

The Personalized Treatment of Cancer

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Thesis abstract

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1.INTRODUCTION

Personalized medicine is the direct result of the recent technological and scientific developments. Personalized medicine is a medical model that proposes the customization of healthcare—with medical decisions, practices, and/or products being tailored to the individual patient. Cancer field is one of medicine specialties that benefited a lot from the developments in molecular biology: personalized approaches are used routinely now to guide patient management.

2. CURRENT KNOWLEDGE STATUS

At present, there is a switch from “populational” studies, based on statistics where the same protocol is applied to all patients for a certain type of cancer to personalized treatments where the characteristics of the individual tumor are taken into consideration. At the molecular level, there do not exist two identical tumors; each individual cancer has a unique profile. Once identified this unique profile with the help of molecular biology techniques, each tumor could be treated, at least in

theory, with a personalized treatment tailored specifically to the particular pattern of genetic alterations present.

The focus on the genomic aspects of cancer are due to the dominant paradigm in oncology today that describes cancer as a disease principally caused by the acquisition of somatic alterations (mutations, translocations, etc) in the genes. The consequence of these alterations is thought to be the rewiring of key intracellular signaling pathways and the “addiction” of the cancer cells the (hiper) activity of an altered protein belonging to a particular pathway. The genes responsible for this “bizarre circuitry” present inside the cancer cells are called “driver” genes in order to point to their relevance in oncogenesis (they are the “drivers” of the cancer process) as opposed to “passenger” genes which are also genes mutated in the cancer cell but they are considered to lack oncologic pathophysiologic relevance. The protein products of the “driver” genes confer growth advantage to the cells harboring them and, therefore, have been positively selected during cancer evolution. In the thesis we also presented briefly an original model of metastatic cancer published this year in *Oncolog Hematolog Journal* [1] and also several alternatives to the genomic-targeted treatments based on new oncogenesis paradigms recently reviewed [2] and also described in an editorial published 2 years ago [3]. One of these alternatives has been developed and implemented by us and, currently, it is tested in a Phase I clinical study that is currently enrolling patients (<https://clinicaltrials.gov/ct2/show/NCT02130492>). The term “biologic targeted therapy”, “molecular targeted therapy” or simply „targeted therapy” refers to a new generation of cancer drugs designed to interfere with a specific molecular target (typically a protein) that has been proven to have a critical, „driver” role, in tumor growth or cancer progression. In order to get an impression of the efficacy and costs of the targeted agents currently available in 2015 we did a survey of the molecular targeted agents routinely used for the treatment of solid tumors in USA. At present, in August 2015, in USA there are thirty one FDA approved molecular targeted agents for the treatment of solid tumors. In general, the targeted agents are either orally administered small molecules or monoclonal antibodies, administered intravenously. The first member of the new class of molecular targeted therapeutic agents was introduced by Brian J. Druker in 1996, who developed STI571, a small-molecule inhibitor, currently known as imatinib mesylate (Gleevec), for the treatment of chronic

myelogenous leukemia (CML). The reason for imatinib's spectacular efficacy in CML is related to the special pathophysiology of this disease; in CML the tumors become "addicted" to a unique, constitutively active „driver" translocation of the ABL kinase that has a direct, causal relationship with the development of CML. This favorable prognosis should not make us extrapolate positive results of this level of magnitude to solid tumors. In contrast to the idiosyncratic etiology of CML that is driven by only one „driver" alteration, solid tumors are much more complex than CML, and numerous „driver" alterations have been described in each solid tumor type. The presence of a unique „driver" alteration that can be targeted is relatively rare in solid tumors which have in average two to eight driver mutations present. The presence of multiple „driver" alterations per tumor genome and redundant or alternate pathways in the tumor cells makes the majority of solid tumors resistant either de-novo or after a variable course of treatment and, in general, solid tumors are much more difficult to treat than CML.

Lung cancer is a leading cause of death from cancer worldwide, accounting for approximately 19% of cancer related deaths worldwide and is responsible for more deaths than the next three most prevalent cancers (breast, prostate and colorectal) combined resulting in more than 1.5 million deaths per year (1.59 million deaths reported in 2012). Adenocarcinoma is the most common histological type of lung cancer (approximately 40%). Adenocarcinoma of the lung is also one of the main type of cancer where genomic-driven treatment approaches proved to be successful. Hence, we decided to focus on the genomic-driven treatment of metastatic adenocarcinoma of the lung (MAL) in order to investigate in detail, as a proof of concept, the clinical benefit of the genomic-driven paradigm. Molecularly targeted therapies have dramatically improved the treatment benefit for patients with lung cancer whose tumours harbor somatically activated oncogenes and molecular genotyping is now routinely used to guide clinical care of adenocarcinoma of the lung. The benefit of tyrosine kinase inhibitors (TKIs) in the treatment of MAL has been proven by several Phase 3 studies comparing an epidermal growth factor receptor (EGFR) TKIs to standard first-line chemotherapy. A meta-analysis [4] of data from 1502 patients enrolled in 6 trials that compared the results of using gefitinib, erlotinib or afatinib versus standard chemotherapy demonstrated an improvement in the progression free survival (PFS) and overall response rate (ORR)

but did not show an overall survival benefit (OS) benefit with the EGFR TKIs in patients with EGFR-mutated tumors. The long term survival (LTS) of patients treated in the large Phase 3 trials that enrolled hundreds of patients has not been yet reported.

3. PERSONAL CONTRIBUTION

As a direct result of new scientific discoveries, the personalized genomics-driven treatment paradigm has been recently challenged by other treatment frameworks such as immunotherapy, tumor microenvironment targeting, and stem cell-based approaches that are competing for the forefront of cancer therapeutics. Given the different competing treatment choices that are becoming available, it is a top research priority to investigate in detail the benefits of personalized genomic-informed driven approaches in order to decide what treatment strategy to choose for the best benefit of the cancer patients.

A1. First, we chose to focus on the erlotinib treated EGFR-mutated metastatic adenocarcinoma of the lung (MAL) as erlotinib has been the first targeted agent to be approved in USA for this disease subset and therefore more data on this agent is available than on the other targeted agents. The main question was the nature of the factors associated with long term survival for the MAL patients; in particular we were interested to find out whether erlotinib increases the long term survival (LTS) of patients with EGFR-mutated MAL or not. The patient information was extracted from the North Shore Hospital tumor registry and from the Montefiore Cancer Center medical records. With 32 full time medical oncologists, Montefiore Cancer Center is one of the largest cancer care programs in the New York metropolitan area, offering a spectrum of outpatient cancer services to more than 4,000 people with cancer per year. In order to characterize the factors associated with LTS, we performed a univariate retrospective analysis of 174 patients with MAL diagnosed at our institution between 2009-2011. 2009 was chosen as the start date as this is the year when a large randomized studies, from ASIA (IPASS study) [5] proved the benefit of tyrosine kinase inhibitors in the treatment of patients with EGFR mutated MAL. Following this study and a European study (EURTAC) in which similar results were obtained [6] erlotinib was approved by the Food and Drug Administration (FDA) and started to be used in the frontline setting of EGFR-mutated

MAL in USA. Most patients received multiple treatment modalities. Overall survival was estimated using the product-limit method and compared using the log-rank test patients alive at last follow-up were censored. In our series, 19% (33), of all patients (174) received erlotinib as part of their treatment and 40% (13/33) had EGFR mutations.

B1. Concerning the second objective of our study, we focused on the number and the nature of the „driver” genes altered in „wild” type MAL, the targetability of these genes and any clinical benefit based on the use of genomic-driven personalized treatment in as a result of a next-generation gene sequencing (NGS) analysis. For this purpose we obtained data from the North Shore Hospital pathology department and from the Monter Cancer Center medical records and we identified a cohort of 42 patients with metastatic adenocarcinoma of the lung for which detailed information regarding the molecular analysis of the tumor genomes performed at the Foundation Medicine laboratory using next-generation sequencing (NGS) techniques and their clinical outcome was available. We obtained clinical data for the each individual patient. Our series is one of the largest „wild type” MAL series reported so far, detailing individual information regarding the „driver” genetic alterations, the clinical outcome, and the targeted agents used. No two patients had the same genetic alterations.

A2. The results of the retrospective univariate analysis showed that although the 2-year and median survival were statistically superior($p=0.0129$) in patients receiving erlotinib and chemotherapy compared to patient receiving chemotherapy only, none of these treatment modalities improved the 5-year survival rate. Surprisingly, comparing the LTS rate in the group with MAL that received erlotinib (regardless of the EGFR mutational status) with the LTS rate of the group with MAL that did not receive erlotinib the 5-year survival rate was higher in the **no erlotinib arm. The only treatment modality that significantly improved LTS was lung surgery.** For the patients treated with erlotinib and chemotherapy, regardless of EGFR mutations, all observed deaths occurred within 4 years. Factors statistically significantly associated with LTS were: female gender ($p=0.009$), lung surgery ($p<0.0001$), early nodal stage, N0 ($P=0.0083$), bronchioalveolar histology ($p=0.0016$) and the presence of metastatic disease confined to the the lungs ($p=0.0054$). The PFS of patients with EGFR-mutated MAL treated with erlotinib was approximately

23.5 months. The preliminary results of this retrospective analysis were recently reported at the 2015 ASCO meeting [7] and presented under poster format at the 2015 IASLC meeting [8]. In our series, among the 33 patients treated with erlotinib, we identified four patients with MAL and EGFR mutations treated with erlotinib that survived more than 44 months. Two of them had exon 19 mutations and the other two had exon 21 mutations. Three of these four patients have been on erlotinib for at least 44 months. Three of them had a PFS of 44 months while taking erlotinib continuously (unfortunately one of them progressed after 44 months). Two of these patients had lung cancer localized to the lungs only, and one patient has a remarkable survival with brain + liver + lung lesions. She is alive for 44 months since diagnostic and continue to take erlotinib.

B2. The results for the genomic observational study. A total of 78 genetic „driver” alterations were identified in 71 genes and an average of 4.4 genetic „driver” alterations were present per patient. **The most commonly encountered number of genetic „driver” alterations was 4/tumor (10/42; 24%).** 30/42 tumors had TP53 mutations (71%) and 15/42 had KRAS mutations (36%). In terms of the **general function** of the „driver” **genes** that presented alterations: 42/71 (60%) of the genes were involved in **cell survival**, 20/71 (28%) of the genes were involved in **cell fate** and 7/71 (10%) genes were involved in **genomic integrity maintenance**. The most common **specific function** of the genetic „driver” alterations was signal transduction pathways (21/71) (30%). Surprisingly, the second most common **specific function** of genetic „driver” alterations was epigenetic control. (12/71) (16%). The third most common type of genetic „driver” alterations were in genes involving cell cycle regulation, (7/71)(10%) and controlling genome integrity, (7/71)(10%). **A total of 43% (18/42) of the patients had „driver” mutations in genes involved in epigenetic regulation making it the second most common hallmark of cancer in our cohort after TP53 mutations.** In terms of the **number** of „driver” alterations present across the 78 types of genetic „driver” alterations in the 71 genes there was a total of 184 genetic „driver” alterations overall: **mutations** were the most common alterations present in our series (127/184)(71%), **amplifications** were the second most common genetic alterations present in 46/184 (25%) of the patients and gene losses were the third most common (11/184)(6%) genetic „driver” alterations. In terms of nature of the 184 genetic „driver” alterations, 61 of the alterations were

related to signal transduction pathways (33%), 37 alterations were related to genome integrity (20%), 23, were related to epigenetic regulation (13%) and, 12, to cell cycle regulation (7%). Our analysis also showed that most of the tumors, 34/42 (81%) had both oncogenes and tumor suppressors genes present, 5/42 of the tumors (12%) had tumor suppressors genes only present and only a minority (7%) of the tumors, (3/42), had oncogenes only present. Overall, the number of tumor suppressor genes altered in our 42 patients MAL series was higher than the oncogenes altered (95 tumor suppressor genes vs 90 oncogenes). In the 42 patients with „wild” type MAL, targeted treatment was overall administered in only 5 of them (12%) and positive responses were obtained in only 2 of them. 30 out of the 42 patients in our series are now deceased. By the current 7.2015 nccn.org guidelines, 5 out of these 30 patients had potentially targetable mutations. Due to various considerations (rapid progression of the disease, poor performance status, knowledge regarding targeted treatment not available at the time of disease progression, etc) a targeted treatment was attempted in only one patient with a Her-2 neu mutation with, unfortunately, no response. 12 patients included in our series are currently alive and in 4 of them potentially targetable DNA alterations were found. The tumors of three of the four patients had Her 2 neu mutations and the tumor of the 4th patient had a V600E BRAF mutation. One the patients with Her-2 neu mutations received afatinib and trastuzumab, the two other patients received afatinib alone. One of the two patients that received afatinib alone responded favorably to the treatment and is curently still receiving the medication. The fourth patient had a V600E BRAF mutation and was treated with vemurafenib with a favorable response and is also currently still receiving the medication.

A3. It is not clear whether erlotinib treatment increases the LTS in patients with EGFR-mutated MAL or not and our study did not provide a definitive answer to this question. An interesting observation is the fact that although the majority of patients with EGFR mutated tumors in our series progressed after an initial response of approximately 15.3 months, three patients have been taking erlotinib for more than 44 months **without progression**. This raises the hypothesis of the existence of a subgroup of patients with EGFR-mutated tumors with unexpected long PFS. A recent study from Japan reported the results of a multivariate analysis regarding factors related to LTS in patients with EGFR-mutated MAL. Neither first line

treatment with a TKI or with a platinum doublet, influence in a statistically significant way the long term survival in patients with EGFR-mutated NSCLC [9].

B3. Recently, the NCI-Match trial has started enrolling patients in the US and the number of potentially druggable targets has expanded. Based on the inclusion criteria of the NCI-Match trial and tumor alterations profile, at least in theory, 31/42 (74%) of the patients on our series would have been potential candidates for the NCI-Match study.

Personalized cancer treatment using the genomic-driven approach is a paradigm whose clinical benefit in terms of long term survival still awaits definitive proof. In other tumor locations, for example in breast cancer, cases of very long survival have been described, including a case recently published by Professor F. Bădulescu [10]. We have also described a case of very long survival of advanced colorectal cancer with large liver metastasis cured using classical chemotherapy [11]. Both molecular targeted treatments and chemotherapy have their role in the treatment of cancer patients and must be personalized according to each patient. The reason for the limited efficacy of the molecular targeted approaches in cancer is, in our opinion, on one side, related to the inevitable appearance during their use of the phenomenon of resistance, caused principally by tumoral heterogeneity, on the other side, to the fact that, in general, targeted treatments, selected based on the presence in the cancer cell of idiosyncratic „driver” mutations, have a minimal influence on the metastatic process that represents the main cause of mortality and morbidity of cancer patients.

4. FINAL CONCLUSIONS

1.a) In our cohort the only treatment modality that improved LTS was lung surgery. This is an important finding as surgery is usually not cited in cancer guidelines (i.e. NCCN, for example) as one of the treatment options of metastatic lung cancer. Surgery could be offered selectively to patients with early nodal stages (N0), with lung only lesions without distal metastasis for whom surgery is done with curative intent.

2. a) As also shown by the randomized Phase III studies the erlotinib treatment improves the PFS and median survival of patients with mutated-EGFR MAL but it is

unclear at present whether erlotinib increases LTS in patients with EGFR-mutated MAL. A direct comparison in terms of LTS of the two groups with the best theoretical chance of LTS (a group of patients with EGFR-mutated tumors that received erlotinib and a group of patients with unknown EGFR mutational status that did not receive erlotinib and had lung surgery) showed that the outcomes of the two interventions are very similar: in patients with MAL candidates for surgery with curative, surgery is probably the best chance of LTS; if surgery is not an option and they have EGFR-mutated MAL one of the currently available TKIs for this indication should be used.

3. a) The analysis of 42 tumors with „wild” type MAL using NGS demonstrated that in average each lung tumor harbors, in average, 4 genetic „driver alterations and 43% (18/42) of the patients in the group had „driver” mutations in genes involved in epigenetic regulation making it the second most common hallmark of cancer in our cohort after TP53 mutations. Our observation has been confirmed by larger studies [12].

b) Also, another clinically significant finding of our study, is that 7/15 (47)% of the tumors bearing KRAS gene mutations, that, in general, are considered undruggable had a second, potentially „druggable” target.

4. In theory, 74-95% of the patients in our series of „wild” type MAL could have received, in theory, a genomic-driven molecular targeted treatment, but, in reality, because of different logistical problems and the clinical profile of the individual patients, targeted treatments were administered only to a minority of them (12%) and the clinical benefit was modest (5%).

5. The genomic-driven personalized treatment of lung cancer represents a therapeutic progress as it may help some patients achieve a better and longer quality of life than classical treatments.

In the dawn of the immunotherapy era, our pilot data obtained in patients with metastatic adenocarcinoma of the lung is a benchmark that can be used for further evaluation of different types of personalized treatment.

5. SELECTIVE BIBLIOGRAPHY

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