"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

THE FIELD OF MEDICINE

Personalization of oncological treatment in patients with lung and pancreatic neoplasms: from the choice of cytotoxic therapy to the use of multigene testing

PHD THESIS SUMMARY

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Content

I. The general part

1. Personalization of the administration of cytotoxic chemotherapy

Most cytotoxic chemotherapies induce immediate response and narrow therapeutic index. Small variations in the administered dose can lead to severe, even life-threatening toxicity in some individuals and underdosing in others, which can compromise cancer outcomes. The importance of correct dose calculation especially in patients with potentially curable diseases such as lymphoma or testicular cancer or in adjuvant treatment (eg breast and colon cancer) is overwhelming. This is also complicated by the fact that individuals have a highly variable ability to metabolize and eliminate drugs.

The most relevant pharmacokinetic parameter is the area under the curve (AUC) of plasma concentration x time after a single dose. During drug development, sampling it at multiple time points helps define the relationship between drug administration and AUC [1].

1.1 Defining the optimal dose

BSA-based administration does not account for most of the interindividual variation in drug exposure. For cytotoxic agents, interindividual variability in drug clearance based on area under the curve (AUC) is expressed as the percent coefficient of variation (which is the standard deviation divided by the mean x 100).

1.1.1 Dosing based on patient weight

Weight-based dosing is used primarily for monoclonal antibodies, but also for several cytotoxic agents, including cladribine, melphalan, and arsenic. In the absence of data suggesting increased toxicity for underweight or obese individuals receiving weight-based doses, doses should be based on actual body weight [2,3].

1.1.2 Dosing based on body surface area

In an attempt to minimize interindividual variation in drug exposure, various methods have been developed, mainly using body parameters. Body surface area (BSA) dosing has been widely adopted for most cytotoxic agents and some monoclonal antibodies (rituximab, cetuximab). However, no regimen has been shown to be superior, except for AUC-based dosing for carboplatin [4].

1.1.3 Dosing based on AUC (area under the curve)

AUC-based dosing is applicable to drugs that are eliminated by glomerular filtration, such as carboplatin, because there is a strong correlation between carboplatin clearance and creatinine clearance. AUC-based dosing is not applicable to other chemotherapeutics (with the possible

exception of pemetrexed) because there are no features that can be used to predict drug clearance, drug elimination involving multiple pathways [5,6].

1.1.4 The use of fixed dose in oncology

There is a tendency to use fixed doses in treatment with monoclonal antibodies in oncology. Monoclonal antibodies are usually distributed in blood plasma and extracellular fluid compartments, which do not increase in proportion to body weight, so weight-based dosing may not be necessary. Furthermore, monoclonal antibodies typically have a wider therapeutic window and thus could be subject to a fixed dose. Pharmacokinetic data from clinical trials have been analyzed and indicate that interpatient variation in exposure is comparable for fixed and weight-dependent dosing [7]. .

2. The standard of treatment in pulmonary neoplasm other than metastatic small cell neoplasm

2.1 Choice of systemic treatment in patients without driver mutations

Key factors influencing the choice of initial therapy for advanced NSCLC include:

● Expression level of programmed cell death ligand 1 (PD-L1).

● Presence or absence of a driver mutation (pathogenic mutation, eg, epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], oncogene c-ROS 1 [ROS1], BRAF, etc) for which a specific inhibitor is available . Analysis of either the primary tumor or a metastasis for EGFR and ALK is indicated for all patients whose tumor contains an element of adenocarcinoma, regardless of the clinical characteristics of the tumor [8].

● The extent of the disease, including the number and sites of metastases, and the presence or absence of associated symptoms.

● Squamous versus non-squamous histology.

For patients with non-squamous or squamous NSCLC, the approach depends on the level of PD-L1 expression.

For those with tumor PD-L1 expression of 50% or greater, pembrolizumab or atezolizumab monotherapy is recommended, which has demonstrated an improvement in overall survival (OS) compared to doublet chemotherapy in this population [9] .

For patients with PD-L1 expression less than 50 percent, the doublet combination of chemotherapy with concurrent pembrolizumab is recommended. Although pembrolizumab monotherapy is an

FDA-approved option for patients with PD-L1 expression of 1 to 49 percent, the chemotherapy/pembrolizumab combination is preferred when feasible .

For patients with non-squamous NSCLC and PD-L1 expression <50%, the preferred option is the combination of pemetrexed, carboplatin or cisplatin and pembrolizumab. This regimen has demonstrated efficacy by improving several survival parameters, including OS, compared with pemetrexed and carboplatin alone [9]. For patients with squamous NSCLC and PD-L1 expression <50 percent, the preferred regimen is carboplatin with either paclitaxel or nab-paclitaxel and pembrolizumab, based on the demonstrated benefit of this regimen over combination chemotherapy and for both NSCLC patients advanced squamous [10].

2.2 Maintenance therapy

For those initially treated with combination chemotherapy, treatment is generally limited to four to six cycles. In the absence of disease progression, systemic maintenance therapy has been shown to prolong progression-free survival and overall survival. The most effective maintenance option is chemotherapy with a single agent and pembrolizumab in the case of non-squamous histologies or only pembrolizumab in the case of squamous histologies [11].

2.3 Data on chemotherapy in NSCLC

For those with good performance status for whom chemotherapy is indicated, combination chemotherapy regimens using a platinum compound (cisplatin, carboplatin) plus a second active cytotoxic agent are preferred, usually for four to six cycles. Extending the duration of initial platinum-based chemotherapy beyond four to six cycles is not recommended given the increased toxicity and modest effect on survival [12].

2.3.1 Number of cytotoxic agents

Evidence suggests that dual cytostatic regimens increase response rate and overall survival compared with monotherapy. Adding a third agent, however, improves response rates, but the impact on survival is inconsistent and toxicity is clearly increased. Thus, the initial use of doublet regimens is recommended, reserving treatment with a single cytostatic for fragile patients. [13]

2.3.2. Chemotherapy options for maintenance treatment

Maintenance therapy options for patients without a driver mutation include single-agent chemotherapy, bevacizumab or pembrolizumab. Patients initially treated with chemotherapy with or without bevacizumab who desire a treatment break and do not appear to be at risk of rapid relapse may be followed without maintenance using close clinical and radiographic monitoring following informed patient discussion. However, for those in whom pembrolizumab was a component of initial treatment, it is usually continued until progression, although discontinuation at two years is an appropriate alternative [10,11].

3. The standard of systemic treatment in locally advanced inoperable or metastatic pancreatic adenocarcinoma

3.1 The standard of first-line systemic treatment

In patients with a good performance status (ECOG 0-1) who are able to tolerate an intensive approach, outside a clinical research protocol, with metastatic pancreatic ductal adenocarcinoma, FOLFIRINOX or modified FOLFIRINOX regimens are recommended in favor of gemcitabine or a doublet based on gemcitabine. Gemcitabine plus nab-paclitaxel represents an acceptable and less toxic alternative than FOLFIRINOX as long as patients have a relatively favorable comorbidity profile and a serum bilirubin level <1.5 times normal values [14].

Superiority of the combination of nab-paclitaxel (125 mg/m2) followed by gemcitabine (1000 mg/m2) given on days 1, 8 and 15 every 28 days compared to gemcitabine alone (1000 mg/m2 weekly for seven weeks , then on days 1, 8 and 15 every four weeks) was demonstrated in the multinational MPACT study in 861 patients with previously untreated metastatic pancreatic adenocarcinoma. Combination therapy was associated with a significantly higher objective response rate (23 vs. 7 percent) and a significantly longer median overall survival (8.5 vs. 6.7 months) [15].

3.2 Monotherapy in the first line

For patients with metastatic pancreatic cancer who are not candidates for a more intensive first-line chemotherapy regimen (eg, those with ECOG performance status 2-3) current guidelines suggest gemcitabine only. Gemcitabine is a nucleoside analogue with structural similarity to cytarabine. Initial studies suggested a low objective response rate (6 to 11 percent) in chemotherapy-naive patients given gemcitabine alone (800 mg/m2 intravenously [IV] weekly for three out of four weeks) [16] .

II. Personal contributions

1. Working hypothesis and general objectives

Study 1: The Importance of Dose Intensity in the Administration of Cytotoxic Chemotherapy in NSCLC—As Relevant Now as It Was in the Past

Working hypothesis: Adherence to the appropriate dose intensity, the rules of preparation and maintaining the stability of the compound and prompt addressing of toxicities related to cytotoxic chemotherapy increases the survival of oncology patients with metastatic NSCLC.

Specific objectives: The present study aims to verify to what extent delaying the treatment and decreasing the doses of cytotoxic chemotherapy in patients with metastatic NSCLC can influence the survival of oncological patients.

Study 2: Clinical impact of FOLFIRINOX administration for more than six months in advanced pancreatic adenocarcinoma: a cohort study

Working hypothesis: Administration of the FOLFIRINOX regimen to patients with advanced pancreatic carcinoma for more than 6 months positively influences the oncological results (survival without progression and overall survival).

Specific objectives: The current study aims to verify whether the administration of the FOLFIRINOX regimen longer than that in the pivotal study positively influences survival in advanced pancreatic carcinoma. It also takes into account the verification of the impact that delaying treatment and reducing doses have on these results.

Study 3: The utility of next generation gene sequencing (Next Generation Sequencing) in making the treatment decision in NSCLC

Working hypothesis:

There are useful classifications of the targetability of gene alterations according to which the targeted treatment can be chosen in patients with lung cancer other than small cell cancer

Specific objectives:

• to identify some essential directions from the literature regarding the applicability of the conclusions from the trials that involved tissue agnostic therapies

• to identify the best ways of classifying targetable gene alterations according to very recent literature

• to select and present the most relevant articles about the establishment of targeted treatment in non-small cell lung cancer in the era of precision medicine

2. General research methodology

Research directions

In order to illustrate ways of personalizing oncological treatment, the present paper followed two research directions. The first direction focused on studying ways to personalize the administration of chemotherapy so as to avoid toxicities and maximize oncological benefit. Patients with pulmonary neoplasm other than metastatic small cell neoplasm and patients with advanced pancreatic neoplasm were considered.

The second direction of research focuses on the personalization of oncological treatment through the genomic characterization of the tumor. In this sense, a general review of the literature was made, presenting the latest trends in the classification of treatments according to the efficiency with which they target genomic alterations in NSCLC.

3. First study : The Importance of Dose Intensity in the Administration of Cytotoxic Chemotherapy in NSCLC—As Relevant Now as It Was in the Past

3.1 Introduction

Although recent research has changed the way the oncology community perceives this, and longer survival has been achieved with both immunotherapy and targeted therapies, cytotoxic chemotherapy is still the mainstay of therapy for most patients in first or later lines.

3.2 Material and method

The present paper is a retrospective study that included all patients with metastatic NSCLC who received combined chemotherapy at the Elias University Emergency Hospital, Bucharest, Romania, between 2014 and 2018. The inclusion criteria for this study were: histological evidence of NSCLC, stage IV disease, ECOG performance score of maximum 2, treatment with cytotoxic chemotherapy for a minimum of 4 courses (patients with fewer treatment courses were excluded). We also excluded patients with ALK rearrangement or EGFR mutations who have received targeted therapy. The percentage of dose reduction, its duration, and the use of granulocyte colony-stimulating factor (G-CSF) were also reported.

To estimate dose reduction, standard dose intensity and relative dose intensity were calculated using the following formulas:

Dose intensity = dose of chemotherapy administered over time (mg/m2 body surface/week)

Relative dose intensity = dose intensity of administered chemotherapy/standard dose intensity [17]

The chemotherapy regimens used for the studied population can be found in the following table.

Table 3.1. Chemotherapy regimens used for the study population

Regim de chimioterapie	Administrare
paclitaxel 200mg/m^2 + carboplatin AUC =6	q3w
paclitaxel 200 mg/m^2 + carboplatin AUC=6+ bevacizumab 15mg/m^2	q3w
pemetrexed 500 mg/m^2 + carboplatin AUC=6	q3w
gemcitabine 1000 mg/m^2 +carboplatin AUC=4.5	Gemcitabina zilele 1,8,15, q4w pentru întregul regim
gemcitabine 1250 mg/m^2 day 1,8+ cisplatin 80mg/^{2}	gemcitabina zilele 1,8 q3w pentru întregul regim
docetaxel 75 mg/m^2+ cisplatin 75 mg/m^2	q3w

3.3 Results

A total of 129 patients were included. The mean age was 62 years (range 29–80, SD = 9.36), 51.93% were female patients. The study included 28.7% of patients with squamous cell carcinoma (n = 37), 68.2% with adenocarcinoma (n = 88), and 3.1% with other subtypes (n = 4), such as large cell or carcinoma sarcomatoid. The response rate in the study population was 69% (with the majority 41.9% having stable disease). 62.8% (n = 81) had no toxicity greater than grade 2. 14% of patients (n = 18) had dose reduction. The maximum dose reduction allowed was 75% (in 5.42% of patients). The mean dose reduction was 81.11%. A significant proportion of patients received primary prophylaxis for febrile neutropenia, with 45.5% receiving filgrastim and 5.4% pegfilgrastim from baseline. Peg filgrastim as secondary prophylaxis was used in 6.9% of patients.

Table 3.2. Patient characteristics

Characteristics of the patients	**N (%)**
Gender	
Male	62 (48.07%)
Female	67 (51.93 %)
Age	
Medium	62
Range	[29-80]
Histology	
Squamous carcinoma	37 (28.7 %)
Adenocarcinoma	88 (68.2 %)
Other	4 (3.1 %)
Chemotherapy regimen distribution	
Paclitaxel+carboplatin	54 (41.9%)
Paclitaxel+carboplatin+bevacizumab	16 (12.4%)

Pemetrexed+carboplatin	16 (12.4%)
Gemcitabina+carboplatin	34 (26.4%)
Other	9 (7%)
Toxicity	
No toxicity	21 (16.27%)
Grade 1	26 (20.15%)
Grade 2	34 (26.35%)
Over grade 2	48 (37.20%)
Toxicities over grade 2	
Hematological	40 (31.8%)
Non-hematological (deafness, paripheral neuropathy, pain)	8 (6.2 %)
Dose reduction	
75%	7 (5.42%)
Between 85% si 75%	11 (8.57%)

Cox regression analysis was used to identify variables that affected survival. Only the presence of dose reduction, treatment delay, and the presence of toxicity greater than grade 2 were correlated with worse survival. The correlation was statistically significant only for treatment delay ($p<0.07$).

No statistically significant differences were observed when comparing progression-free survival in the dose reduction and no dose reduction groups, as shown in Figure 1 ($p<0.07$). The same was demonstrated when comparing progression-free survival in patients with or without treatment delay, $p<0.09$ (Figure 3.1).

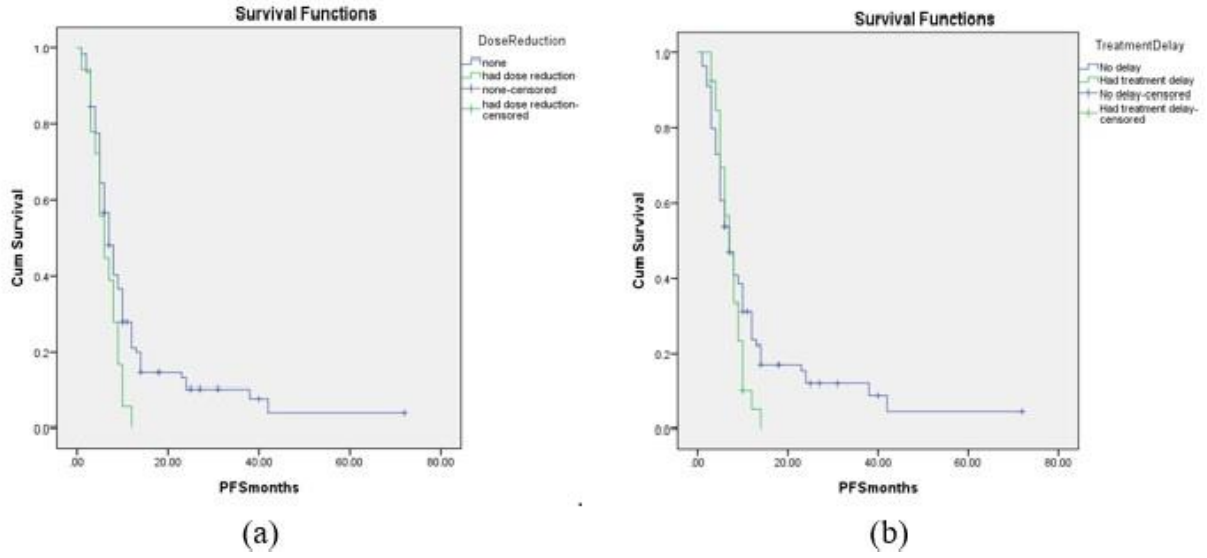

Figure 3.1 . Progression-free survival in (a) dose reduction group and no dose reduction group versus (b) treatment delay versus no treatment delay

Overall survival did not differ significantly in the treatment delay versus no treatment delay group, as shown in Figure 3.2 ($p < 0.25$). However, overall survival was greater in the no-dose-reduction group versus the dose-reduction group ($p < 0.03$).

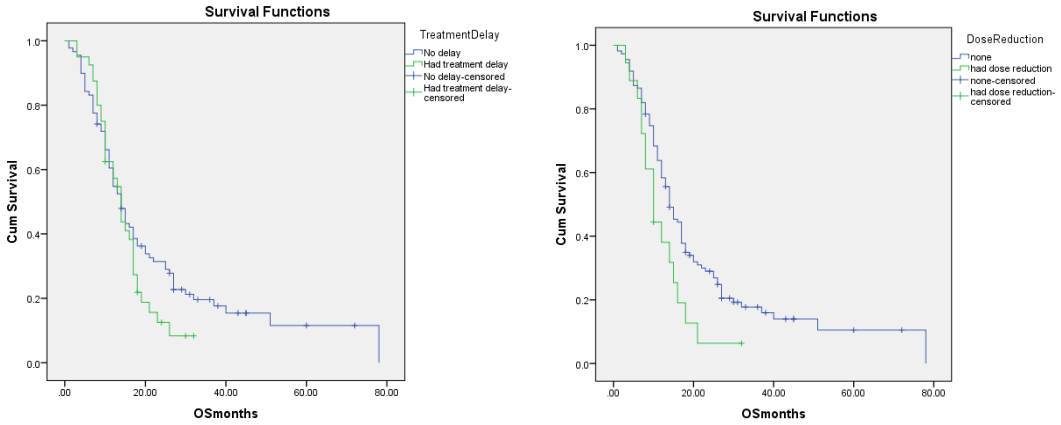

Figure 3.2. Overall survival in (a) treatment delay group and no treatment delay group versus (b) dose reduction and no dose reduction groups

3.4 Discussions

The administration of regimes has some particularities in our institution. The first and most important is the dose calculation method. This was calculated for each presentation, instead of maintaining the dose from the first administration if the patient's body surface area did not decrease by 10%, as is usual practice. When the patient developed chemotherapy-related anemia, supportive measures (such as blood transfusion and use of erythropoiesis-stimulating agents) were adopted, but the attending physicians focused on maintaining the 100% dose. [18,19] The reason why patients with less than 4 courses were excluded is that with short administration the effect of dose intensity on patient outcome is minimal. Primary prophylaxis of febrile neutropenia was always preferred even in the presence of an intermediate risk, after taking into account all risk factors, such as liver dysfunction, renal dysfunction, previous chemotherapy or radiation therapy and age over 65 years. Some of the patients such as those who received pemetrexed + carboplatin were, however, not considered candidates for primary prophylaxis [20].

In the presence of grade 3-4 neutropenia without fever, the first approach was to administer filgrastim for a longer duration after chemotherapy rather than adjusting the chemotherapy dose. When the attending physician considered it necessary, peg-filgrastim was chosen. After administration, patients were monitored with a complete blood count after seven and fourteen days. This helped the attending physician understand the dynamics of the bone marrow and adjust the administration of granulocyte growth factors. The patient was encouraged to collect the complete

blood count in the vicinity of his home, for minimal discomfort. The results were usually sent to the general practitioner or a nurse in the institution [21].

Chemostability and preparation rules were also always taken into account. For each compound, the rules were strictly followed. The clinical antiemesis protocol that included both primary prophylactic medication such as dexamethasone, 5-HT3 receptor antagonists (hydroxytryptamine 3) and sometimes olanzapine, but also hydration administered at each course is another argument for keeping the dose intensity. Premedication, with anti-allergic and toxicity-reducing effects, is also important in ensuring therapeutic success along with the multidisciplinary approach.

A proof of the effectiveness of this approach is the median overall survival reported in the published study of 14 months (higher than that reported in all pivotal studies with the regimens used).

According to our data, there was no difference in overall survival between the two age groups (under 65/over 65). 54/129 (41.8%) were patients over 65 years of age, with cytotoxic chemotherapy for at least 4 courses, and the mean dose reduction was 81.11%. These findings confirm that elderly NSCLC patients can benefit as well as younger patients from conventional dose-intensity chemotherapy. The impact of personalized care during chemotherapy may be a valid explanation for the good tolerability of the regimens, even in the elderly population [22].

3.5 Conclusions

In conclusion, we believe that all the aspects listed above are arguments for better tolerability and less dose reduction of chemotherapy in patients with metastatic NSCLC and, consequently, for better survival.

4. Study 2: Clinical impact of FOLFIRINOX administration for more than six months in advanced pancreatic adenocarcinoma: a cohort study

4.1 Introduction

FOLFIRINOX is a highly effective reference regimen in advanced pancreatic adenocarcinoma. Better survival with this type of chemotherapy compared with gemcitabine monotherapy was demonstrated in the pivotal PRODIGE trial (11.1 vs. 6.8 months, OR for death 0.57; 95% CI; p <.0001) [2. 3]. The number of courses of FOLFIRINOX in advanced pancreatic carcinoma is not standardized. The current study considers the experience with this regimen of the Oncology Clinic of the Elias University Emergency Hospital, administered in advanced pancreatic carcinoma until unacceptable toxicity or disease progression, with a follow-up period of four years, quantifying the benefit on survival, but also the impact maintaining dose intensity on oncological effects.

4.2 Material and methods

The present study is retrospective, observational, monocentric and included histologically confirmed patients with locally advanced or metastatic pancreatic carcinoma, treated in the first line with FOLFIRINOX in the Oncology Clinic of the Elias University Emergency Hospital. The study included patients who presented between 2017 and 2020, and the follow-up period was between 2017-2021. The data considered include the particular characteristics of the patients (sex, age, performance status), the number of treatments administered, details regarding the degree of toxicity (according to the National Cancer Center Common Terminological Criteria for Adverse Events [NCIC-CTCAE]) [24] , the time from the start of the administration to the last dose, the treatment delay, the proportion of dose adjustment for each chemotherapy agent, but also data on the antitumor response. Progression-free and overall survival were measured. Treatment delay and dose reduction were the most important parameters in the assessment of oncological response, regardless of the number of courses administered.

4.3 Results

A total of 42 patients were enrolled in this study, of whom 21 received 6 courses of chemotherapy and 21 received more than 6 courses. Patient characteristics are listed in Table 4.1.

Table 4.1. Characteristics of patients with advanced pancreatic adenocarcinoma

Characteristic	For the whole number of patients N=42	6 courses of FOLFIRINOX	More then 6 courses of FOLFIRINOX
Gender			
Female	13	5	8
Male	29	16	13
Age			
Median	62	67	57
Dev. Std.	10.3	11.2	12.6
Interval	(37-80)	(40-80)	(37-68)
Performance status ECOG			
ECOG=1	20	19	1
ECOG=0	22	2	20
Tumor placement (%)			
Head	30 (71.4%)		
Body	9 (21.4%)		
Tail	2 (4.8%)		
Patients with treatment delay (%)	34 (81%)	18	16
Pacients with dose reductions	18 (42.9%)	10	8

The mean number of courses of FOLFIRINOX was 9.5 (2-25, std dev 6.3), the total number being 399. The maximum duration of treatment was one year and five months, and the minimum was one month with the median of 8.5 months. 57.1% of patients received the full dose throughout the treatment. 17.07% of patients had grade 3-4 toxicity.

Data related to oncological treatment outcome and stratification by number of courses received are summarized in Table 4.2.

Table 4.2 Data on oncological efficiency in patients with advanced pancreatic adenocarcinoma

Data on oncological outcome after follow-up conclusion	All patients (N=42)	Number of patients with 6 courses FOLFIRINOX	Number of patients with more than 6 courses FOLFIRINOX	P value
Stable disease	2	1	1	
Partial response	3	1	2	
Complete response	0	0	0	
Progressive disease	37	19	18	
Median PFS	7.5	5.17	11.2	.08
(interval)		(1-13)	(3-35)	
Median OS	13.6	8	17.3	.06
(interval)		(4-9)	(5-42)	

Patients who received more than six courses had better progression-free and overall survival ($p<0.0001$) for each case, as shown in Figure 3 and Figure 4. Patients with treatment delay had better overall survival than those without, and so did those with dose reduction. The analysis was done without any other stratification. The results are represented in Figure 4.1 and Figure 4.2.

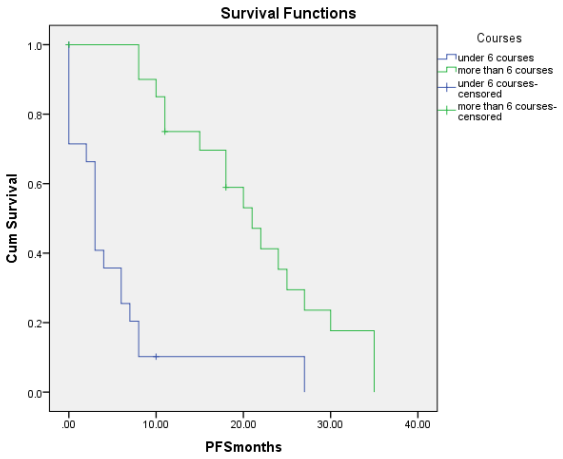

Figura 4.1. PFS stratified by number of couses (p<.0001)

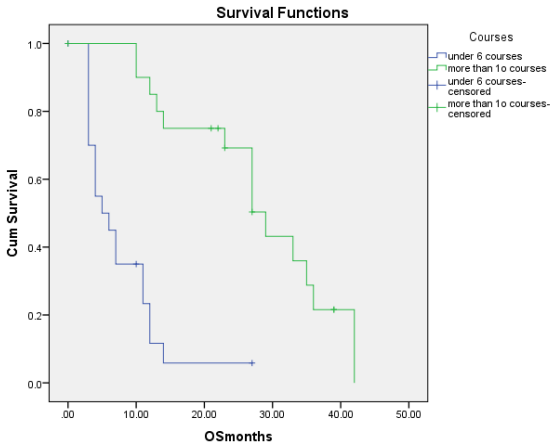

Figura 4.2 OS stratified by number of couses (**p<.001**)

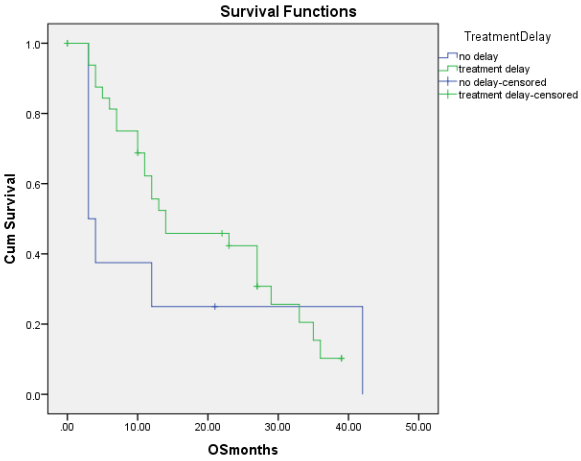

Figura 4.3. OS stratified by presence of treatment delay (**p=0.33**)

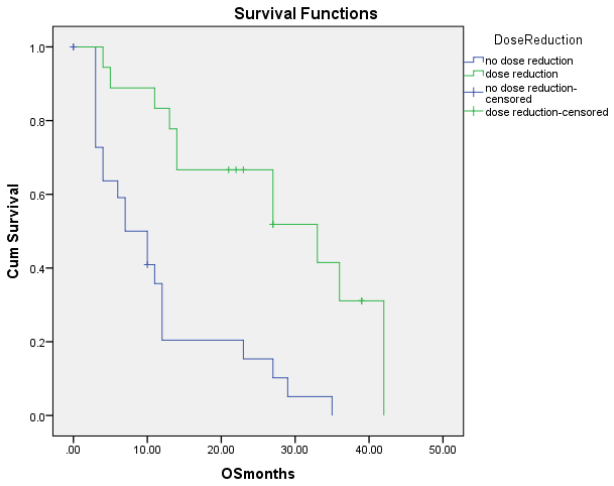

Figura 4.4. OS stratified by dose reduction (**p<.0001**)

4.4 Discussions

For the entire population studied in the present study, values similar to those reported in the literature were obtained (progression-free survival = 7.5 months, overall survival = 13.6 months). When patients were compared according to the number of courses received (less than six vs. more than 6), there were clear differences (progression-free survival: 5.17 months vs. 11.2, p = 0.8, overall survival: 8 months vs. 17.3 months, p = 0.6). In the PRODIGE trial, the most common toxicity was neutropenia (present in 45.7% of patients of any grade), with only 5.4% having grade four neutropenia. There was also one treatment-related death, also in the setting of febrile neutropenia. [25]

Hematologic toxicity was also most common in our study, with a higher percentage of grade 3-4 neutropenia. However, probably no deaths were reported in this context due to the smaller number of patients studied. The rates of thrombocytopenia and anemia were also higher in our study (19.5% vs. 9.1% and 17.07% vs. 7.9%). Sensory neuropathy of varying degrees occurred in 9% of PRODIGE patients. [25]

The much higher rate of sensory neuropathy in our study is, of course, explained by the much longer exposure to oxaliplatin. Success in administering toxic regimens like FOLFIRINOX over a long period of time lies in a few basic principles used in our clinic.

4.5 Conclusions

In conclusion, administration of FOLFIRINOX until unacceptable toxicity or disease progression is superior to administration for six months. However, it appears that the absence of treatment delay and maintenance of the full dose are not factors contributing to better survival, on the contrary. This may be an argument for choosing less toxic maintenance regimens, such as those suggested in the literature.

5. Study III: The usefulness of next generation gene sequencing (Next Generation Sequencing) in making treatment decisions in NSCLC

5.1 Introduction

Next-generation sequencing (NGS) is a fast and relatively inexpensive method to determine a large number of genes of crucial importance in precision medicine. NGS is the most accessible way to describe genomic changes in cancer patients both from tumor tissue samples and from circulating DNA that gives information both on prognosis, but above all can guide therapeutic decisions. The present literature review aims to describe the most important studies focused on treatment personalization in oncology and tissue agnostic therapy, to determine how eligible patients can be selected for these tests and to establish how a gene modification and its corresponding drug they can be classified according to the level of evidence of efficacy in non-small cell lung cancer (NSCLC)[26].

5.2 Insights from important precision medicine studies

We consider the study carried out in the National Cancer Institute - Molecular Analysis for the Choice of Therapy (NCI-MATCH) and SHIVA (molecularly targeted therapy based on the molecular profile of the tumor versus conventional therapy for advanced cancer) landmark studies for the treatment of histologically agnostic cancer. These trials shaped the way precision medicine is perceived today [27,28] Both in NCI-MATCH and in SHIVA the use of tissue agnostic therapies was not correlated with better survival or response rate than conventional alternatives decided by the investigating doctors, but they were trailblazers in terms of the design of precision medicine studies in oncology.

5.3 Tools to aid decision making in precision medicine

To avoid these problems, classifications have been developed to assist physicians in selecting targeted therapies for the gene alterations found. They organize

the current knowledge about the effectiveness of drugs in different alterations and histologies. All describe the antitumor effect by analyzing the magnitude of the clinical benefit.

The most widely used ranking system is the ESMO Scale for Clinical Utility of Molecular Targets (ESCAT) which relates the genetic alteration to its oncological relevance. To determine which tier a drug is classified into, clinical trials are analyzed for statistical significance [29].vThe most recent recommendations for NGS testing made by ESMO are to use for NSCLC multigene panels that include all alterations with targetability level ESCAT I. Given that gene fusions are very important in this location, the NGS panels used are of the DNA type or RNA [29].

An example of associations for different histologies is shown in Table 5.1.

Table 5.1 ESCAT classification in histologies other than NSCLC (1 Fibroblast growth factor receptor 2 Phosphatase and tensin homolog, 3 Ak strain transforming)

Targetability level	Genetic alteration	Tumor site	Medication used
IA	Germline BRCA 1/ 2 mutation	Breast cancer	Talazoparib
IB	FGFR[1] fusion	Cholangiocarcinoma Breast cancer	Pemigatinib
IC	NTRK fusion	Colorectal cancer Gastric caner	Entrectinib
IIA	PTEN[2] deletion or mutation	Prostate adenocarcinoma	Ipatasertib(+abiraterone)
IIB	AKT1[3] mutation	Breast cancer	AZD5363
IIIA	PIK3CA hotspot mutation	Hepatocellular carcinoma	Alpelisib
IIIB	ERB3 mutation	Breast cancer, Gastric cancer	Neratinib

5.4 The problem of cost-effectiveness in the choice of treatment in NSCLC

Studies on this topic have reported moderate cost-effectiveness in the use of NGS in advanced NSCLC. When analyzing the benefit, a minus point is the implicitly longer time until the results. In addition, and most importantly, the use of NGS can lead to the situation where the patient has, according to the literature and guidelines, the indication of a targeted treatment, but this is not reimbursed in the country. These situations can be foreseen by the forums that deal with public health in each country and personalized solutions can be proposed after the discussion in a panel of experts [30,31]

5.5 Conclusions

In conclusion, NGS testing in NSCLC for genetic alterations with ESCAT IA classifiable targetability is of paramount importance and should be considered standard.

6. Case study - Patients with metastatic NSCLC in whom the therapeutic decision was based on next-generation gene sequencing

The last chapter details the utility of NGS multigene testing in patients with non-microcellular lung neoplasm and the complexity of the mutational profile of this histological subtype. The type of NGS test used in both situations was FoundationOne, which used both plasma (circulating tumor cells) and tissue (biopsy from a progressive or recently occurring lesion). Both patients received treatment at the Oncology Clinic of the Elias University Emergency Hospital, coordinated by Professor Doctor Nitipir Cornelia, and the therapeutic decisions were made at the Oncology Commission of the Elias Hospital.

Case 1 reveals the importance of testing EGFR submutations in patients with metastatic lung adenocarcinoma and shows how they can influence the therapeutic decision.

Case 2 presents the course of a smoking patient with KRAS G12c mutation and shows the relevance of multigene testing right from the diagnosis, depending on which decisions can be made for treatment as the disease progresses.

7. Conclusions and personal contributions

In the first study, the one related to the maintenance of dose intensity in metastatic NSCLC, the administration steps of cytotoxic chemotherapy regimens in the Oncology Clinic of the Elias University Emergency Hospital were listed. They include important particularities and attention to these details can be decisive in maintaining the intensity of the dose. They include how to calculate the dose, supportive measures that allow the maintenance of the 100% dose even in the presence of hematological toxicity (anemia, neutropenia), prophylactic measures for various toxicities, checking drug interactions recurrently during treatment, details related to preparation and administration, the importance of premedication in reducing the toxicity rate, of nursing measures and of close collaboration with other specialties during the treatment. A proof of the effectiveness of this approach is the median overall survival reported in the published study of 14 months (higher than that reported in all pivotal studies with the regimens used).

In the second original article, the one that includes patients with advanced pancreatic carcinoma treated with FOLFIRINOX, it is again emphasized the importance of observing the administration details in order to administer this toxic regimen in the long term. Reference is made to the particular protocol of the department on which the research was carried out, which includes measures that are simple to apply, but easy to overlook: avoiding exposure to cold of the extremities to prevent neuropathy induced by oxaliplatin, maintaining an active lifestyle, respecting time administration of chemotherapeutics, collaboration with related specialties (especially with neurologists in the case of patients with co-morbidities that may predispose them to more severe neuropathy), maintaining hydro-electrolytic balance and avoiding the consumption of substances that can induce nerve damage, compliance with the recommendations of diet. Their clear enumeration is a

particular advantage of this work, and their observance can allow the administration of a toxic, triplet regimen even for 1 year and 5 months.

The literature review related to the utility of NGS in metastatic NSCLC belongs to the list of own contributions. The most important personal contribution in this case is the general perspective related to the vast majority of genetic alterations in NSCLC, bringing light on the number of alterations that a test used in the treatment decision of metastatic NSCLC must contain in order to be relevant especially through cost-effectiveness.

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List of published papers

1. Nitipir C, Vrabie R, Parosanu AI, Tulin R, Cretu B, Cursaru A, Slavu I, Miron A, Calu V, **Orlov Slavu MC** Clinical Impact of the Administration of FOLFIRINOX Beyond Six Months in Advanced Pancreatic Adenocarcinoma: A Cohort Study**.** Cureus. 2021 Nov 8;13(11):e19361. doi: 10.7759/cureus.19361. PMID: 34925974; PMCID: PMC8654089.
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