Case Reports and Reviews

Review Article

Selective and Adaptive Targeted Approach to Influence Genomics and Epigenomic Signature in Lung Cancer

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Abstract

Application of single targeted therapies in cancer has caused resistance in tumors, especially the heterogeneous tumors such as lung cancer. Here we propose a different strategy in approaching heterogeneous tumors, looking at a sequential but systemic and pan-genomic targeted therapy through epigenetic modifications. We aim to trigger new hypotheses and generate provoking scientific methods to address current challenges in oncology care.

Introduction

It is well known that heterogeneous tumors are a wide group of solid tumors that are recently described and defined based on their genomic signature consisting of a variety of biomarkers, and colonies which differ in their biological behavior [1-3]. Unfortunately, as much as our understanding of new targets in cancer is evolving, we still face two main problems, one being unable to target many of the newly described targets, and second being unable to translate a "target response" to a "clinical response" [4]. Such problem is mainly related to the fact that tumors are not anymore defined based on their location, rather their behavior which is mainly under the influence of their genomic signature. The more we discover the genomic signatures, the more we realize that a simple biopsy of a tumor may certainly not reveal its real "heterogeneous" character, as if we would need hundreds or thousands of samples in a single tumor to be able to show the entire picture. Newly described strategies have been undertaken to resolve the problem in research, including geographic diffusion molecular profiling, but again as mentioned, the critical question remains as we still are not able to pinpoint the driver settings of genes whose alteration has the potential to correlate with survival. This problem would be even further complicated by implementing cytotoxic and targeted therapies, which patients would receive in a standard setting at the time this paper is published. First category, the cytotoxic therapies, can cause activation of multiresistance genes, cause mutation in the tumor, and further stimulate the tumor's stem cells, and make it more difficult to treat. Second group, targeted therapies, also can cause resistance by inducing mutations in the DNA as well as enhancing the process called "selective advantage" of the cells that are not responding to the targeted therapy. There is also another phenomenon described in the literature called "oncogenic addiction" which is a major problem with even responding tumors, such as is the case with non-small cell lung cancer or lymphomas treated with targeted therapies. This phenomenon is especially problematic when a tumor is more heterogeneous, as not only the tumor is now "addicted" to the treatment and possible flare-ups are seen very commonly with stopping the therapy, but also continuation of the treatment causes further selective advantage to the resistant subgroup of the cells not responding to the treatment. This is a pattern commonly seen again in non-small cell lung cancer or breast cancer where heterogeneity of the tumors is well described. Physicians face a big challenge here as if they stop the treatment, the disease flares up by the "already treated" cells, and if they continue the same regimen, this increases the suppression of the already treated cells, giving space to the untreated cells, which now require a further additional therapy. The studies have confirmed that stopping the first targeted therapy "even after its failure" causes 16 percent increase in tumor size and activity, talking about Erlotinib therapy in NSCLC, to the point that current data suggests continuing the treatment even when a patient has failed to respond. To the standard current practice of conventional oncology, this is unacceptable as a physician is asked to continue a therapy when it has already failed and ask the patient to tolerate the major toxicity involved with these therapies, just because there is no real other option. This has made researchers try to come up with new treatments including second-generation or third-generation tyrosine kinase inhibitors,

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but yet this sounds like changing the seats on the Titanic as it is going down, because neither of these new regimens (such as AZT, Clovis drug inhibitors of T790M) is able to provide a solution to the cause of the problem: HETEROGENEITY of the tumor. Finally, there have been strategies around "sequential tyrosine kinase inhibition" which is intended to reduce the potential and strongly possible effect of secondary mutations in DNA, confirmed by post-therapy circulatory DNA assessments when a targeted therapy is used. The best example again is using the EGFR inhibitory drugs when pre-CTC analysis shows single alteration and post-CTC analysis shows a wide range of mutations, confirming the fact that the drug itself has promoted "HETEROGENEITY" of the tumor.

The other reason that we do not like the EGFR blockade has to do with the fact that EGF is involved in STAT regulation, which in contrast to the understanding of many, upregulates the cyclin-dependent kinase and has "pro" apoptotic effect, as well as increasing caspase. This concept was shown in prior studies that showed activation of EGFR could enhance apoptosis. Conversely, the inhibition of EGFR can cause resistance to apoptosis, and this is why the combination of cytotoxic therapies has failed to improve survival when added to the EGFR blockade in non-small cell lung cancer in every trial.

Case studies

Here we review thirteen (13) cases of non-small cell lung cancer and review their outcome, but before that we specifically will discuss three cases of lung adenocarcinoma with and without EGFR positive status resistant to standard of care, in detail, whom we treated successfully with this approach. On the case one, who was status post conventional cytotoxic drugs, and radiation and surgery, with progressive disease, with advanced dissemination, although tumor was positive for actionable EGFR, our treatment was effective without using TKI (independent effect) AND also in combination with TKI. We showed eradication of CTC which carried c-MYC overexpression just by our therapy in two weeks. In combination phase, we were able to use minimum dose of the targeted therapy, Erlotinib, EGFR blockade for NSCLC, aiming to reduce the oncogenic addiction (this is an alternate dosing of 1/16 of standard dose, instead of once a day dosing), as a result patient received only a metronomic, if you wish to say, of the standard dosing. We were also able to taper and stop the TKI long before the failure, this was performed in 6 weeks. Patient was followed closely and we showed improved surrogate markers for her survival, documented by complete eradication of CTC, progression-free survival and overall survival, which translated to a complete remission with only minimum residual disease, and no FDG-avid tumor in her lungs and elsewhere. (Please see our other abstract, "Prognostic Surrogate Markers for Survival," on circulatory tumor cells and intratumoral hypoxia.)

Second case was a lung adenocarcinoma with negative KRAS and EGFR and ROS1 on biopsy BUT positive KRAS/c-MET and ROS1 in liquid biopsy, who presented with brain metastatic lesions, and was treated ONLY with our therapy, showing stable disease after 6 months, with reduced c-DNA MAF of KRAS, c-MET, ROS1. He has received no cytotoxic chemotherapies and has passed expected overall survival for a patient with brain mets. (Please see below.)

Third case was a lung adenocarcinoma status post failure of many regimens of therapies, chemotherapy along with antiangiogenic therapies, and immune therapies, presented with disseminated disease and liver and bone mets and peritoneal metastasis. She was treated with our therapy again independently for over a year, and in combination with metronomic chemotherapy. She has passed 7 years of survival with minimum residual disease with no FDG-avid activity in all her chest (mediastinum, lungs, LNs) and liver and bone lesions, at the time of this paper. She has no circulatory DNA or CTC identified at this time.

This example proves the concept that a multitargeted epigenetic therapy can be proposed as a superior alternative to current standard of care.

Discussion

Here we propose a new strategy to use a "heterogeneous" approach for a heterogeneous tumor. In this approach, we have looked in the literature already published in systemic review for the mechanisms of resistance in targeted therapies [5-9] and we have identified the following facts:

1. The resistance of a tumor, by selective pressure phenomenon, is a common end result of using any and all TKI.
2. The resistance of the tumor correlates with the patient's survival.
3. The strategies of current standard of care to resolve the resistance (such as TKI sequential therapies) have failed. In fact:
4. The current standard of care induces "heterogeneity" of the tumor by three mechanisms: one, inducing hypoxia, mainly by cytotoxic therapies; second, by DNA mutation through all targeted therapies; and thirdly, through negative impact on cancer stem cells by increasing their plasticity [10,11].

To overcome the above problems, we consider the following:

We propose to consider a MULTI-TARGETED approach rather than one target therapy. We propose that such approach replaces current best standard of care for heterogeneous tumors which is suggested as a sequential targeted therapy. So instead of using different targeted therapies at different times, we propose using several targeted therapies at once. Such approach has also been suggested by a few researchers in the field, an example was using Erlotinib with Everolimus compared to Erlotinib alone in lung CA. Unfortunately, the study failed to show any improved survival. The conclusion was that perhaps the EGFR blockade is bypassing the mTOR blockade or there are other downstream targets that are activated by time, besides the mTOR, such as MAPK kinase. There was also a possibility of activation of feedback loops by using mTOR inhibitors itself. This, if true, again confirms our theory that using a targeted therapy can (and most likely will) induce the upstream molecules/genes, as well as parallel transduction pathways.

Now the main question was what targets we have to aim for to be able to maximize the impact on resistance and at the same time minimize the oncogenic addiction pattern. So we started to look at the upstream targets, rather than downstream targets, as the more a target is downstream, the more likely.

The discovery around the feedback loops and the upstream targets activation pointed again to the lack of long-term survival benefit in most patients when a single target was treated alone. Unfortunately, all the upstream targets are still under investigation for a new drug, and many of them are not approved. In lung cancer, it has been suggested that the HSP-70 and 90 are a main target for both resistance to EGFR blockade as well as ERBB2, Akt, and HIF.

It is worth noticing that the combination of multitargeted drugs such as Regorafenib/Nexavar/Sutent/Dasatinib,… have also failed to transition into better survival in many trials when compared to the standard of care, which is in contrast to our hypothesis. However, we explain the failure being due to the fact that these drugs, although being multitargeted in nature, are not adapted to the mutation alteration fraction (MAF) of the tumor. Even the combination of these drugs that ultimately blocks all pathways has failed in trials to improve survival as the RATIOS for the blockage are more important than the number of targets. In other words, if the tumor is driven by the BRAF and at the same time has mTOR and KRAS mutations, targeting all these targets would perhaps be unnecessary and in fact detrimental as it can cause selective pressure on the other existing cells and activate feedback loops. For example, recently we know that ultimately all colon cancers are RAS positive in a certain ratio, and targeting EGFR positive cells only increases the growth of KRAS positive minorities. Therefore, a multitargeted approach which consists of targeting the main upstream genes to avoid resistance and activation of upstream genes was initially thought to be reasonable. For example, a combination of HSP-70 and 90 inhibitors with EGFR blockade (this has been suggested in the literature using Geldanamycin after Erlotinib failure in non-small cell lung cancer). Another example was the KRAS. Due to frequent mutations in lung, pancreatic, and colon cancer, KRAS offered a good theoretical therapeutic target. Tipifarnib, an inhibitor of farnesylation of RAS protein, failed in clinical trials. BRAF inhibition was not at all better. Oral multikinase inhibitor Regorafenib inhibits BRAF and VEGFR, PDGFRβ, FGFR, KIT, and RET. Drug resistance, however, occurs early, which is supported by loss of function of PTEN and activation of AKT. Additional mechanisms of resistance to BRAF inhibitors include secondary KRAS mutations and activation of MEK/ERK. MEK inhibitor Selumetinib produced encouraging results but caused resistance through upregulation through WNT signaling.

The end result is that the RATIOS of the DRIVING mutated cells with actionable targets determine what drugs need to be used, and unnecessarily blocking the targets that are not drivers would enhance resistance.

Therefore:

1. Before using any TKI (we do not recommend in addition to cytotoxic chemotherapies for reasons explained), we propose to identify the driving mutations. We propose to use cDNA as it can guide for the possible driving cells through identification of the MAF (Mutation Alteration Fraction). Here we could see that assessment of the tumor signature by using circulatory DNA is a useful method as it can give a snapshot of the mutations in real time, and also provides a prognostic value for the therapy's effectiveness. Here the tumor targets are identified, and their ratio of penetrance calculated, and the therapy designed to have a real effect on the most relevant cells with minimum effect on the feedback loops. Here we propose that more is not necessarily better. So we propose to use minimum dosage of the targeted drug, for example in non-small cell lung cancer with EGFR positivity we have shown using 1/16 of the standard dosage as effective, and the rationale is that the anti-EMT response and CSC response by TKIs are NOT dose-dependent. We use targeted therapies at this low dose only as a measure to reduce oncogenic addiction and we keep in mind that we avoid inducing tumor selective pressure at all times. Epigenetic therapies are indeed extremely important to achieve this, as is the case for EGFR blockade. We now know that EGFR target, when methylated, does not respond to the EGFR blockade and therefore epigenetic demethylation of EGFR is vital to the response to EGFR TKI and prolongs the response much beyond the estimated 12 months in the trials (please see the case report below). In fact, we reverse the potential failure of such drugs substantially.
2. Second, we propose to change the tumor's heterogeneous feature by modifying its behavior. We were especially interested in the targets that are involved with the heterogeneity of the tumor. We found that the more hypoxic tumors disseminate more cDNA, and the more hypoxic a tumor, more heterogeneity is seen. Therefore, we were interested to regulate the intratumoral hypoxia through epigenetics (please see our abstract 10). In concert with this, we identified a major target—HIF-1 and 2—and we designed the MTET therapy around the epigenetic regulation of HIF. Here we have shown in vitro studies to prove our concept by looking at the HIF and tumor integrity in 3-dimensional culture media and proving the effectiveness of the MTET over HIF-related pathways and response elements.

We believe that by changing the tumor's behavior, by reducing the tendency for "Genometastasis" and dissemination of the tumor's signature through CTC and cDNA, we reduce the tumor's ability to metastasize. We believe that failure of the current targeted therapies has to do with the non-adaptiveness of such method, where the tumor genetic instability causes a very dynamically transforming signature that can only be treatable IF this instability is reduced (by epigenetic therapy), as if a target for the shooting gun needs to stay at one place and not as rapidly move, as the Darwinian evolution pertains to [12-15]. It is mentioned earlier that this approach is revolutionary as it contradicts current standard of care, which is more a phenotypical therapy, as we know all cytotoxic therapies and majority of targeted therapies increase the heterogeneity of the tumor and its behavior. Studies have confirmed that presence of cDNA increases by cytotoxic drugs and all trials so far (such as S0500) have failed to prove a strategy around targeting the CTC by switching the chemotherapy regimens in breast cancer, for example. This is common sense, as if you use a very broad-spectrum antibiotic you will end up with resistant colonies, as if you are winning the battle and losing the war, even in the cases that the current standard of care defines success by RECIST criteria, which was questioned in our prior abstract (Surrogate markers for survival).

3. It has been proposed that targeting genome-level heterogeneity represents an effective strategy in the treatment of cancer, as emphasis on the pattern of system evolution rather than specific pathways provides a global and synthetic approach. This is also important in relation to current subject of discussion for tyrosine kinase resistance [16-21]. The rapid kinetics, the reversibility of acquired drug resistance, and the absence of genetic mutations suggest an epigenetic basis for drug insensitivity. Therefore, the multitargeted approach should also target the epigenetic targets to enhance stem cell differentiation and reduce the heterogeneity as well as drug resistance. This has been described in our abstract described earlier, called Multitargeted Epigenetic Therapy, as well as other colleagues, in Epigenetic

Dream Team, in 2014, pointing into the fact that there is plasticity for evolution of cancer stem cells during tumorigenesis that can involve movement between cell populations in a reversible fashion. Epigenetic plasticity could impact altered genetic expressions, in the creation of cellular HETEROGENEITY in cancers of all types. Further, a reversed epigenetic modification that can correct the aberrancies can reduce the "stemness" of such multipotential cells to a more defined clonogenicity, and reduction in dynamic heterogeneous tumor cell population state. Such genomic architecture changes are modifiable even after genetic and epigenetic mutations have occurred. It is also important to know that heterogeneity also is seen in epigenetic signature of tumors.

Conclusion

We propose to consider a MULTI-TARGETED approach rather than one-target therapy. We propose that such approach replaces current best standard of care for heterogeneous tumors which is suggested as a sequential targeted therapy.

References

1. Jamal-Hanjani M, Quezada SA, Larkin J, et al. Translational implications of tumor heterogeneity. Clin Cancer Res. 2015;21(6):1258–1266. doi:10.1158/1078-0432.CCR-14-1429
2. Rich JN. Cancer stem cells: understanding tumor hierarchy and heterogeneity. Medicine (Baltimore). 2016;95(1 Suppl 1):S2–S7. doi:10.1097/MD.0000000000004764
3. Burrell RA, McGranahan N, Bartek J, et al. The causes and consequences of genetic heterogeneity in cancer evolution. Nature. 2013;501(7467):338–345. doi:10.1038/nature12625
4. Diaz LA, Williams RT, Wu J, et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. Nature. 2012;486(7401):537–540. doi:10.1038/nature11219
5. Kleppe M, Levine RL. Tumor heterogeneity confounds and illuminates. Nat Med. 2014;20(4):342–344. doi:10.1038/nm.3522
6. Marusyk A, Almendro V, Polyak K. Intra-tumour heterogeneity: a looking glass for cancer? Nat Rev Cancer. 2012;12(5):323–334. doi:10.1038/nrc3261
7. Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. Science. 2013;339(6127):1546–1558. doi:10.1126/science.1235122
8. Neelakantan D, Drasin DJ, Ford HL. Intratumoral heterogeneity: clonal cooperation in epithelial-to-mesenchymal transition and metastasis. Cell Adh Migr. 2015;9(4):265–276. doi:10.4161/19336918.2014.972761
9. McGranahan N, Swanton C. Clonal heterogeneity and tumor evolution: past, present, and the future. Cell. 2017;168(4):613–628. doi:10.1016/j.cell.2017.01.018
10. Kreso A, Dick JE. Evolution of the cancer stem cell model. Cell Stem Cell. 2014;14(3):275–291. doi:10.1016/j.stem.2014.02.006
11. Negrini S, Gorgoulis VG, Halazonetis TD. Genomic instability: an evolving hallmark of cancer. Nat Rev Mol Cell Biol. 2010;11(3):220–228. doi:10.1038/nrm2858
12. Lee AJ, Endesfelder D, Rowan AJ, et al. Chromosomal instability confers intrinsic multidrug resistance. Cancer Res. 2011;71(5):1858–1870. doi:10.1158/0008-5472.CAN-10-3604
13. Mettu RK, Wan YW, Habermann JK, et al. A 12-gene genomic instability signature predicts clinical outcomes in multiple cancer types. Int J Biol Markers. 2010;25(4):219–228. doi:10.5301/jbm.2010.6079
14. Gerlinger M, Swanton C. How Darwinian models inform therapeutic failure initiated by clonal heterogeneity in cancer medicine. Br J Cancer. 2010;103(8):1139–1143. doi:10.1038/sj.bjc.6605912
15. Jamal-Hanjani M, Wilson GA, McGranahan N, et al. Tracking the evolution of non-small-cell lung cancer. N Engl J Med. 2017;376(22):2109–2121. doi:10.1056/NEJMoa1616288
16. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415–421. doi:10.1038/nature12477
17. Tomasetti C, Vogelstein B, Parmigiani G. Half or more of the somatic mutations in cancers of self-renewing tissues originate prior to tumor initiation. Proc Natl Acad Sci U S A. 2013;110(6):1999–2004. doi:10.1073/pnas.1221068110
18. Fisher R, Pusztai L, Swanton C. Cancer heterogeneity: implications for targeted therapeutics. Br J Cancer. 2013;108(3):479–485. doi:10.1038/bjc.2012.581
19. Haber DA, Settleman J. Cancer: drivers and passengers. Nature. 2007;446(7132):145–146. doi:10.1038/446145a
20. Tatematsu A, Shimizu J, Murakami Y, et al. Epidermal growth factor receptor mutations in small cell lung cancer. Clin Cancer Res. 2008;14(19):6092–6096. doi:10.1158/1078-0432.CCR-08-0332
21. Taniguchi K, Okami J, Kodama K, et al. Intratumor heterogeneity of epidermal growth factor receptor mutations in lung cancer and its correlation to the response to gefitinib. Cancer Sci. 2008;99(5):929–935. doi:10.1111/j.1349-7006.2008.00782.x