THE ROLE OF FIBROBLAST GROWTH FACTOR RECEPTOR (FGFR) ALTERATIONS IN ADVANCED UROTHELIAL CARCINOMA

Potential clinical impact of a consensus molecular classification of muscle-invasive bladder cancer

Introduction

Bladder cancer is one of the most prevalent cancers worldwide and approximately 90% of bladder cancers are urothelial carcinomas (UC).[1,2] Globally in 2020, there were more than 573,000 new cases of bladder cancer and over 212,000 bladder cancer deaths,[1] with a 3–4 times higher incidence in men than in women.[1,2] The majority (70–75%) of UC cases present as non-muscle-invasive (i.e., lower tumour stage), but around 20–40% of these will progress to muscle invasive disease.[2] Around half of patients with muscle-invasive UC will develop distant metastases.[3] Patients with advanced or metastatic UC (mUC) experience an extremely poor prognosis, with a median overall survival of only 8.1 months.[4] Five-year survival is just 38% in those with bladder cancer that has spread to nearby lymph nodes or organs, and 6% in those with distant metastases.[5]

Most patients with advanced or mUC eventually experience disease progression following first-line cytotoxic chemotherapy, and have limited responses to subsequent lines of chemotherapy.[6,7] In second line, immune checkpoint inhibitors (ICI) benefit only a subset of patients (ORR estimated 13–21%), and median progression-free survival is approximately 2 months.[6,7] To date, clinical factors, including presence of visceral disease and Karnofsky performance status, have been the main predictors of survival in mUC.[8] Even taking clinical and pathological factors into account, prognosis varies substantially, presenting challenges for optimal treatment selection.[9]

Identification of molecular biomarkers has transformed patient outcomes in a range of cancer types by facilitating the selection of precision therapies.[10,11,12] However, the use of biomarkers to guide treatment selection for mUC is limited.[6,13] Current and emerging potentially predictive biomarkers for UC include programmed cell death ligand 1 (PD-L1) expression, fibroblast growth factor receptor (FGFR) alterations and tumour mutational burden.[6,14] This article will outline the current understanding of the fibroblast growth factor (FGR)/FGFR pathway and its potential role in mUC.[14–16]

The FGF/FGFR pathway in oncology

FGFRs are widely distributed transmembrane tyrosine kinase receptors involved in a range of biological processes including development, angiogenesis, tissue homeostasis, wound repair and carcinogenesis.[14,15,17,18] In humans, there are four receptors (FGFR1 to FGFR4), which can activate several downstream pathways including PI3K-AKT, RAS-MAPK, and PLCγ (**Figure 1**).[15,18,19]

Alterations to FGF/FGFR signalling may hyperactivate these pathways, and promote tumorigenesis through the upregulation of cell proliferation, anti-apoptosis, angiogenesis, epithelial to mesenchymal transition, and increased invasive potential.[15,19,20] FGF2, specifically, upregulates several tumorigenic mechanisms, including:[15]

- Synergising with the vascular endothelial growth factor (VEGF) pathway to increase tumour blood vessel density and promote tumour neoangiogenesis
- Potentially conveying resistance to anti-VEGF therapy – increased FGF2 levels have been found following anti-VEGF treatment in patients with glioblastoma and colorectal cancer
- Contributing to tumour-associated macrophage recruitment and programming
- Contributing to chemotherapy and radiotherapy resistance via the upregulation of proteins which confer refractoriness to cell death by these treatments.

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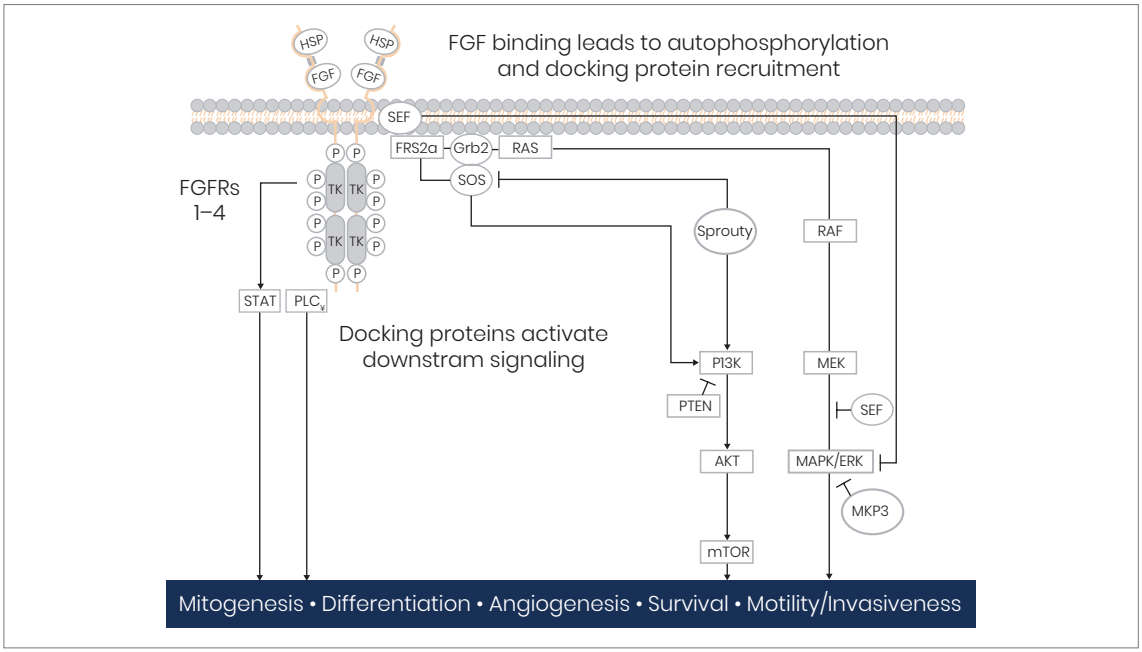
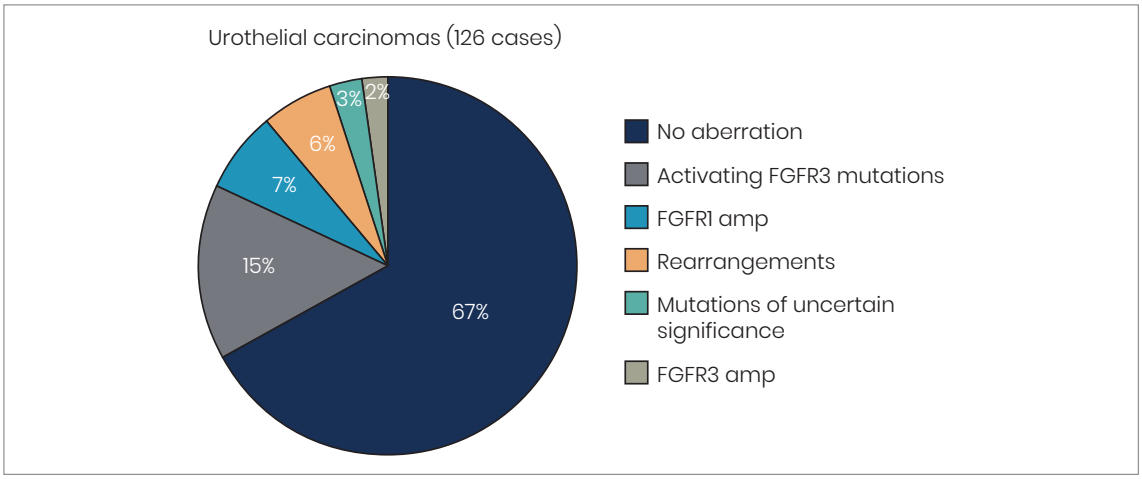
Figure 1. The FGF/FGFR signalling pathway.



Source: Corn PG et al, 2013 and Yang J et al, 2019[35,36]

Figure 2. Distribution of FGFR abnormalities in UC.



Source: Helsten et al, 2016.[14]
Amp, amplification

Moreover, FGF may induce the activation of cancer-associated fibroblasts, which promote tumour growth and progression.[15] Finally, FGFR1 has been found to play a critical role in promoting epithelial to mesenchymal transformation, resulting in increased invasive potential and potential progression to metastatic disease.[19]

The prevalence of FGF/FGFR alterations in mUC

FGFR alterations are present in a wide variety of tumour types, with one study finding that 7% of the 4,853 solid tumour patient samples analysed contained FGFR alterations.[14] The same study included 126 UC tumour samples, of which 31.7% had FGFR alterations (**Figure 2**).[14,21] Among the UC samples, *FGFR3* was the most frequently identified alteration (22.2%), followed by *FGFR1* (8.7%), *FGFR2* (~1%), and *FGFR4* (0%) alterations.[21] Around 15% of FGFR alterations observed in urothelial tumour samples are known to be activating.[14]

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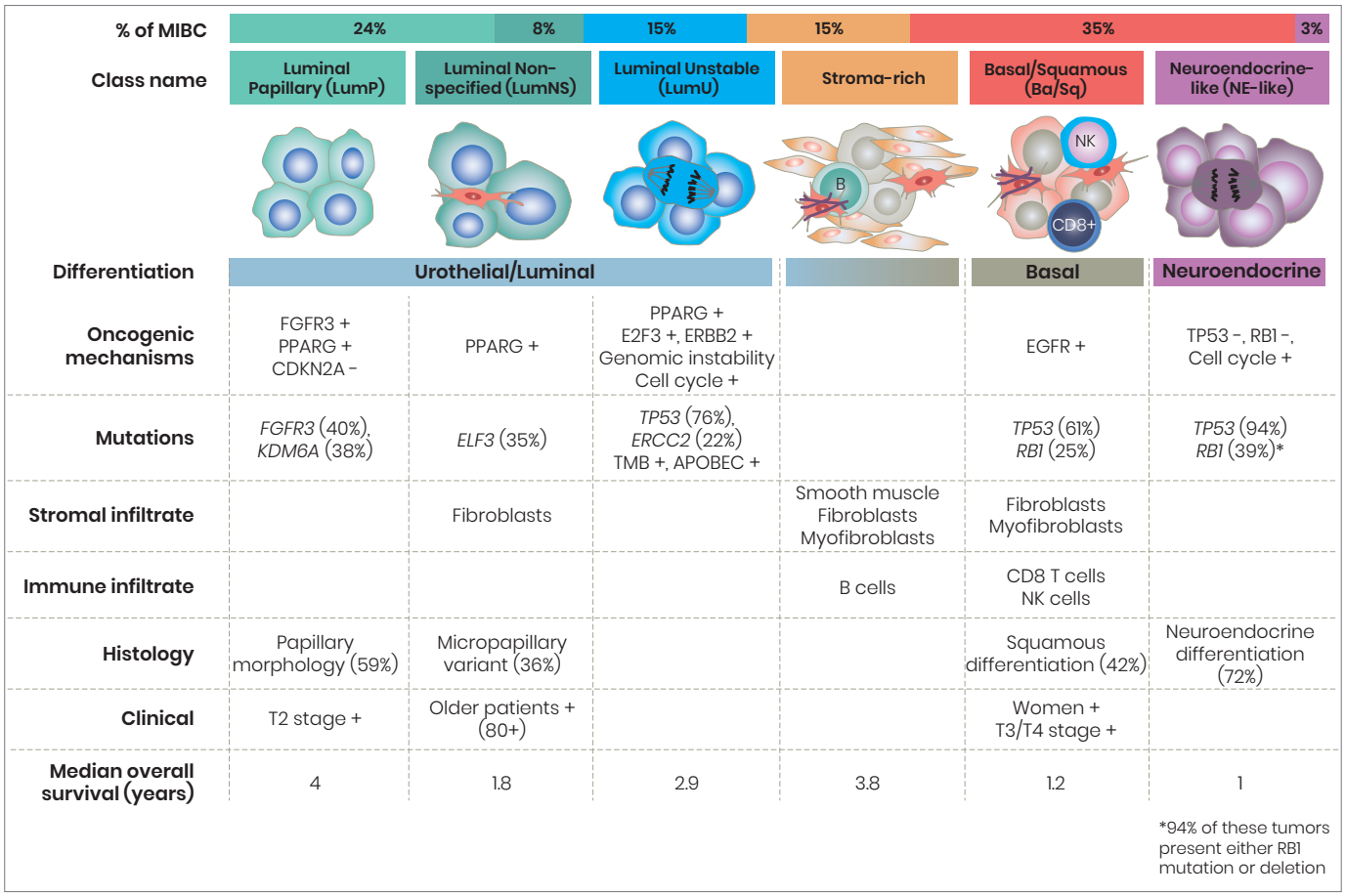
Figure 3. Summary of the main characteristics of the molecular subtype consensus classes of UC.



Source: Kamoun et al, 2020.[16]
Ba/Sq, basal/squamous; LumNS, luminal nonspecified; LumP, luminal papillary; LumU, luminal unstable; MIBC, muscle-invasive bladder cancer; NE, neuroendocrine; NK, natural killer.

FGFR alterations in UC are prevalent potential tumour drivers, and can be found in up to 20% of patients with tumours of stage T2 or above.[22] Furthermore, it has been suggested that FGFR alterations may be more prevalent in those with upper genitourinary tract UC, than in other types of UC.[23]

Molecular classification of advanced UC

Muscle-invasive UC demonstrates high genomic instability and a high mutation rate.[16] Specific molecular subtypes have been associated with different responses to chemotherapy and immunotherapy.[16,24,25] As such, knowing a bladder tumour's molecular subtype could help to predict clinical and treatment outcomes for patients.[12,16]

A consensus classification system has defined six molecular subtypes of muscle-invasive UC on the basis of oncogenic mechanisms, infiltration of immune and stromal cells, histological characteristics, clinical characteristics and clinical outcomes.[16] These are: luminal papillary (LumP; 24%), luminal nonspecified (LumNS; 8%), luminal unstable (LumU; 15%), stroma-rich (15%), basal/squamous (Ba/Sq; 35%), and neuroendocrine-like (NE-like; 3%) (**Figure 3**).[16] These six subtypes are associated with differential overall survival, with the highest median survival in patients with LumP tumours (4 years) and lowest in NE-like tumours (1 year).[16]

LumP, LumU and NE-like subclasses are also characterised by low immune infiltration in the tumour microenvironment.[16] Commonly known as "cold tumours", a lack of T-cells in the tumour microenvironment can present a barrier to treatment with ICI, as no adaptive immune response has been established.[26] Each of the six muscle-invasive UC subtypes demonstrate specific transcriptomic and genomic alterations, in addition to clinical characteristics.[16] All three luminal subgroups overexpress PPARG/GATA3/FOX3.[16] LumP

tumours are frequently associated with genomic alterations in *FGFR3* (40%) and *KDM6A* (38%), and are strongly associated with FGFR3 transcriptional activity.[16] LumNS tumors are associated with *ELF3* mutations (35%), and LumU tumors associated with mutations in *TP53* (76%) and *ERCC2* (22%).[16] By contrast, Ba/Sq and NE-like tumors most commonly have alterations in *TP53* (61–94%) and *RB1* (25–39%).16 Stroma-rich tumors had no specific genetic signature.[16]

Overall, this consensus classification system highlights the importance of molecular profiling in UC, particularly in its ability to identify therapeutic targets for certain subtypes of advanced UC.[16]

Molecular/genetic testing in the management of advanced UC

Increasing understanding of relevant biomarkers and precision medicine targets has the potential to expand the role of genetic testing in the routine management of mUC.[6,16,27] Guidelines now recommend molecular testing early in the diagnosis of mUC, to facilitate treatment decision making and prevent delays in administering later lines of therapy.[28] Widely-used tests to detect genetic alterations include real-time PCR (to detect specific predefined mutations), and next generation sequencing (which can simultaneously interrogate multiple genomic loci for gene mutations).[27,29] Both methods can use formalin-fixed paraffin embedded (FFPE) tissues, and operate with a turn-around time of 1–12 days depending on the technique used.[29–34]

Conclusion

In conclusion, an improved understanding of the molecular pathology of various cancer types has enabled the use of biomarker-led precision medicines, which may lead to improved outcomes for select subsets of patients.[10,11] FGFR alterations have been identified as both an important driver of tumorigenesis,[15] and as a prevalent genetic alteration in mUC.[14] These developments may facilitate improved disease management for patients with mUC.[12,16]

For more information, please visit FGFR alterations in oncology.

This report was developed as part of the touchFEATURE activity, ***The role of fibroblast growth factor receptor (FGFR) alterations in advanced urothelial carcinoma***. To view the full touchFEATURE activity, which also includes informative videos, please visit: https://www.touchoncologytmc.com/bladder-cancer/learning-zone/role-of-fibroblast-growth-factor-receptor-alterations-in-advanced-urothelial-carcinoma

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