Molecular Precision Chemotherapy: Overcoming Resistance to Targeted Therapies?

Stefan Burdach

Cytotoxic drugs may have specific effects on oncogenes and their downstream targets. Increase of cancer cell sensitivity due to repression of an oncogene downstream target can be specifically addressed by combined precision chemotherapy, increasing the therapeutic index of chemotherapy and overcoming resistance to highly selective targeted therapies. Clin Cancer Res; 20(5); 1064–6. ©2014 AACR.

In this issue of Clinical Cancer Research, Grohar and colleagues (1) discuss that trabectedin interferes with the activity of the pathognomonic fusion oncogene in Ewing sarcoma EWS-FLI1 and that EWS-FLI1 drives the expression of the Werner syndrome protein (WRN) in Ewing sarcoma cells. The DNA-binding tetrahydrosocholin-alkaloid trabectedin is an orphan drug, first isolated from a sea squirt in the 1960s. WRN is an antiaging helicase, inactivated epigenetically in some tumors and genetically in Werner progeria. These children display, for example, a high mutation rate due to deficient DNA repair and are prone to sarcomas (2). Because WRN-deficient cells are known to be hypersensitive to campothecins such as irinotecan, the authors used trabectedin to block EWS-FLI1 activity, thereby suppressing WRN expression and selectively sensitizing Ewing sarcoma cells to the DNA-damaging effects of the active metabolite of irinotecan SN38. They show that trabectedin and SN38 are synergistic and cooperate to augment the suppression of EWS-FLI1 downstream targets, leading to an increased therapeutic index in vivo (Fig. 1). Ewing sarcoma is a rare, but molecularly well-defined malignancy of children and adults, characterized by EWS-ETS (mostly FLI1) and early metastatic spread. Ewing sarcoma represents the paradigm of metastatic cancer.

Molecular precision chemotherapy can be used to increase the therapeutic index of chemotherapy. In addition to their nonspecific effects, certain cytotoxic drugs such as trabectedin have specific effects on oncogenes, to which the cancer cell is addicted, as well as on the downstream targets of these oncogenes. In the case of Ewing sarcoma, trabectedin and plicamycin block the binding of EWS-FLI1 to chromatin (3). Increase of therapeutic sensitivity due to decrease of the downstream targets of the oncogene (4) can be specifically addressed by precise selection of partners in combination chemotherapy. Such oncogene addiction–directed combined precision chemotherapy may overcome the resistance to more selective targeted therapies.

High-throughput genomics technologies such as expression profiling or next-generation sequencing have generated great hopes for the development of targeted therapies, which were expected to increase the therapeutic index. So far, targeted therapies have widely failed in acute malignant diseases of childhood to provide less toxic, more specific, and above all more efficacious cancer treatment (5, 6). In contrast, targeted therapies seem to prime for resistance in malignant diseases, characterized by high genomic and, in case of pediatric cancer, in particular epigenomic plasticity (7, 8). Targeting a single target will never cure a true cancer (9). There are just too many pathways in a cancer cell that can bypass the pathway addressed by the targeted therapy of interest. Moreover, at each meeting, we learn that there are more than we imagined before; there may be a myriad of pathways ahead, unknown to us, but well known to the cancer cell in need to bypass our targeted therapies. Thus, the bottom line of translational medicine re targeted therapy is priming for resistance (10). An exception to this rule is the targeting of those oncogenes, without which a cancer cell cannot survive. This phenomenon has been termed oncogene addiction and is provided by e.g., the AKT serine/threonine kinases or by MLL translocation–induced SET domain loss and DOT1L partnering.

However, many addiction targets such as mutated P53, RB, Ras, NF1, or EWS-FLI1 fusion and other transcription factor activations are not actionable by targeted therapies. Is, thus, cytotoxic poisoning without alternative in these cancers, characterized, for example, by transcription factor oncogenes such as EWS-ETS?

Possibly, the strict distinction between cytotoxic chemotherapy and targeted therapy is less dichotomized than it was previously hoped. mTOR inhibitors, for instance, do cause a lot of toxicity in combination not only with chemotherapy but also with tyrosine kinase inhibitors (TKI), revealing that so-called targeted therapies are nor as selective as expected, at least if they address such widespread targets as in the case of TKI and inhibition of the mTOR pathway.
The present thinking about targeted therapies has been dominated by the cancer stem cell model, assuming that there is a hierarchy of differentiation within the tumor. This concept is the basis for aiming to target one ultimate culprit, the mother cell of the tumor population. This model may not fully represent genomic and, in particular, epigenomic plasticity in childhood cancer. Moreover, plasticity in gene expression in pediatric cancer may be more analogous to the mutation-prone plasticity of HIV when under selective pressure (11). Thus, as long as targeted therapies do not target oncogene addiction pathways, they may well prime for resistance, raising selective pressure to bypass the targeted pathway with alternate rescue signaling. Here, molecular precision chemotherapy may overcome resistance by maintaining the nonselective cytotoxicity, while increasing the therapeutic index, i.e., increasing the sensitivity of the tumor as compared with normal cells to a defined dose of a cytotoxic drug. Increasing the therapeutic index has undergone proof-of-principle decades ago, with the establishment of stem cell rescue from high-dose chemotherapy (or radiotherapy; ref. 12). The most recent affirmation of this paradigm was the introduction of chimeric antigen receptor T cells (CART) into immunotherapy. CARTs bypass an evolutionary safety feature that restricts recognition of surface molecules to soluble immune effectors that arose later in evolution than the cellular effectors, which can recognize antigen only when presented by MHC.

How far is this molecular precision chemotherapy approach from the clinic?

The answer depends on your perspective: The major obstacle of translational medicine is the irreproducibility of research findings in the clinic. Only 5% of successful preclinical therapies make it into the clinic. Nevertheless, targeted approaches such as 111I-metaiodobenzylguanidine therapy or immunotherapy with anti-GD2 for children with neuroblastoma have shown efficacy in the clinic. However, pharmacokinetics are a major challenge of clinical translation. What is the optimal dose and the optimal timing of the two synergistic drugs: (i) the oncogene repressing sensitizer and (ii) the drug of action to which the cancer cells, once depleted of the downstream target, are hypersensitive? Are achievable serum levels of trabectedin sufficient to effectively repress EWS-ETS in humans? Dependent on the kinetics of interaction between trabectedin and WRN depletion, trabectedin levels, although not sufficient in repression to overcome oncogene addiction, may be sufficient for consecutive repression of the downstream target WRN to make the cancer cell vulnerable for camptothecins.

There is some hope on the horizon as far as serum levels go, as there are trabectedin analogs under development that reach 15 times higher serum level than the parent drug. As an alternative to the oncogene interference described here, repression of WRN may be achieved by epigenetic silencing.

In addition, it might be very helpful to measure the DNA damaging profile after irinotecan with and without trabectedin to definitively prove in the clinical setting, that the DNA damage by irinotecan is selectively increased in cancer cells by sensitization to camptothecins via repression of the oncogene and consecutive repression of its downstream target WRN by trabectedin, which, by itself, is not sufficiently cytotoxic to kill the cancer and to cure the patient. In conclusion, molecular precision chemotherapy targeting oncogene addiction may have a potential to overcome resistance to targeted therapies.

**Disclosure of Potential Conflicts of Interest**

S. Burdach has an ownership interest (including patents) in PDL BioPharma.

**Grant Support**

This work was supported by the Translational Sarcoma Research Network (TransSaRNet: 01GM0870), “Rare Diseases” and Prospective Validation of Biomarkers in Ewing Sarcoma for Personalised Translational Medicine (PROVARES: 01KT1311), Funding Programs of the Federal Ministry of Education and Research BMBF, Federal Republic of Germany and unrestricted grants from...
the Wilhelm Sander Stiftung (2009.901.1), the TransAid Foundation (13/0506), and the Curaplacida Foundation (CP101/120714).

Received December 12, 2013; accepted January 16, 2014; published OnlineFirst February 17, 2014.

References

Molecular Precision Chemotherapy: Overcoming Resistance to Targeted Therapies?

Stefan Burdach


**Updated version**
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-13-3194

**Supplementary Material**
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2014/03/04/1078-0432.CCR-13-3194.DC1

**Cited articles**
This article cites 10 articles, 1 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/20/5/1064.full#ref-list-1

**E-mail alerts**
Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.