L1) expression on at least 1% of tumor cells whose disease progressed during or after platinum-based chemotherapy [7]. Furthermore, during 2016 pembrolizumab approval was expanded to previously untreated advanced NSCLC patients with PD-L1 expression on at least 50% of tumor cells [8]. It was possible based on results of two randomized, controlled clinical trials that demonstrated statistically significant improvements in progression-free survival (PFS) and OS for patients randomized to pembrolizumab compared with chemotherapy [7,8]. It

* Corresponding author at: Servizo de Oncoloxía Médica, Hospital Clínico Universitario de Santiago de Compostela, c/Travesa da Choupana s/n. 15706, Santiago de Compostela, Spain.
E-mail address: jurruba@gmail.com (J. Ruiz-Bañobre).

http://dx.doi.org/10.1016/j.lungcan.2017.04.007
Received 21 July 2016; Received in revised form 1 April 2017; Accepted 12 April 2017

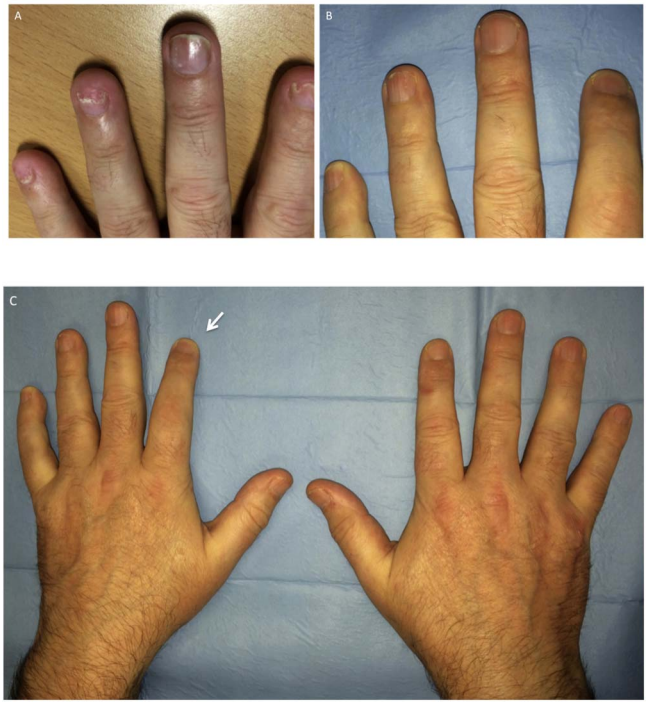

Fig. 1. Psoriatic nail dystrophy before (A) and after (B) methotrexate initiation. Deformation of the 2nd left finger 11 months after psoriatic arthritis diagnosis (C).

opens up a new horizon in which atypical types of tumor responses and a specific toxicity profile generated by nivolumab and other anti-PD-1 antibodies are a challenge to the clinical practice of the medical oncologist [9,10].

2. Case report

A 47-year-old male ex-smoker was referred to our department diagnosed with metastatic NSCLC (adenocarcinoma) with lymph node involvement. He had a history of psoriasis vulgaris with psoriatic nail dystrophy (Fig. 1), which was well-controlled without treatment, but no family history of psoriasis. He also was previously diagnosed with arterial hypertension and paroxysmal atrial fibrillation. Our patient received four cycles of pemetrexed-cisplatin induction treatment (pemetrexed 500 mg/m2 intravenously [IV] and cisplatin 75 mg/m2 IV on day 1 of 21-day cycles) and three cycles of maintenance pemetrexed therapy (pemetrexed 500 mg/m2 IV), but the disease progressed at lymph nodes and lung levels. At this moment, due to the growth of the right lower lobe intra- and peribronchial mass the patient had hoarseness, cough, dyspnea and mild hemoptisis (Fig. 2). To treat this symptomatic lesion the patient received a 8 Gy single fraction radiotherapy and the same day it was initiated as second line therapy nivolumab at 3 mg/kg every two weeks. Two weeks after the second course of nivolumab, previously described symptoms disappeared. After eight cycles of nivolumab, a computed tomography (CT) scan showed a partial response at lung and lymph nodes levels. Until then the adverse events experienced by our patient were asthenia grade 1 after 6 infusions and arthralgia grade 1 after 8 infusions. But after the eleventh cycle of nivolumab, the patient complained of joint pain again, and with the clinical suspicion of inflammatory arthritis, he was referred to the rheumatology department. Physical examination showed synovitis at the right distal interphalangeal joint, left knee and ankle and right and left metatarsophalangeal joints. Besides, the patient had plaque psoriasis with psoriatic nail dystrophy and dactylitis in the second digit of the left hand. 30 mL of serohematic liquid were extracted from the left knee by arthrocentesis without evidence of crystals but with a lot of erythrocytes and polymorphonuclear leukocytes. Antinuclear antibodies, rheumatoid factor (RF) and cyclic citrullinated peptide antibodies were negative. Erythrocyte sedimentation rate and c-reactive protein showed values of 14 mm and 6.15 mg/dL respectively. Serum urate level was normal. Both hands and feet antero-posterior radiographs show only osteopenia in feet (Fig. 3). The patient was diagnosed with psoriatic arthritis (PsA) and a specific treatment was initiated (one intra-articular injection with 40 mg of triamcinolone acetonide, methylprednisolone 4 mg q.d. and naproxen 500 mg b.i.d.), achieving a partial response. After sixteen cycles of nivolumab, a CT scan showed a greater reduction in tumor disease in relation to the previous assessment (Fig. 2). Looking for a minimal disease activity, sulfasalazine (500 mg b.i.d.) was added to the anti-rheumatic treatment, but 3 weeks later, the patient decided to suspend this drug due to side effects (headache and intense asthenia). At this moment, given that only active PsA with peripheral arthritis as major domain (DAS28 of 5.21) was worsening the patient's quality of life, methotrexate 10 mg per week was initiated with the concomitant administration of folate 5 mg per week (to minimize toxicity). Nine weeks later, a low disease activity was achieved (DAS28 of 2.95) with a great improvement in the quality of life [the only symptom being ankylosis of the 2nd left proximal and distal interphalangeal joints (Fig. 1)]. Thanks to the early initiation of the anti-rheumatic treatment, the radiographic image only reveals the decrease in the interarticular space of these interphalangeal joints (Fig. 3). At present, the patient continues with nivolumab and anti-rheumatic therapy, mantains a partial tumor response and there have been no new immune-related adverse events.

3. Discussion

PsA is a heterogeneous chronic inflammatory disease with a wide clinical spectrum and a variable clinical course that affects musculoskeletal structures, skin, nails, joints, entheses, synovial sheaths of tendons and the axial skeleton [11]. The prevalence of PsA is around 0.5 − 1% of the general population and up to 30% of all those suffering from psoriasis. Although arthritis can appear prior or simultaneously to cutaneous manifestations in about 15 − 30% of PsA cases, the common scenario is that psoriasis has its onset approximately 10 years before PsA. Despite the fact that there are very few studies dealing with the onset of PsA, it generally occurs in the fourth and fifth decades of life [12]. Patients with PsA can also have ocular and intestinal complications and an increased prevalence of metabolic syndrome and cardiovascular disease [11]. CASPAR classification criteria for PsA includes evidence of psoriasis (current, personal history or familiar history), psoriatic nail dystrophy, negative test for RF, dactylitis and radiological evidence of juxta-articular new bone formation [13].

As an autoimmune disease, different cells of the innate and adaptive immune systems are involved in PsA pathogenesis. In the last years, a critical role of interleukin (IL)-23–IL-17 axis is emerging, and the central role of the T helper (Th) 17 cell is being defined. Increased frequencies of IL-17+ and IL-22+ Th cell have been found in the peripheral blood from patients with PsA. An elevated expression of IL-23p19–IL-23 receptor (R) and IL-17A–IL-17R in psoriatic skin and synovial fluid from these patients is also described. Besides, it is known Th17 cells produce not only IL-17, but also other inflammatory mediators such as IL-22, IL-21 and tumor necrosis factor (TNF), all of them involved in the systemic and articular symptoms of PsA. The results of different clinical trials using antibodies that target IL-17A, IL-17RA, both IL-17A and TNF, the p40 subunit of IL-12 and IL-23 or the p19 subunit of IL-23 support the main contribution of IL-23–IL-17 immune pathway to the pathogenesis of PsA. On the other hand and related to the above described, the role of synovial T cells is also relevant in the pathogenesis of PsA, inducing osteoclastogenesis and bone resorption via receptor activator of nuclear factor kappa-B ligand, that can be triggered by TNF, IL-23 and IL-17 [14].

Although in the literature there are several cases of arthritis in