IN THE SPOTLIGHT

A Combined Epigenetic Therapy Equals the Efficacy of Conventional Chemotherapy in Refractory Advanced Non–Small Cell Lung Cancer
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Summary: A new study by Juergens and colleagues provides the first successful example of a combined epigenetic therapy capable of achieving results similar to those of conventional chemotherapy in refractory metastatic non–small cell lung cancer. Furthermore, the authors describe interesting blood-based DNA methylation biomarkers that may be useful in predicting clinical response. Cancer Discovery; 1(7): 557–9. ©2011 AACR.

Commentary on Juergens et al., p. 598 (4).

BACKGROUND

No one doubts that tumorigenesis is a consequence of not only genetic but also epigenetic alterations (1). Indeed, cancer epigenomes are characterized by global changes in DNA methylation and covalent histone modification patterns. Moreover, the disruption of the different machineries in charge of the main epigenetic mechanisms (the two just mentioned as well as nucleosome positioning by ATP-dependent chromatin remodeling and the deposition of histone variants), by either mutation, deletion, or altered expression of the genes encoding their components (e.g., due to microRNA dysregulation), is a hallmark of cancer (1). Malfunction of epigenetic processes during tumorigenesis has strong implications in the fight against the disease. First, the CpG-island promoter methylation status of some genes is already used as a reliable biomarker for cancer detection, tumor prognosis, or prediction of treatment response. The best example may be provided by the MGMT gene in glioma, where its promoter hypermethylation leads to greater sensitivity to carmustine- and temozolomide-based therapies (2, 3). Second, whereas genetic mutations are permanent, cancers depend on microRNA dysregulation), is a hallmark of cancer (1). Malfunction of epigenetic processes during tumorigenesis has strong implications in the fight against the disease. First, the CpG-island promoter methylation status of some genes is already used as a reliable biomarker for cancer detection, tumor prognosis, or prediction of treatment response. The best example may be provided by the MGMT gene in glioma, where its promoter hypermethylation leads to greater sensitivity to carmustine- and temozolomide-based therapies (2, 3). Second, whereas genetic mutations are permanent, cancer-related epigenetic abnormalities, such as CpG-island promoter hypermethylation of a given gene or an incorrect covalent histone modification pattern, can be reverted using drugs.

The current arsenal of so-called epi-drugs includes inhibitors of the DNA methyltransferases (DNMTi), histone acetyltransferases and deacetylases (HATi and HDACi, respectively), sirtuins (SIRTi), and histone methyltransferases and demethylases (HMTi and HDMi, respectively) (1). Some of these epi-drugs, such as the DNMTis vidaza (the cytidine analog 5-azacytidine) and decitabine, or the HDACis vorinostat and romidepsin, have already been approved by the U.S. Food and Drug Administration (FDA) for the treatment of several hematologic malignancies. Increasing evidence indicates that future cancer therapies will take advantage of the synergistic effects achieved with different combinations of these epi-drugs and other conventional antitumor agents.

STUDY RESULTS

In this issue of Cancer Discovery, Juergens and colleagues (4) report the results of a phase I/II clinical trial in which they used a combined epigenetic therapy based on the well-known DNMTi 5-azacytidine and the HDACi entinostat (MS-275), a quite potent HDACi capable of inhibiting HDAC1, HDAC2, HDAC3, and HDAC9. The authors obtained encouraging results in a cohort of 45 patients with refractory metastatic non–small cell lung cancer (NSCLC). Whereas in other studies epi-drugs tended to be used at high concentrations, seeking to cause maximal cytotoxicity, here the authors used much lower doses. This approach, successfully used in patients with certain hematologic malignancies, such as myelodysplastic syndrome (MDS), not only resulted in fewer (and more easily managed) side effects, but also had key effects on the aberrant epigenome of the patients’ tumor cells.

Thus, among the patients included in the trial, median progression-free survival and overall survival were 7.4 weeks and 6.4 months, respectively, good numbers if we compare them with the median overall survival achieved using erlotinib, the only FDA-approved drug for this kind of disease (6.7 months); notably, patients who completed at least one cycle of the combined epigenetic therapy with 5-azacytidine and entinostat displayed a higher median survival of 8.6 months. Because of this prolonged survival, up to 19 patients in the study (21%) were able to undergo subsequent chemotherapy and, most important, 4 of these patients reacted very positively. It is important to highlight that the results of the study also include a patient who...
showed a complete response, as well as a second patient displaying a partial response. Regarding the first patient, 14 months after receiving the combined epigenetic therapy, she was found to have another pulmonary nodule that turned out to be a molecularly different primary NSCLC (KRAS-mutant). At the time of its resection, no viable tumors were observed at prior sites of the disease. Although she had no symptoms for almost 12 months, eventually the KRAS-mutant tumor relapsed and progressed fatally. With respect to the patient with a partial response, the combined epigenetic therapy originally achieved a full radiographic resolution of his multiple liver metastases, as well as a partial resolution of his lung and mediastinal disease. However, after recovering from a different primary small cell lung cancer and a long period without any symptoms, he has recently been found to have a recurrence of the NSCLC in his chest.

Finally, Juergens and colleagues (4) studied whether the combined therapy was capable of reverting the aberrant CpG-island promoter hypermethylation of four genes: CDKN2A, CDH13, APC, and RASSF1A. The epigenetic silencing of at least 2 of these 4 genes was previously defined as a prognostic marker associated with rapid tumor recurrence and, eventually, death (5). In fact, the authors studied this issue by using the free-circulating tumor DNA of 26 patients before and after cycle 1 of epigenetic therapy, because they did not have available pretreatment tumor biopsies. The presence of DNA hypermethylation events in serum DNA from cancer patients has been recognized since 1999 (6). Of the 10 patients displaying promoter hypermethylation of at least 2 of these genes before treatment, 8 (80%) showed stable disease or objective responses after epigenetic therapy; median progression-free and overall survival were 3.3 and 10.4 months, respectively. Of the 16 patients without the positive methylation signature before treatment, only 4 (25%) presented stable disease and there were no objective responses; the median progression-free and overall survival of this group of patients were clearly worse: 1.7 and 6.5 months, respectively.

**VIEWPOINT**

This work is quite interesting for a number of reasons. First, as the authors point out, there have been no articles describing such a successful epigenetic therapy in solid tumors. This by itself would be a remarkable fact but, additionally, we should bear in mind that the combined therapy with 5-azacytidine and entinostat was shown to be as effective as the typical conventional chemotherapy with erlotinib in patients with refractory metastatic NSCLC. In this regard, it is important to highlight that NSCLC accounts for approximately 80% of lung cancer cases, and that this disease continues to be the main cancer-related cause of death worldwide. Second, the fact that, in comparison with previous unsuccessful clinical trials in solid tumors, the patients here received lower doses of 5-azacytidine seems to establish that at least in a variety of malignancies (including, obviously, the known hematologic cancers), the effectiveness of this epi-drug is based more on its capacity to revert the abnormal cancer-related epigenetic DNA methylome than on its mere cytotoxicity (reached at higher doses). This is a finding that may be taken into account for future trials in which 5-azacytidine could also be delivered by elaidic acid esterification, because this recently has been observed to improve its cellular uptake and anticancer activity (7).

On the other hand, we wonder what kind of results would be obtained by combining this epigenetic therapy with erlotinib or other conventional chemotherapy compounds, especially when a better clinical outcome was observed in some of the patients who underwent subsequent chemotherapy once the trial was finished; we agree that stable gene expression changes caused by the epigenetic therapy could account for this effect, and, in this respect, it is important to remember that the general improved access to chromatin provoked by some epi-drugs (e.g., HDACi) is already known to improve radiotherapy (8) and may also lead to a better performance of DNA-damaging agents. One example of successful synergistic combination between an epi-drug and a conventional drug comes from a recent phase II study with 5-azacytidine and the thrombopoietin mimetic romiplostim in patients with MDS (9). It is also remarkable that a putative combination with erlotinib should take into account the recently described connection between the appearance of cancer cell resistance to this drug and an increase of the histone demethylase KDM5 (10).

Finally, the study of the DNA methylation status of the previously reported NSCLC poor prognosis biomarkers (CDKN2A, CDH13, APC, and RASSF1A) before and after cycle 1 of therapy, in the free-circulating tumor DNA, is an interesting contribution. Given the positive correlation found between the demethylation of the starting aberrant promoter hypermethylation of these genes and a good final response, this evaluation, and others such as DNMT3B gene amplification (11), are worthy of inclusion in future trials involving DNMTIs as predictors of clinical benefit.

![Figure 1](https://www.aacrjournals.org/cancer_discovery/2011/11/212011f1.jpg) **Figure 1.** Current status of epigenetics drug portfolio in treatment of human cancer.
CONCLUSION

This article describes the encouraging results obtained from a new combined epigenetic therapy, involving 5-azacytidine and entinostat, against refractory advanced NSCLC. It also defines new biomarkers for clinical outcome that could be used in similar future trials. Most important, with this work Juergens and colleagues (4) may open the door to the possibility of an effective epigenetic therapy against solid tumors. Furthermore, if DNA demethylating agents and histone deacetylase inhibitors are the ground-breaking epigenetic drugs that reach clinical development, many other compounds targeting other elements of the epigenetic machinery (Fig. 1) are just knocking on the door—brave oncologists and pharmaceutical pioneers are needed to start new clinical trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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