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Dovitinib (TKI258) - A Novel Therapeutic Option in Advanced-Stage Endometrial Cancer?

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Abbreviations: DFS: Disease-fee Survival; EC: Endometrial Cancer; ER: Estrogen Receptor; FGF: Fibroblast Growth Factor; FGFR: Fibroblast Growth Factor Receptor; ICH: International Conference of Harmonization; OS: Overall Survival; VEGF: Vascular Endothelial Growth Factor

Introduction

Novel therapeutic options in human cancers, especially in advanced-stage tumors with a mutation in the putative target genes, has been recently applied [1,2]. One of the mostly investigated signaling pathways is the FGFR-pathway, playing a crucial role in various cellular processes, including proliferation and differentiation, angiogenesis, embyogenesis as well as tissue homeostasis [3,4]. The FGFR-signaling pathway consists of 4 highly-conserved FGFRs (named FGFR 1-4) and 18 ligands, which expression pattern is cell- and type-specific [3]. Interestingly, FGFR ligand binding leads to dimerization of the receptor and subsequently enzymatic kinase activity leading to downstream signaling pathway [3]. The expression of FGFs as well as their specific receptors has been investigated in normal endometrial cells during the menstrual cycle in humans and in animals, showing different expression patterns [5,6]. In particular, inhibition of the FGFR2-pathways leads to reduced cell growth as well as increased antitumor activity in endometrial cancer cells *in vitro* [7].

The mutational status of *FGFR2* has also been identified in various types of human neoplasms, including ECs [8-11]. *FGFR2* alterations, included gene amplification and overexpression, activating point mutations as well as various chromosomal translocations are implicated in the transcriptional regulation of mRNA and functional activation of the protein/s/ [10]. It is worth pointing out that 6.5-16% of ECs harbor *FGFR2* mutations, and women affected by early-staged tumors with gene mutations were associated with significantly shorter DFS and OS [12]. Therefore, it is of utmost important for the preclinical trials to implement agent/s/, in combination with chemotherapy, inhibiting of the *FGFR*-pathway [13]. Clinical trials of agents targeting *FGFR2/VEGF*-pathways have been tested in women with advanced-stage, metastatic and/or recurrent ECs, although most of them are multi-targeted and inhibit also other signaling pathways, beyond *FGFR2* [2]. Recently, *in vitro* study showed that dovitinib significantly inhibited the growth of *FGFR*-mutated EC xenograft models [14].

For these reasoning, it is worth overview the study recently published in The Lancet Oncology by a group leading by Konecny [15]. This study was a non-randomized, multicenter, open-label, two-stage, phase 2 clinical trial. Altogether, they enrolled a population of 283 women (from 46 sites in seven countries) with advanced or metastatic ECs with progressive disease who received a second-line antineoplastic agent -dovitinib- in a specific manner. However, a first-line neoplastic treatment, including at least one cytoxoxic drug, has previously been administrated. During the protocol, patients received dovinitib orally at a dose of 50mg on a 5-day-on and 2-day-off schedule until disease progression, unacceptable toxicity, death, or discontinuation for the study due to any other reasons. This trial was performed in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with application local regulations, and with the ethical principles of the Declaration of Helsinki. All patients were subdivided into two groups based on *FGFR2*-status, investigating the five main hot-spot mutations reported for ECs within exons 7, 8, 9, 11, and 13. Of the 248 patients, 27 (11%) showed *FGFR2* mutations, especially S25W and N549K. Between Feb 17, 2012, and Dec 13, 2013, 22 patients with *FGR2* mutations and 31 women with no mutations, were enrolled. Interestingly, a high incidence of endometrioid cancer type and G2 histological grade was observed in $FGFR2^{mut}$ group. Median time since initial diagnosis of $FGFR^{mut}$ and $FGFR^{non\text{-}mut}$ group was 33.3 and 16.4 months, respectively. As of the data cutoff, March 27, 2014, all patients had discontinued study treatment, mostly due to progressive disease (66%). Unfortunately, no patients received a complete response, and the proportion of patients achieving an overall response was 5% (one of 22 patients) in the $FGR2^{mut}$ group and 16% (five of 31) in the $FGR2^{non\text{-}mut}$ group. The median exposure to dovitinib was 15.9 weeks in the $FGFR^{mut}$ group and 11.1 weeks in the $FGFR^{non\text{-}mut}$ group. Unfortunately, more than a third of all patients were treated for less than 6 weeks. Across both groups, the main reasons for discontinuation within 6 weeks of treatment were severe adverse events, disease progression, and patient or guardian decision. Altogether, adverse events were similar between the groups and were gastrointestinal (diarrhoea, vomiting, nausea, fatigue, and/or rush), hypertension, hypertriglyceridemia, increase of the lipase activity, as well as pulmonary embolism. Of the five on-treatment patients' deaths, four women died of tumor progression, whereas one $FGFR2^{mut}$ woman succumbed from primary cardiac arrest with contributing reason of grade 4 pulmonary embolism suspected to be drug-related. Block and Dowdy [16], who recently commented the article, reported that "the rate of treatment discontinuation due to toxicity exceeded that seen with aggressive combination cytotoxic chemotherapy (10% of patients with advanced endometrial cancer treated with adjuvant paclitaxel, cisplatin, and doxorubicin)."

Altogether, the clinical activity of dovitinib was limited, and neither group met the response threshold to continue a stage two study.

Unfortunately, mutational *FGFR2*-status did not seem to correlate with increased clinical benefit, with a high rate of incidence of severe adverse events as well as no patients' complete response. Interestingly, the authors also analyzed molecular abnormalities in *FGFR* or ligands of 44 samples from 48 patients enrolled, but no alterations were reported (data not shown).

Finally, the authors concluded that "this is the first report showing activity of a single-agent tyrosine-kinase inhibitor in patients with recurrent advanced or metastatic $FGFR2^{mut}$ endometrial cancer" [15]. The proportion of patients who achieved clinical benefit was 64%, progression-free survival was 4 months, and the median overall survival was 20 months. However, we must take into consideration that a study group was strictly enrolled and only affect patients with advanced metastatic or recurrent ECs. For future research, a combination of dovitinib with a selective ER-antagonist (for example ICI182.780, fulvestrant), apart from chemotherapy, may probably be more effective in advanced ECs carrying *FGFR2* mutations [7]. Synergistic effect of PD173074, a pan-*FGFG* inhibitor, with standard chemotherapeutic agents in 3 *FGFR*-mutant EC cell lines has been recently presented [11]. However, toxic effects during multi-agent therapies may cause a high rate of patients' discontinuation exceeding the FGFR-targeted benefits. In conclusion, "second-line dovitinib in $FGFR^{mut}$ advanced or metastatic endometrial cancer had single agent activity, but did not meet the endpoint for stage two of the trial" [15]. Combination therapy awaits the results of larger scale clinical trials in patients with advanced and recurrent ECs to evaluate their efficacy and safety [17].

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Conflict of Interest

The authors declare no conflict of interest.

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