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# THE KEY ROLE OF THE CLINICAL PHARMACIST IN THE MANAGEMENT OF ANTICANCER THERAPIES: A PILOT STUDY IN THE TREATMENT OF PATIENTS WITH NON-SMALL CELL LUNG CANCER

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**Abstract**

Lung cancer accounts for a quarter of all mortality cases worldwide. To date, numerous efforts have been done to identify the best therapeutic approach, especially in the advanced stage of the disease, and to extend the overall survival of patients. Careful surveillance of patients during therapy is essential in order to identify undesirable effects and to evaluate possible adverse reactions in case of co-administration. This study aims to compare two types of anticancer therapy, immunotherapy and chemotherapy, administered to NSCLC patients in the Medical Oncology Unit of the ARNAS "Di Cristina Benfratelli" Civic Hospital in Palermo (Italy), and to highlight the key role of clinical pharmacist in the management of anticancer therapies, by analysing the side effects in the short-term post-administration and the adverse drug reactions, in particular drug-drug interactions, in case of comorbidities.

**Keywords**: *non-small cell lung cancer; immunotherapy; chemotherapy; clinical pharmacist; adverse drug reactions*

## Introduction

Lung cancer still remains a major health problem worldwide, accounting for one-quarter of all cancer deaths, although the incidence is slowly decreasing thanks to the reduction in tobacco use.[1] According to the Cancer American Society, about 235,760 new lung cancer cases and about 131,880 lung cancer deaths are estimated for 2021, including men and women.[2] There are several risk factors associated with the aetiology of lung cancer; indeed, together with tobacco smoke, still considered the main one, the combustion of biomass, air pollution, occupational exposure to asbestos fibers, human papillomavirus (HPV) infection, genetic predisposition, diet, are some of the factors that contribute to the development of this devastating disease.[3] Currently, two main histological subtypes are known: small cell lung cancer (SCLC) with a rate of incidence approximately of 10-15%, and non-small cell lung cancer (NSCLC) which represents 85% of cases, half of which are diagnosed in advanced stage, already difficult to treat. For several years, the conventional therapy for the treatment of NSCLC was focused on platinum-based chemotherapy, especially cisplatin which was preferred to carboplatin. Moreover, over the past two decades, non-platinum-based chemotherapy, which includes paclitaxel or docetaxel, gemcitabine, vinorelbine or irinotecan, or combination therapy modalities (platinum plus non-platinum), have been positively evaluated for their potential benefit. Particularly, docetaxel is considered the gold-standard for second-line treatment, while gemcitabine in combination with cisplatin is regarded as first-line treatment when platinum-based regimen alone is contraindicated.[4] Since lung cancer is a molecularly heterogeneous disease, knowing its biological characteristics is important to approach the best treatment in order to obtain positive results. Several studies have been focused on the genetic mutations that drive the development and progression of NSCLC, including mutations in epidermal growth factor receptor (EGFR), Kirsten rat sarcoma (KRAS) and translocations in genes encoding for anaplastic lymphoma kinase (ALK). Their detection allowed the use of tyrosine kinase inhibitors (TKIs), including first-generation TKIs (such as gefitinib and erlotinib), second-generation TKIs (such as afatinib), and third-generation TKIs (osimertinib), alone or in combination with the conventional therapy.[5] Although targeted therapy provided a response in 70% of cases, a relapse occurs in most patients after 8-16 months, that together with the development of drug resistance, contributes to poor success of the therapy.[6] Despite numerous efforts in understanding cancer biology and the use of innovative treatments, the five-year survival rate of metastatic NSCLC is still less than 20%,[1] mostly due to the advanced stage of the disease at the time of diagnosis or/and the oncogenic alteration non suitable for the targeted therapy. Therefore, to overcome this weak response to therapy, new and effective approaches are needed to address the advanced stages of cancer. Over the past decade, immunotherapy has changed the therapeutic approach to cancer, being effective in treating several types of tumor, including advanced NSCLC, with minimal, manageable and well-tolerated side effects. At this regard, Immune Checkpoint Inhibitors (ICIs) are widely used in anticancer therapy. In particular, they work blocking the immune checkpoint programmed cell death protein 1 (PD-1) an its ligand (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), thus reprogramming the immune response to tumors. Currently, nivolumab and pembrolizumab (PD-1) and atezolizumab (PD-L1) targeted antibody have been approved in the therapeutic program of metastatic NSCLC in agreement with the "NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) - Non-Small Cell Lung Cancer - Version 2.2019", while ipilimumab is under investigation as CTLA-4 inhibitor.[7] Unfortunately, only 20-30% of patient benefit from the block of PD-1/PD-L1 axis when ICIs are used alone, mainly due to the complex tumor microenvironment (TME) capable of inducing resistance, and to the expression levels of PD-L1.[8] To escape this problem and improve clinical outcomes, a reliable strategy is the combination therapy, known as chemoimmunotherapy, which has already demonstrated preclinical and clinical results, although the mechanism underlying the interaction is still under investigation for a complete understanding. Pembrolizumab with carboplatin and also paclitaxel or nab-paclitaxel, atezolizumab associated with 1) carboplatin/paclitaxel ± the

antiangiogenic drug bevacizumab, 2) pemetrexed and platinum-based chemotherapy are well known combinations.[7]

Nowadays, the clinical pharmacist (CP), as an integral part of the medical team, helps to ensure the best health care, thus playing a relevant role in patient management.[9] In fact, thanks to the knowledge in pharmacokinetics, pharmacodynamics and pharmacogenomics, the CP performs various functions, including prescriptions, monitoring patients during medical treatment, especially in the case of comorbidities, evaluation of the right dose of drug and any side effects by focusing on the drug-drug or drug-food interactions.[10,11] The following study, conducted in the Medical Oncology Unit of the ARNAS "Di Cristina Benfratelli" Civic Hospital in Palermo (Italy) in collaboration with its Hospital Pharmacy Unit and, in particular, the Antiblastic Drugs Unit (ADU), shed light on the differences between the immunotherapy and chemotherapy in NSCLC patients. In particular, the data collected by the use of a questionnaire to which the patients were subjected, highlighted the lower side effects and adverse drug reactions (ADRs) of the immunotherapy compared to the chemotherapy. In this regard, the role of CP in the management of patients with NSCLC should be highlighted, in fact these data were collected and analyzed by the CP who was in close contact with the patients, identifying and outlining both the side effects of specific anticancer therapies, and ADRs due to concomitant therapies

## Methods

The pilot study was conducted from January to June 2019 on a population of patients with NSCLC undergoing anticancer treatment in the Medical Oncology Unit of the ARNAS "Di Cristina Benfratelli" Civic Hospital of Palermo (Italy), in collaboration with its Hospital Pharmacy Unit and, in particular, the Antiblastic Drugs Unit (ADU). Patient characteristics: the total number of patients was 47, 10 of which were women and 37 were men. The average age of the population taken into consideration was 67. Twenty-one out of forty-seven patients followed the immunotherapy regimen: 13 patients received nivolumab, 2 atezolizumab and the remaining 6 pembrolizumab. Instead, twenty-six patients followed the chemotherapy regimen: 1 patient received cisplatin alone, 1 cisplatin + vinorelbine, 1 carboplatin alone, 2 carboplatin + paclitaxel, 3 carboplatin + gemcitabine, 4 carboplatin + pemetrexed, 1 paclitaxel alone, 1 etoposide alone, 2 docetaxel alone, 2 gemcitabine alone, 2 vinorelbine alone and 6 pemetrexed alone. Eleven out of the twenty-one patients undergoing immunotherapy and twelve of the twenty-six patients undergoing chemotherapy were receiving concomitant therapies, thereby possible unwanted drug interactions were investigated.

All patients completed the five-question questionnaire (Figure 1): question #1 "Have you had any of these effects on the same day of therapy? If so, which ones?"; question #2 "Have you had any of these effects in the days following therapy? If so, which ones?"; question #3 "Do you smoke?"; question #4 "Does your work involve the inhalation of chemicals potentially harmful to your health (asbestos, polycyclic aromatic hydrocarbons, nickel, radon, arsenic, cadmium) or coming into contact with ionizing radiation, X-rays, gamma radiation, or substances contained in paints?"; question #5 "Are you taking any other medication?".

Based on the answers to question number 5, the InterCheck® website (www.intercheckweb.it) was used to evaluate possible drug-drug interactions between the different therapies, including immunotherapy, chemotherapy, drugs used to prevent side effects from anticancer therapy, drugs administered to patients for concomitant morbidity.

## Results and Discussion

The pilot study aimed to explore differences in the approach to anticancer therapy of NSCLC patients undergoing immunotherapy or chemotherapy. A relevant role in this study was played by the CP who collected a series of data to evaluate the outcome and effectiveness of the treatments by monitoring patients with NSCLC and building the patient's history through simple questions. In the healthcare team, the CP is considered a link between physician and patients, in fact, CP educates patients on any undesirable effects of drug therapy, and through constant monitoring of medical records and adverse effects,

communicates to the physician any problems during the therapy in order to improve adaptability to the therapeutic plan.[12] The study reported was conducted on a population of forty-seven NSCLC patients under anticancer treatment from January to June 2019, in the ARNAS "Di Cristina Benfratelli" Civic Hospital of Palermo (Italy). Patients ranged in age between 43 and 82 years (table 1 shows patients' characteristics, including sex, age, lung cancer treatment, concomitant therapies, and switch from chemotherapy to immunotherapy) with an average age of 67 years. During the observation period, twenty-one patients (from 1 to 21) (44.7%) underwent immunotherapy treatment, while twenty-six patients (from 22 to 47) (55.3%) were treated with conventional chemotherapy. Among all patients, twenty-three out of forty-seven followed a polytherapy scheme due to concomitant morbidities, while the remaining twenty-four received anticancer therapy alone.

It should be noted that some patients underwent a switch from chemotherapy to immunotherapy in order to escape from side effects. In particular, ten patients switched from carboplatin/cisplatin-gemcitabine or carboplatin/pemetrexed to nivolumab or atezolizumab; while six patients received pembrolizumab as first-line treatment. All patients were subjected to a questionnaire in order to obtain useful information especially on the undesirable effects induced by the type of anticancer treatment and ADRs due to concomitant therapies (Figure 1).

Question #1 of the questionnaire was "Have you had any of these effects on the same day of therapy? If so, which?" To this first question, only two out of twenty-one patients under immunotherapy treatment replied that they experienced skin reactions (itching) and swollen leg (patient 4), and flu symptoms (patient 9, cold and fever). Conversely, twelve out of twenty-six patients receiving chemotherapy showed side effects on the same day as therapy: nausea/vomiting (patients 27, 33, 38, and 47), flu symptoms (patient 30 back pain, 39 muscle pain, 43 shoulder and pelvic pain, swollen legs (patient 42), headache (patients 25, 33, 35, 36, 41, and 42), cough (patient 35), other (patient 22 insomnia, and 46 heat in the head).

Question #2 of the questionnaire was "Have you had any of these effects in the days following therapy? If so, which?" In the days following therapy administration, the number of patients experiencing side effects increased in both groups, especially among patients treated with conventional chemotherapy. Interestingly, no side effects were observed in patients 4 and 9 the days after immunotherapy administration, and only five patients out of twenty-one declared having health problems, especially skin reactions (patient 20, itching), flu symptoms (patients 17 tiredness, and 18, fever), other (patients 5, diarrhea and intestinal pain, and 10, 16, and 18 wheezing). The situation was very different for patients who received chemotherapy, in fact, only five replied that they did not have any side effects, while all the other patients suffered from nausea/vomiting (patients 22, 24, 25, 27, 31, 32, 33, 34, 35, 36, 37, 38, 42, 45, and 47), skin reaction (patients 34, skin reddening), flu symptoms (patients 23, generalized pain, 28, weakness and headache, 30 back pain, 32 weakness, 33 lower back pain, 38 and 39 muscle pain, 40 muscle weakness and pain, 43 shoulder and pelvis pain, 45 weakness and leg pain), and other (patients 26,wheezing, and 34, lack of taste and nosebleed).

Thus, it is clear that patients undergoing immunotherapy had fewer side effects on the same day of treatment, as well as in subsequent days than patients receiving conventional chemotherapy. These data are extremely interesting in order to guarantee patients a therapeutic approach with fewer side effects and increasing compliance, especially for therapies that involve multiple courses of administration, such as the anticancer ones.

The data described above should be related to the patients' lifestyle and concomitant therapy. For this reason, questions three and five aim to assess the correlation between therapy and inductive or inhibitory factors of metabolism. Instead, the intention with questions three and four is to investigate the major risk factors for developing lung cancer that patients have or have been in contact with.[13-15]

Question #3 of the questionnaire was "Do you smoke?" Patients 6, 9, 17, 18, 30, 31, 33, 38, and 47 replied yes. Specifically, patients 6, 9, 38, and 47 said that they were currently smoking about ten

cigarettes a day. Patients 17, 30, 31, and 33 said they smoked an average of five cigarettes a day, while patient 18 replied that he smoked about 20 cigarettes a day. Most patients were ex-smoker (2, 3, 4, 5, 7, 8, 10, 11, 12, 13, 14, 15, 16, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 32, 34, 35, 36, 37, 39, 40, 41, 42, 43, 44, 45, and 46), whereas only patient number 1 replied no. Although tobacco smoke is responsible of 90% of lung cancer cases, this question was also placed with the aim of investigating how the change in the expression of metabolizing enzyme can affect the therapy and invalidate its efficacy. The expression levels of CYP1A1, CYP1A2, CYP1B1, CYP2E1, and CYP2A6 occur in response to cigarette smoking which is mediated by the polycyclic aromatic hydrocarbons (PAHs) that are inhaled, including the benzo[*a*]pyrene, nitrates, and tobacco-specific N-nitrosamines (TSNAs), such as 4-(methylnitrosamino)-1-(13-pyridyl-1-butanone) (NNK). As result, the metabolism of certain drugs would be accelerate.[16,17] However, it would appear that none of that type of CYP is involved in the metabolism of anticancer drugs used to treat NSCLC patients of this study. Instead, these data could once again confirm how cigarette smoking causes cancer. In fact, even though most of the patients were former smokers, lung cancer develops slowly and there is about a decade of latency between the start of smoking and the onset of cancer.[18]

According to the answers of question #4 "Does your work involve the inhalation of chemicals potentially harmful to your health (asbestos, polycyclic aromatic hydrocarbons, nickel, radon, arsenic, cadmium) or coming into contact with ionizing radiation, X-rays, gamma radiation, or substances contained in paints?" the number of patients who replied with no or yes were approximately the same (twenty-three patients replied yes: 1, 3, 4, 5, 12, 13, 14, 16, 18, 20, 24, 25, 27, 28, 29, 33, 35, 37, 39, 40, 41, 42, 43, and 46, while twenty-four replied no: 2, 6, 7, 8, 9, 10, 11, 15, 17, 19, 21, 22, 23, 26, 30, 31, 32, 34, 36, 38, 44, 45, and 47). Albeit tobacco combustion produces at least 60 different carcinogens, several other "invisible" ones, as cited in the question number four, are known to cause lung cancer. About half of the patients said they were not in contact with the aforementioned carcinogens at the time of their illness. However, with a special focus on asbestos, it is necessary to remember that this survey was conducted on patients residing in a geographical area, Italy, which was the main producer and consumer of asbestos in the twentieth century, and only since 1992, its production, processing and sale has been banned. Although 30 years have passed since the ban, cancers appeared 10-15 years after the last occupational exposure. Furthermore, asbestos deposits are still visible in some areas of Italy, indeed, many people continued to keep asbestos containers for water conservation until a few years ago, especially in socio-economically disadvantaged areas, despite the contributions made available by the Italian state to eliminate the asbestos and sanitizing.[19]

Question #5 of the questionnaire was "Are you taking any other medication?" The patients who replied yes were: 3, 4, 5, 7, 8, 10, 11, 13, 14, 17, 21, 22, 23, 26, 28, 29, 31, 34, 39, 42, 43, 44, and 45. While patients who replied no were: 1, 2, 6, 9, 12, 15, 16, 18, 19, 20, 24, 25, 27, 30, 32, 33, 35, 36, 37, 38, 40, 41, 46, and 47. Knowing if the patient is undergoing concomitant therapies is extremely important to choice the best therapy and dosage, and to evaluate in advance the possible ADRs that may occur during treatment. Often, immunotherapy over chemotherapy has the advantage of avoiding the co-administration of preventive drugs for nausea and allergic reactions, such as antiemetics (ondansetron/ palonosetron) and cortisone (dexamethasone) which could interact with any home therapy of the patient under examination. It should be considered that prescriptive inadequacy leads to an increase in outpatient visits, hospitalization rates and the risk of death, with a consequent clinical and economic impact.[13] It has been reported that 20-30% of adverse reactions are the result of drug-drug interactions due to polytherapy, while the other interactions refer to those between drug and food, or with supplements or external factors, such as smoking cigarette. Unwanted drug interactions occur both at the pharmacokinetic level, thus influencing the process of drug absorption, distribution, metabolism and excretion, and at the pharmacodynamic level, according to the target.[20] However, the potential effects of interactions can be predicted and avoided

on the basis of the properties of the drug, the route of administration and the clinical/genetic profile of the patient, by careful monitoring and dose adjustment, or by choosing therapeutic alternatives. Therefore, with the aim of assessing the adequacy of therapy for individual patients and the risk of ADRs, we used the InterCheck® software, available on the website www.intercheckweb.it, through which it was possible to register a patient, enter the therapy performed and evaluate drug interactions. The software classified interactions into four types: 1) type A minor interactions: not clinically relevant; 2) type B moderate interactions: associated with an uncertain or variable event; 3) type C major interactions: associated with a serious but manageable event; 4) type D contraindicated or very serious interactions: associated with a serious event for which co-administration must be avoided or careful monitoring must be instituted. Tables 2, 3 and 4 showed the most significant adverse events of type B, C, and D occurred in patients undergoing polytherapy treatments, taking into consideration all types of treatments: immunotherapy, chemotherapy, drugs used to prevent unwanted side effects from anticancer therapy, drugs taken for concomitant morbidity. No immunotherapeutic drugs appeared to have interactions of type B, C and D, and the same cannot be said for chemotherapeutics, as type B interaction was found between gemcitabine and levofloxacin. Furthermore, as can be seen from Tables 2, 3 and 4, many patients on chemotherapy treatment have used drugs for the prevention of undesirable effects from anticancer therapy which in turn interact negatively with co-administered drugs for other diseases. One of the goals linked to the development of the immunotherapy in the oncology field is the possibility of reducing the side effects and risks that unfortunately are often associated with traditional therapies, such as chemotherapy. However, the health care team must keep in mind that, since immunotherapy is a practice that aims to strengthen the immune system, side reactions depend on the specific characteristics of the subject under examination and thus they are extremely variable.

The limitation of our study is the small number of patients enrolled. Furthermore, being a study conducted for a limited period from January to June 2019, we do not know anything about long-term therapy and possible patient relapses. However, the study provides optimal information needed to prepare future studies for the treatment of NSCLC patients undergoing immunotherapy or chemotherapy.

## Conclusions

Non-small cell lung cancer is an aggressive cancer with a high incidence and mortality rate worldwide. The advanced stage of the disease at the time of diagnosis is the cause of the poor prognosis with a five-year survival of less than 20%. Several therapeutic approaches have been done to increase the overall survival of patients suffering from this serious disease. In addition to conventional therapy based on the use of platinum or non-platinum agents, including their combinations, and the use of targeted therapy resulting from extensive research on cancer biology, in recent years immunotherapy, based on the PD-1 / PD-L1 immune checkpoint theory, has produced important clinical results. Nivolumab, pembrolizumab, and atezolizumab are the best-known inhibitors that block immunosurveillance. The pilot study reported in this work highlights the advantages of using immunotherapy over chemotherapy in treating patients. In fact, the data collected showed that few patients receiving immunotherapy treatment experienced mild symptoms caused by the side effects of anticancer therapy, either on the same day or in the days following administration, compared to patients receiving chemotherapy. Furthermore, thanks to the support of InterCheck® web, no ADRs were found between immunotherapy and concomitant therapies. These favourable data could direct scientific research towards the discovery of new immunotherapeutic drugs and new methods for selecting patients who might benefit from them.

## List of abbreviations

ADR: Adverse Drug Reaction; ALK: Anaplastic Lymphoma Kinase; CP: Clinical Pharmacist; CTLA4: Cytotoxic T-Lymphocyte-Associated Protein 4; EGFR: Epidermal Growth Factor Receptor; HPV: Papilloma Virus; KRAS: Kirsten Rat Sarcoma; NNK: 4-(methylnitrosamino)-1-(13-pyridyl-1-butanone);

NSCLC: Non-Small Cell Lung Cancer; PAHs: Polycyclic Aromatic Hydrocarbons; PD1: Programmed Death 1; PD-L1: Programmed Death-Ligand 1; SCLC: Small Cell Lung Cancer; TKIs: Tyrosine Kinase Inhibitors; TME: Tumor Microenvironment; TSNAs: Tobacco-Specific N-Nitrosamines; ADU: Antiblastic Drugs Unit.

## Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

## Author's contribution statement

All individuals listed as authors have contributed substantially to designing, performing or reporting the study.

## Approval of the manuscript

All authors read and approved the final version of the manuscript.

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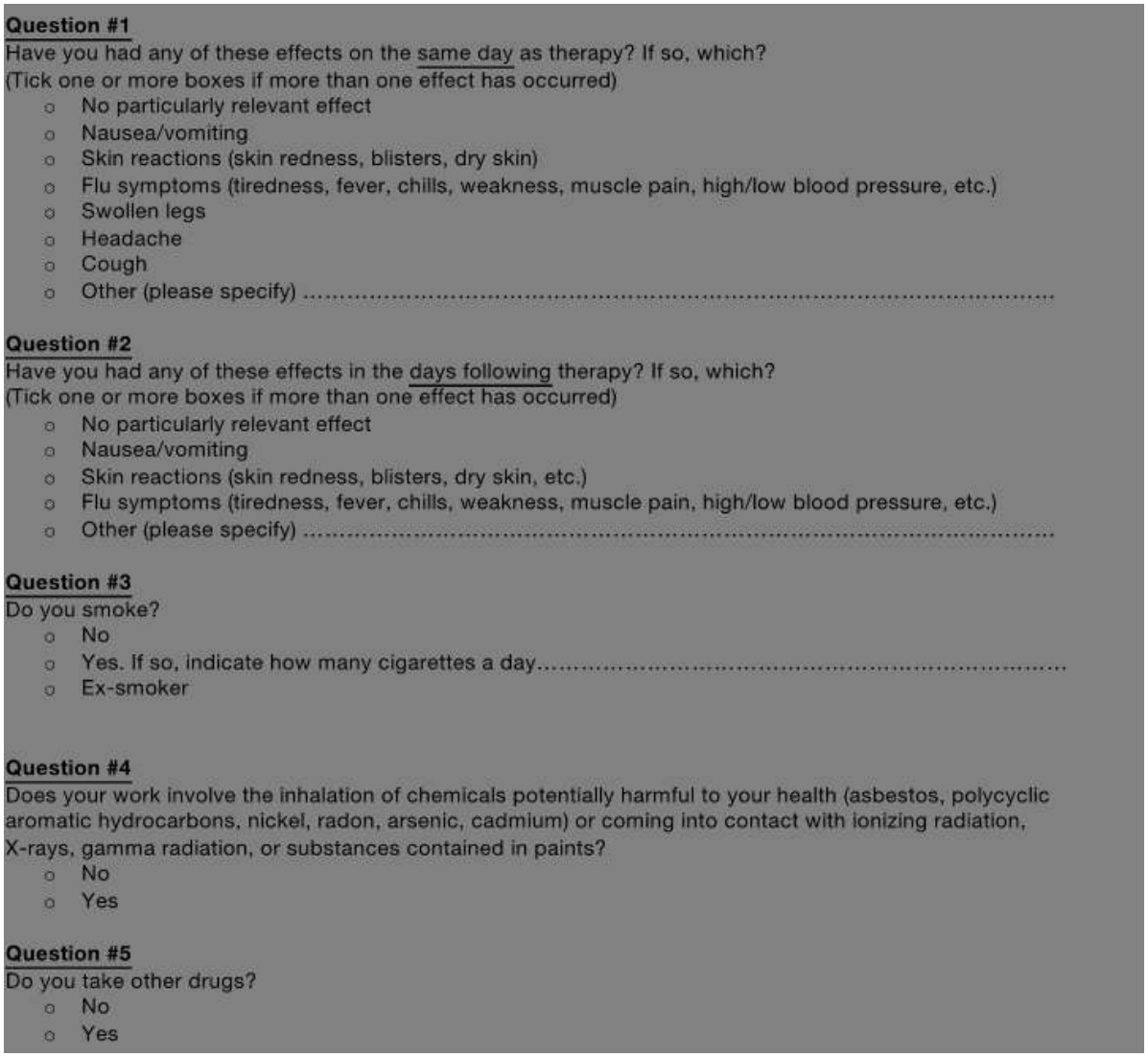

**Question #1**
Have you had any of these effects on the same day as therapy? If so, which?
(Tick one or more boxes if more than one effect has occurred)
- o No particularly relevant effect
- o Nausea/vomiting
- o Skin reactions (skin redness, blisters, dry skin)
- o Flu symptoms (tiredness, fever, chills, weakness, muscle pain, high/low blood pressure, etc.)
- o Swollen legs
- o Headache
- o Cough
- o Other (please specify) .....

**Question #2**
Have you had any of these effects in the days following therapy? If so, which?
(Tick one or more boxes if more than one effect has occurred)
- o No particularly relevant effect
- o Nausea/vomiting
- o Skin reactions (skin redness, blisters, dry skin, etc.)
- o Flu symptoms (tiredness, fever, chills, weakness, muscle pain, high/low blood pressure, etc.)
- o Other (please specify) .....

**Question #3**
Do you smoke?
- o No
- o Yes. If so, indicate how many cigarettes a day.....
- o Ex-smoker

**Question #4**
Does your work involve the inhalation of chemicals potentially harmful to your health (asbestos, polycyclic aromatic hydrocarbons, nickel, radon, arsenic, cadmium) or coming into contact with ionizing radiation, X-rays, gamma radiation, or substances contained in paints?
- o No
- o Yes

**Question #5**
Do you take other drugs?
- o No
- o Yes

**Figure 1.** Example of questionnaire to which patients have been subjected.

| Patients | Sex | Age | Anticancer Therapy | Concomitant therapy | Switch therapy |
|---|---|---|---|---|---|
| 1 | M | 61 | Nivolumab | / | No |
| 2 | M | 69 | Nivolumab | / | Yes |
| 3 | M | 57 | Nivolumab | Levetiracetam | Yes |
| 4 | M | 75 | Nivolumab | Acetylsalicylic acid, Simvastatin, Fosinopril | Yes |
| 5 | M | 62 | Nivolumab | Dronedarone, Edoxaban, Sildenafil, Tiotropium, Amlodipine | Yes |
| 6 | M | 63 | Nivolumab | / | No |
| 7 | M | 65 | Nivolumab | Doxazosin, Irbesartan-hydrochlorothiazide | No |
| 8 | M | 67 | Nivolumab | Lansoprazole, Tamsulosin, Dutasteride | Yes |
| 9 | M | 63 | Nivolumab | / | No |
| 10 | M | 75 | Nivolumab | Lactulose, Pregabalin, Bromazepam, Repaglinide, Oxicodone + Paracetamol | No |
| 11 | F | 53 | Nivolumab | Fentanyl, Omeprazole, Naproxen, Dexamethasone, Lactulose, Levofloxacin | No |
| 12 | M | 76 | Nivolumab | / | Yes |
| 13 | M | 78 | Nivolumab | Atorvastatin, Clopidogrel, Metformin, Ceterizine, Dexamethasone, Ramipril | Yes |
| 14 | M | 76 | Atezolizumab | Lisinopril, Ezetimibe + Simvastatin, Acetylsalicylic acid | Yes |
| 15 | M | 71 | Atezolizumab | / | Yes |
| 16 | M | 72 | Pembrolizumab | / | No |
| 17 | F | 55 | Pembrolizumab | Olmesartan Medoxomil + Hydrochlorothiazide, Bisoprolol | No |
| 18 | M | 80 | Pembrolizumab | / | No |
| 19 | F | 58 | Pembrolizumab | / | No |
| 20 | M | 78 | Pembrolizumab | / | No |
| 21 | M | 68 | Pembrolizumab | Bisoprolol, Olmesartan Medoxomil, Acetylsalicylic acid, Tapentadol, Atorvastatin, Clopidogrel, Omeprazole, Dexamethasone | No |
| 22 | F | 43 | Cisplatino | Hydroxychloroquine | No |
| 23 | M | 72 | Cisplatino + Vinorelbina | Tramadol, Alfuzosin, Ramipril | No |
| 24 | F | 66 | Docetaxel | / | No |
| 25 | M | 64 | Docetaxel | / | No |
| 26 | M | 75 | Gemcitabina | Tamsulosin, Omeprazole, Levoxacin | No |
| 27 | M | 78 | Gemcitabina | / | No |
| 28 | M | 75 | Vinorelbina | Omeprazole | No |
| 29 | M | 68 | Vinorelbina | Atorvastatin | No |
| 30 | M | 72 | Paclitaxel | / | No |
| 31 | F | 63 | Etoposide | Acetylsalicylic acid, Telmisartan, Omeprazole, Tramadol, Lactulose, Dexamethasone, Albendazol | No |

| | | | | | |
|---|---|---|---|---|---|
| 32 | F | 63 | Pemetrexed | / | No |
| 33 | M | 64 | Pemetrexed | / | No |
| 34 | M | 71 | Pemetrexed | Acetylsalicylic acid, Metoprolol | No |
| 35 | M | 65 | Pemetrexed | / | No |
| 36 | M | 69 | Pemetrexed | / | No |
| 37 | M | 67 | Pemetrexed | / | No |
| 38 | F | 60 | Carboplatino + Paclitaxel | / | No |
| 39 | F | 69 | Carboplatino + Pemetrexed | Omeprazole, Furosemide, Insulin, Amiodarone, Pregabalin, Methylprednisolone, Tramadol | No |
| 40 | M | 67 | Carboplatino + Gemcitabina | / | No |
| 41 | 41 | 74 | Carboplatino + Pemetrexed | / | No |
| 42 | M | 47 | Carboplatino + Pemetrexed | Furosemide, Pregabalin, Omeprazole | No |
| 43 | M | 65 | Carboplatino + Gemcitabina | Valsartan, Omperazole, Furosemide | No |
| 44 | M | 82 | Carboplatino + Gemcitabina | Amlodipine, Metoprolol, Omeprazole, Acetylsalicylic acid | No |
| 45 | M | 73 | Carboplatino + Paclitaxel | Paracetamol + Codeine, Etoricoxib, Mebeverine, Desloratadine, Alfuzosin | No |
| 46 | M | 80 | Carboplatino | / | No |
| 47 | F | 44 | Carboplatino + Pemetrexed | / | No |

**Table 1.** Patient's characteristics.

| Drug interaction | Patient | Possible side effects | Mechanism | Clinical management |
|---|---|---|---|---|
| Dexamethasone + acetylsalicylic acid | 21, 31, 44 | Reduction in blood levels of the acetylsalicylic acid; increased incidence of gastrointestinal bleeding | Increased glomerular filtration rate and metabolism of acetylsalicylic acid. | Monitoring of signs/symptoms of gastric injury; with interruption of the corticosteroid, salicilism may occur |
| Dexamethasone + bisoprolol | 21 | Dexamethasone antagonizes the action of antihypertensives | Sodium and fluid retention caused by corticosteroids | Monitoring of the development of edema and congestive heart failure; periodic check of blood pressure and electrolyte levels |
| Dexamethasone + metoprolol | 44 | Dexamethasone antagonizes the action of antihypertensives | Sodium and fluid retention caused by corticosteroids | Monitoring of the development of edema and congestive heart failure; periodic check of blood pressure and electrolyte levels |
| Dexamethasone + levofloxacin | 11, 26 | Increased risk of tendon ruptures | Not known | Discontinuation of levofloxacin in case of pain, inflammation or tendon rupture |
| Dexamethasone + furosemide | 39, 43 | Hypokalemia | Additive pharmacological effects | Monitoring of potassium levels |
| Dexamethasone + albendazole | 31 | Increased adverse effects of albendazole (nausea, vomiting, dizziness) | Increased time of exposure to the active metabolite | Monitoring of side effects |
| Dexamethasone + lactulose | 11, 31 | Hypokalemia | Loss of electrolytes and potentiated hypokalemia | Do not exceed recommended dosage of laxative |

| | | | | |
|---|---|---|---|---|
| Dexamethasone + telmisartan | 31 | Dexamethasone antagonizes the action of antihypertensives | Sodium and fluid retention caused by corticosteroids | Monitoring of the development of edema and congestive heart failure; periodic check of blood pressure and electrolyte levels |
| Dexamethasone + metformin | 13 | Reduced hypoglycemic activity of metformin | Interference of dexamethasone on glycemic control, glucose intolerance and / or exacerbation of a pre-existing diabetic | Monitoring of blood glucose in diabetic patients; probable dose adjustment of metformin |
| Dexamethasone + ramipril | 13 | Dexamethasone antagonizes the action of antihypertensives | Sodium and fluid retention caused by corticosteroids | Monitoring of the development of edema and congestive heart failure; periodic check of blood pressure and electrolyte levels |
| Ondansetron + omeprazole | 39, 43, 44 | Increased risk of cardiotoxicity | Cardiac toxicity due to direct effects on the QT interval associated with alterations in electrolytes | Periodic electrocardiographic and electrolyte dosage checks |
| Omeprazole + acetylsalicylic acid | 21, 31, 44 | Reduced efficacy of acetylsalicylic acid and increased risk of cerebrovascular events | Reduced absorption of acetylsalicylic acid | Monitoring |
| Omeprazole + levofloxacin | 11, 26 | Increased risk of cardiotoxicity | Cardiac toxicity due to direct effects on the QT interval associated with alterations in electrolytes | Periodic electrocardiographic and electrolyte dosage checks |
| Omeprazole + furosemide | 39, 43 | Increased risk of cardiotoxicity | Cardiac toxicity due to direct effects on the QT interval associated with alterations in electrolytes | Periodic electrocardiographic and electrolyte dosage checks |

| | | | | |
|---|---|---|---|---|
| Omperazole + tramadol | 31, 39 | Increased risk of cardiotoxicity | Cardiac toxicity due to direct effects on the QT interval associated with alterations in electrolytes | Periodic electrocardiographic and electrolyte dosage checks |
| Omeprazole + amiodarone | 39 | Increased risk of cardiotoxicity | Cardiac toxicity due to direct effects on the QT interval associated with alterations in electrolytes | Periodic electrocardiographic and electrolyte dosage checks |
| Gemcitabine + levofloxacin | 26 | Possible reduction of the bioavailability of levofloxacin | Reduced absorption of levofloxacin; alteration of the intestinal mucosa caused by chemotherapy | Monitoring |
| Vinorelbine + atorvastatin | 29 | Increased risk of peripheral neuropathies | Additive pharmacological effects | Monitoring of the onset of symptoms of peripheral neuropathy |
| Clopidogrel + atorvastatin | 13, 21 | Possible reduction in the metabolic activation of clopidogrel and its therapeutic efficacy | Reduced metabolic activation of clopidogrel partially mediated by cytochrome P450 3A4 | Prefer statins that follow other metabolic pathways, such as fluvastatin or pravastatin |
| Clopidogrel + acetylsalicylic acid | 21 | Increased risk of bleeding | Inhibition of platelet aggregation | Monitoring |
| Acetylsalicylic acid + metoprolol | 44 | Increased blood levels of acetylsalicylic acid with risk of toxicity | Inhibition of acetylsalicylic acid metabolism | Monitoring |
| Acetylsalicylic acid + amlodipine | 44 | Reduced hypotensive effects; increased risk of gastrointestinal bleeding | Alteration of vascular tone; additive effects on bleeding risk | Monitor blood pressure and signs and symptoms of gastrointestinal bleeding |
| Acetylsalicylic acid + lisinopril | 14 | Reduced antihypertensive effect of lisinopril | Interference with prostaglandin production | Monitoring of blood pressure, cardiovascular function, potassium and renal function; modification of lisinopril doses if necessary |

**Table 2.** Type B interactions.

| Drug interaction | Patient | Possible side effects | Mechanism | Clinical management |
|---|---|---|---|---|
| Dexamethasone + naproxen | 11 | Increased risk of gastrointestinal adverse effects | Additive gastrological effects | Evaluate the use of gastroprotective treatment in the elderly |
| Dexamethasone + netupitant | 26 | Increased exposure to dexamethasone | No known | Reduce the dexamethasone dose by approximately 50% |
| Dexamethasone + etoricoxib | 45 | Increased risk of gastrointestinal adverse effects | Additive gastrological effects | Evaluate the use of gastroprotective treatment in the elderly |
| Dronedarone + edoxaban | 5 | Increased exposure to edoxaban by about 80% | Inhibited elimination of edoxaban mediated by P-glycoprotein, with less contribution from CYP 3A4 inhibition | Use caution in co-administration, monitoring more closely the possible risk of bleeding |

**Table 3.** Type C interactions.

| Drug interaction | Patient | Possible side effects | Mechanism | Clinical management |
|---|---|---|---|---|
| Omeprazole + clopidogrel | 21 | Reduced efficacy of clopidogrel | Inhibited activation of clopidogrel (mediated by cytochrome P450 2C19) caused by omeprazole (moderate 2C19 inhibitor) | Prefer pantoprazole or H2 antagonists, such as ranitidine |
| Ondansetron + furosemide | 39, 43 | Increased risk of cardiotoxicity | Additive effect on prolongation of the QT interval | Co-administration should be avoided; otherwise it would be advisable to carry out periodic checks of the electrocardiogram |
| Ondansetron + alfuzosin | 45 | Increased risk of cardiotoxicity | Additive effect on prolongation of the QT interval | Co-administration should be avoided; otherwise it would be advisable to carry out periodic checks of the electrocardiogram |
| Ondansetron + tramadol | 39 | Increased risk of cardiotoxicity | Additive effect on prolongation of the QT interval | Co-administration should be avoided; otherwise it would be advisable to carry out periodic checks of the electrocardiogram |
| Ondansetron+ amiodarone | 39 | Increased risk of cardiotoxicity | Additive effect on prolongation of the QT interval | Co-administration should be avoided; otherwise it would be advisable to carry out periodic checks of the electrocardiogram |
| Furosemide + amiodarone | 39 | Increased risk of cardiotoxicity | Additive effect on prolongation of the QT interval | Co-administration should be avoided; otherwise it would be advisable to carry out periodic checks of the electrocardiogram |

| | | | | |
|---|---|---|---|---|
| Furosemide + tramadol | 39 | Increased risk of cardiotoxicity | Additive effect on prolongation of the QT interval | Co-administration should be avoided; otherwise it would be advisable to carry out periodic checks of the electrocardiogram |
| Amiodarone + tramadol | 39 | Increased risk of cardiotoxicity | Additive effect on prolongation of the QT interval | Co-administration should be avoided; otherwise it would be advisable to carry out periodic checks of the electrocardiogram |

**Table 4.** Type D interactions.