Identification of targeted therapy for an aggressive subgroup of muscle-invasive bladder cancers

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Abbreviations: EGFR; epidermal growth factor receptor; mTOR; mechanistic target of rapamycin.

A quarter of bladder tumors are diagnosed with muscular layer infiltration. The treatment of this invasive disease is still based on cystectomy, despite a greater than 40% failure rate at 5 years. In most cases, these failures correspond to non-organ-confined carcinoma; i.e., stage T3-4 tumors with potential positive lymph node or distant metastasis. For these tumors, surgery alone is not sufficient and chemotherapy is needed together with surgery, or alone if surgery is not possible.1 Limited progress has been made since the 1990s, and only cisplatin-based chemotherapy and vinflunine have been demonstrated to be beneﬁcial. Moreover, the beneﬁt of these treatments is quite small, with only a 5% overall survival beneﬁt in the neoadjuvant setting.2 These disappointing results are probably a result of the high heterogeneity of bladder tumors, together with their poor sensitivity to standard chemotherapy. The identiﬁcation of targeted therapies is urgently needed. No targeted therapy has yet been shown to improve survival in bladder cancer, except in isolated case reports. Constitutive activation of the phosphoinositide 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) signaling pathway, mostly as a result of genetic alterations of genes involved in this pathway, is observed in various types of cancer, including bladder cancers.3 Everolimus, a mTOR inhibitor, has been tested,4,5 and an encouraging effect was observed in patients harboring TSC1 mutations.5 Unfortunately, these mutations are relatively rare. In addition, everolimus resistance can occur through the activation of alternative pathways.

By applying unsupervised analyses to 7 independent transcriptomic datasets of muscle-invasive bladder cancers, Rebouissou et al. identiﬁed a homogenous subgroup that overexpressed epithelial basal cell genes6 (Fig. 1). This subgroup, described as “basal-like,” may account for up to a quarter of muscle-invasive tumors (23.5% in their study). In addition to the expression of basal cell markers, this subgroup was found to have several features in common with the well-described basal-like subgroup of breast cancers. These features include poorer clinical outcome, higher stage or grade, a high percentage of TP53 mutations, and deregulation of the retinoblastoma (RB)/E2F pathway. In the case of basal-like bladder cancer, most deaths occurred within 1 year of diagnosis. Moreover, the basal-like phenotype was found to be an independent factor for poor prognosis in a multivariate survival analysis including tumor stage and lymph node and metastasis status. At the histologic level, approximately 40% of basal-like muscle-invasive bladder cancers were found to be urothelial carcinomas with squamous differentiation, whereas this phenotype was rare (3%) among other muscle-invasive tumors.
Transcriptomic and proteomic evidence indicated that the epidermal growth factor receptor (EGFR) pathway was activated in the basal-like subgroup of muscle-invasive bladder cancer. Using a 40-gene expression classifier derived from the human tumor transcriptomic data sets, the authors identified human bladder cancer cell lines and a mouse model of bladder cancer representing the basal-like subgroup. In vitro, basal-like cell lines were much more sensitive to a small EGFR kinase inhibitor, erlotinib, and to an EGFR-targeting antibody, cetuximab. One exception to this was a basal-like cell line presenting an *NRAS* mutation. Rebouissou et al. investigated whether basal-like cells were also sensitive to EGFR inhibition in vivo using human tumor xenografts and a chemically-induced mouse model of basal-like tumors. Only basal-like tumor xenografts responded to erlotinib treatment (again with the exception of the cell line presenting an *NRAS* mutation). In the mouse model, erlotinib delayed the appearance of tumors and increased survival.

**Figure 1.** Epidermal growth factor receptor (EGFR) as a potential therapeutic target for a subgroup of aggressive bladder cancers displaying a basal-like phenotype. Various bioinformatics tools were applied to large-scale transcriptomic datasets of muscle-invasive bladder cancers (MIBC), leading to the identification of a distinct subgroup displaying molecular and clinical similarities to the well-known basal-like subgroup in breast cancer. Tumors of this basal-like subgroup of bladder cancers displayed autocrine activation of the EGFR pathway. Preclinical models representative of this subgroup were identified using a 40-gene expression classifier and were found to be sensitive to anti-EGFR therapy. An immunohistochemical signature was also proposed for identification of the basal-like subtype of MIBC in clinical settings to allow the selection of patients most likely to benefit from targeted EGFR therapy for future clinical trials.
Rebouissou et al. identified an immunohistochemical pattern characteristic of the basal-like subgroup that might be useful in clinical practice for the identification of basal-like tumors. They showed that the combination of cytokeratin (CK) 5/6-positivity and forkhead box A1 (FOXA1)-negativity reliably distinguished between basal-like and non–basal-like muscle-invasive bladder cancers.

The results of this work, summarized in Figure 1, have 2 major clinical applications. First, if the basal-like phenotype is confirmed as an independent prognosis factor, more aggressive treatment schedules, including extensive surgery, could be introduced for this specific subgroup of patients. Second, these results provide hope for a targeted treatment. The poor outcomes of patients with localized bladder cancer should now be reconsidered in light of the findings of Rebouissou et al., as most (approximately three-quarters) of the tumors included in previous studies were not basal-like. The focus for this targeted treatment should now shift to the basal-like subgroup, and we should rapidly move toward clinical trials.

For decades, no real progress has been made toward a cure for muscle-invasive bladder tumors. With the recent emergence of new targets (e.g., programmed cell death 1 [PD1]-PD-L1 and fibroblast growth factor receptor 3 [FGFR3]), it is becoming possible to prolong patient survival for specific subgroups of aggressive diseases. The basal-like subgroup of bladder cancer was also recently identified by Sjödahl et al., the Cancer Genome Atlas (TGCA), and Choi et al., demonstrating the robustness of this subgroup. The team of François Radavanyi has now reported better clinical characterization, preclinical models, a therapeutic target, and markers for this subgroup of tumors, raising genuine hope for the development of effective targeted therapies for this aggressive subgroup of muscle-invasive bladder tumours.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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