Editorial: The Long and Winding Road to Better Cancer Cell–Specific Therapies

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In the last decade, our understanding of the molecular mechanisms underlying malignancies has greatly improved, not the least because of advances in molecular techniques. This has facilitated the development of multiple cancer cell–specific compounds such as tamoxifen and the aromatase inhibitors, and more recently, monoclonal antibodies and tyrosine kinase inhibitors (TKIs). These drugs, which inhibit the functional activity of “tumor-driving” factors, have resulted in superior outcomes for patients with common tumor types including breast and colorectal cancer.

Soft tissue sarcomas (STSs) are a heterogeneous and rare group of tumors accounting for about 1% of all malignancies. Patients presenting with advanced disease have a poor prognosis, given a median overall survival time of approximately 1 year with the currently available treatment options. This stresses the need for more effective treatment. The group of STSs comprises >50 diverse histopathological tumor entities, which differ importantly between each other in terms of pathogenesis, clinical behavior, and sensitivity to systemic agents. Despite this heterogeneity, most STSs are treated in a similar way regardless of the exact histopathological subtype. In recent years, however, this approach has changed considerably because the insight has emerged that the different subtypes should be separately managed rather than similarly. That this is indeed the way to go has clearly been demonstrated by the successes obtained in gastrointestinal stromal tumors (GISTs), one of the STS subtypes. GISTs are driven by constitutive activation of c-Kit, a transmembrane receptor, the function of which can be blocked by the TKIs imatinib and sunitinib. These drugs have revolutionized the treatment outcome of advanced GIST patients, improving the 5-year overall survival rate from <20% to >50% [1, 2]. In this respect, it is certainly warranted to assess whether similar approaches that have proven to be so successful in GISTs apply to other STS entities as well.

In the previous issue of The Oncologist, two papers addressed whether or not the epidermal growth factor receptor (EGFR), also known as the human epidermal growth factor receptor (HER)-1, is a valid drug target in synovial sarcoma, a disease accounting for 5%–8% of all adult STSs. The first paper was from Ray-Coquard et al. [3] on behalf of the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer. Because it was previously demonstrated that EGFR is overexpressed in a substantial number of synovial sarcomas [4, 5] and that the ligand of EGFR can induce proliferation in synovial sarcoma cell lines [6], the EGFR-targeting TKI gefitinib was screened for its antitumor activity in patients with synovial sarcomas. All patients included had EGFR-expressing synovial sarcoma and displayed progressive disease after standard chemotherapy. The primary endpoint of this study was the progression-free rate at 3 months. Currently, this is considered a more relevant endpoint [7] than response rates in phase II studies aiming to screen the antitumor activity of drugs such as gefitinib. It is increasingly being recognized that TKIs exert antitumor effects not only by inducing tumor shrinkage but also by stabilizing the size
of the previously progressing disease. In fact, the overall survival of advanced GIST patients achieving a radiological response to imatinib is not different from that of patients reaching stable disease [2]. Likewise, sunitinib as second-line therapy induces a response rate of only 7% in advanced GIST patients failing imatinib, but has clear antitumor effects in a higher number of cases [8]. In the study by Ray-Coquard et al. [3], gefitinib was considered as deserving of further exploration as an active drug for synovial sarcomas if it would yield at least 15 of 44 patients being progression free at 3 months after treatment initiation. However, because only five of 46 eligible patients were progression free at this time point, gefitinib was deemed ineffective.

The second paper was from Tawbi et al. [9], who studied the EGFR status in synovial sarcomas and malignant peripheral nerve sheath tumors. In addition to the determination of EGFR expression, the phosphorylation status of EGFR, which is thought to reflect the activation status of EGFR, and the presence of mutations in the encoding gene, HER-1, were explored. Consistent with previous findings [4, 5], EGFR expression was found in >70% of the synovial sarcoma cases. However, the occurrence of phosphorylated EGFR appeared to be rather low, being detected in only 18% of all cases. Mutations in exons 17–21 of the HER-1 gene could not be found in any of the examined synovial sarcomas.

Considering these two papers, the question arises whether the study of Tawbi et al. [9] provides reasons explaining why the clinical trial with gefitinib failed and, maybe even more importantly, which data should at least be available before commencing trials assessing the antitumor activity of a particular cancer cell–specific drug in a certain malignancy. Obviously, the latter is of utmost importance in order to avoid exposure of patients to treatments that are likely to lack activity. Furthermore, it is impossible to explore all potentially attractive drugs given the limitations in terms of financial resources and the number of patients that can be included in trials. The latter applies in particular to STS histopathological entities, given their rarity.

The most critical factors determining the success of a molecular-targeted drug in a certain malignancy are that the drug target should be the only, or at least a predominant, factor driving malignant behavior and that the drug tested should be able to inhibit the targeted factor in the form in which it is active. Unfortunately, to determine the reliance of a malignancy on the aberrant activity of a certain factor is not a simple task. Of course, studies using cell lines in combination with specific inhibitors and knockdown experiments may suggest that inhibition of a particular factor is worthwhile exploring, but this is absolutely no guarantee for clinical success. For example, monoclonal antibodies toward EGFR are active against renal cell carcinoma cell lines in vitro [10], while compounds inhibiting EGFR have all failed in clinical trials. Also, the mere presence of the target in tumors is clearly not sufficient for success, because a wide spectrum of drugs failed to have activity in patients with tumors strongly expressing the factor toward which the drug was directed. This also holds true in the study of Ray-Coquard et al. [3], in which only patients with EGFR-expressing tumors were included. Probably more indicative of the importance of a certain factor than its presence as such is its activational status. There are several means by which the activation status of a potential target can be assessed. For targets that are kinases themselves or rely on kinases for their activation, the phosphorylation status of specific sites within the factor can be a suitable readout. If the target is part of a signaling cascade, then the phosphorylation status of downstream factors and/or their expression can be used as surrogate markers. However, it is currently unknown to what extent they adequately reflect the activation status and how relevant this is. Tawbi et al. [9] measured EGFR activity using a phospho-specific antibody (pY1068-EGFR). Assuming that this test properly assesses EGFR activation status, the finding that approximately 18% of all synovial sarcomas harbor phosphorylated EGFR suggests that adequate EGFR inhibition would yield possible antitumor activity in only a small subpopulation of synovial sarcoma patients.

In addition to the necessity that the targeted factor is indeed the predominant driving force for a malignancy, it is essential to administer the right inhibitor. Besides crucial pharmacokinetic issues such as reaching the target at adequate concentrations, it is important to know the mechanism responsible for activation of the targeted factor. With respect to increased activation of EGFR, several mechanisms have been identified, including increased expression of its ligand, overexpression of EGFR, and gain-of-function mutations in the HER-1 gene, which result in a constitutively activated form of EGFR that does not require ligand binding anymore. In cases where a gain-of-function mutation underlies the activation of a particular factor, it is unlikely that a monoclonal antibody directed toward the ligand or the extracellular domain of a receptor will exert antitumor activity. In those circumstances, a TKI that has a higher affinity for the mutated form of the factor than the wild-type form is more appropriate. Also, gefitinib is mainly active against certain forms of mutated EGFR, rather than against wild-type EGFR [11]. Because no mutated HER-1 genes were found in synovial sarcomas, in retrospect, gefitinib was unlikely to exert antitumor activity in these entities, consistent with the findings from the clinical study [3]. Accordingly, gefitinib inhibited proliferation of synovial sarcoma cell lines only at high concentrations, which are too high to be reached in humans [12]. If EGFR is indeed involved in the
pathogenesis of synovial sarcomas, it is in its wild-type form. Therefore, an antibody directed toward the receptor, interfering with its ligand-dependent activation, or an EGFR TKI with a high affinity for the wild-type form can be expected to have a higher chance of displaying activity.

Collectively, the minimal requirements prior to initiating a trial with a molecular-targeted drug should be that the targeted factor is present in the tumor patients, is more or less uniformly expressed, and is in an activated status, and that the drug studied is able to inhibit either the wild-type or mutant forms of the target, whichever is appropriate. However, even if these conditions are met, success is still not guaranteed. It may well be that the enormously encouraging results obtained with GISTs and imatinib are more an exception than the rule. In contrast to GISTs, in which the constitutive activation of c-Kit is apparently the main malignant transformation, most tumors probably rely on several factors simultaneously, with extensive crosstalk among distinct signaling pathways. An example is the recent finding in colorectal cancer patients treated with anti-EGFR monoclonal antibodies. There is increasing evidence that, in colorectal carcinomas, increased signaling activity from wild-type EGFR plays an important role. However, blocking EGFR by antibodies does not produce antitumor activity in those tumors with mutated KRAS because such mutations result in persistent activation of the EGFR pathway despite adequate blocking of EGFR [13].

Given the complexity of solid malignancies and the plasticity of the cancer cell, future successes are most likely to be gained by multitargeted approaches rather than by applying therapies that are directed toward a single target. We should therefore continue to further unravel those factors largely contributing to malignant behavior. It is only by such efforts that we will learn which targets to aim for and how to hit them most effectively. The road to novel cancer cell–specific therapies is long and winding, but we are still making progress.

**AUTHOR CONTRIBUTIONS**

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**REFERENCES**


