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Epigenetic approaches to overcoming chemotherapy resistance

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Tumour cells are well known to develop genetic alterations that cause drug resistance during disease progression. These acquired genetic changes and resistance patterns were long thought to be permanent and unalterable, which led to the assumption that a tumour that has progressed after treatment needs a different non-cross-resistant treatment plan. However, growing data of epigenetic changes to the transcriptional potential of cancer cells during tumour progression are transforming this picture. Epigenetic alterations have been shown to contribute to both tumour progression and chemotherapy resistance in a myriad of tumour types, including chronic myeloid leukaemia and lung, gastric, colorectal, breast, bladder, and ovarian cancer.^{1–4} Aberrant epigenetic mechanisms include CpG island methylation and histone acetylation, which can be modulated by DNA methyltransferase and histone deacetylase inhibitors, respectively. Unlike genetic mutations, however, changes to the epigenome are reversible with epigenetic therapy.^{5,6} Growing evidence suggests that epigenetic therapy has the potential to overcome chemotherapy resistance by resensitising cancer cells to previously effective, but refractory treatments. This epigenomic mechanism for resensitisation is coined episensitisation and refers to the reversal of epigenetic changes associated with resistance to treatment^{6–8} and embodies the concept of therapy rechallenge. This ability to overcome chemoresistance challenges the traditional dogma of irreversible acquired resistance and is an attractive strategy to improve clinical outcomes and treatment frameworks.

RRx-001 is a member of a new class of panepigenetic modifying drugs called dinitroazetidines that look exceptionally promising in early clinical development. Under hypoxic conditions, RRx-001 inhibits several DNA methyltransferases and histone deacetylases by mediating oxidation of important Cys residues within their catalytic sites. Such inhibition results in an altered epigenetic profile in cancer cells. In *The Lancet Oncology*, Tony Reid and colleagues⁹ report interesting data from their phase 1 trial of RRx-001, in which signs of clinical activity were observed in some patients (out of 21 evaluable patients, one [5%] had a partial response and 14 [67%] had stable disease). Furthermore, four patients became responsive to therapies to which they had previously responded, but became refractory to. If such data are confirmed in larger ongoing trials, these findings could alter the treatment framework and potentially offer patients new hope for longer survival.

We declare no competing interests.

A number of early trials support the hypothesis that epigenetic modifying agents have the potential to resensitise tumours that have become refractory to treatment. The synergy of DNA demethylation and histone deacetylase inhibition in reversing gene silencing has been shown with the combination of DNA methyltransferases and histone deacetylases inhibitors.¹⁰ This hypothesis continues to be assessed, and RRx-001 specifically is being tested in patients with colorectal cancer (NCT02096354), cholangiocarcinoma (NCT02452970), and small-cell and non-small-cell lung cancer in ongoing phase 2 trials (NCT02489903).

Epigenetic modifying drugs might even sensitise tumours when given before chemotherapy. For example, in the phase 1/2 trial testing the epigenetic drugs, azacytidine and entinostat, in patients with recurrent non-small-cell lung cancer,¹¹ 21% of patients who had discontinued the study went on to have major responses to subsequent therapy. Responses were noted irrespective of whether patients had tumours that were refractory to multiple standard treatments. Moreover, the partial responses seen in patients who received subsequent therapy were rather large, ranging from 45–85%. The response to a wide array of subsequent chemotherapy regimens, including an antimetabolite and immunotherapeutic treatment, is also noteworthy, suggesting that these epigenetic agents have a broad-range resensitising effect and might have the potential to sensitise cancer cells to a wide array of chemotherapy regimens and possibly immunotherapies.

Unfortunately, many patients in general practice have come off previous chemotherapy, not just because of progression but for reasons related to toxicities. Although the data presented by Reid and colleagues is promising, their study only included patients who had no residual toxicities. Therefore, chemotherapy-intolerant patients might not benefit from tumour resensitisation to toxic chemotherapeutic drugs. These patients might still benefit from this work if these drugs are found to induce tumour-specific chemosensitivity, allowing for reduced doses and overall lower toxicities. Additionally, future studies should identify molecular biomarkers (eg, methylation or epigenomic profiling) that would define subsets of patients for whom these therapies would be particularly beneficial. Validation of these predictive biomarkers could help establish which patients are more likely to respond to episensitisation therapy. We are excited about the direction the epigenetics community is exploring and hopeful that future findings will improve the treatment armamentarium we can offer our patients.

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