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European Association of Urology

Words of Wisdom

Re: Effect of Intravesical Instillation of Gemcitabine vs Saline Immediately Following Resection of Suspected Low-grade Non–muscle-invasive Bladder Cancer on Tumor Recurrence

Messing EM, Tangen CM, Lerner SP, et al

JAMA 2018;319:1880–8

Expert's summary:

The authors present results from a randomized double-blind multicenter trial evaluating the role of single immediate instillation (SI) of gemcitabine after transurethral resection (TURB) of presumed low-grade (LG) non–muscle-invasive bladder cancer (NMIBC). Overall, 406 patients were randomized to SI of 2 g of gemcitabine in 100 ml of saline or to 100 ml of saline alone within 3 h after TURB, and 383 completed the trial. After median follow-up of 4 yr, 35% of patients in the gemcitabine arm and 47% in the saline group experienced recurrence in an intention-to-treat (ITT) analysis (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.48–0.90; $p < 0.001$). In the prespecified target population with pathologically confirmed LG NMIBC, 34 of 102 patients receiving gemcitabine (34%) and 59 of 113 patients receiving saline (54%) had recurrences (HR 0.53, 95% CI 0.35–0.81; $p = 0.001$).

Expert's comments:

The trial demonstrated a 12% reduction in recurrence rate (RR) on ITT analysis, in agreement with a previous meta-analysis of individual patient data [1]. The difference in RR between the arms reached 20% in the subgroup with LG tumours. These outcomes support the guideline recommendations on SI in selected patients with NMIBC after TURB. The paper also raises several interesting and clinically relevant issues.

The decision for SI must be based on criteria known at the time of TURB. Although the meta-analysis [1] provided some recommendations for routine practice, the absence of certainty about a malignant diagnosis and tumor stage and grade represents a major drawback. Use of SI in benign or muscle-invasive disease is not well founded and its efficacy in high-grade (HG) tumours is not sufficiently proven. The incidence of unexpected HG or T2 disease of nearly 30% and 10% of benign lesions in the current analysis is higher than previously reported [2]. It is apparent that evaluation and utilization of new urinary markers before TURB are warranted.

In agreement with a recent report [3], the study confirms the low risk of complications after SI. RRs in both the gemcitabine and saline arms were approximately 10% lower than in older studies [1]. This may be explained by the better quality of TURB performed in this decade. This observation suggests that SI may also provide a benefit in patients for whom new tumor visualization tools (such as fluorescence cystoscopy) are used during TURB.

Unfortunately, the design of the study prevents several important conclusions. The efficacy of SI with gemcitabine seems to be at least comparable to mitomycin C; however, the final decision on the optimal drug should be supported by direct comparison. Similarly, we do not know whether SI improves outcomes in patients who will receive further intravesical treatment. Although its benefit is suggested by recently published trials [3,4], the findings must be reconfirmed in a study with a protocol based on current treatment recommendations for different subgroups.

Conflicts of interest: The author has nothing to disclose.

References

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https://doi.org/10.1016/j.eururo.2018.10.035

Re: Circulating Extracellular Vesicles in Human Disease
Shah R, Patel T, Freedman JE

N Engl J Med 2018;379:958–66

Experts' summary:
In their paper, Shah et al provided a sort of brief introduction concerning the existence and role of extracellular vesicles (EVs), with dedicated attention to those translational and clinical studies eventually useful to suggest their potential role in human diseases. EVs are defined in the paper as membrane-bound organelles that are extruded from tissues—tons and of several types—and contain different types of molecular cargo, thus including a variety of proteins, lipids, and nucleic acids that may be specific for the cell of origin and its function. Originally, EVs have been subdivided according to their size and biogenesis, with *exosomes* having a diameter of <150 nm and *ectosomes*, otherwise defined as *microvesicles*, with a diameter up to 1000 nm. The article critically focuses on the importance of the role of EVs in intercellular signaling, which is of increasing interest due to their potential as noninvasive biomarkers in both disease detection and disease prognosis, with partial attention even to the aspect of therapy, both in oncology and non-oncology fields.

Experts' comments:
In multicellular organisms, cells evolved in numerous ways to communicate and the production of EVs represents an efficient way which cells use to deliver key messages. Therefore, EVs have been lyrically compared to Hermes, the wing-shod messenger of the Olympians, who has served as a link between two worlds, transferring messages from the gods to mankind [1]. EVs are hugely involved in several physiological processes, including inflammatory and immune responses, development, reproduction and pregnancy, tissue repair, and blood coagulation. Likewise, EVs are also implicated in pathological events, such as tumor development and progression, immune response deregulation, and the establishment of a pre-metastatic niche [2]. Notably, EVs secreted by transformed cells resemble the significant variations that occur within the disease [3]. Therefore, EVs can be exploited as potential biomarkers in biological fluids. By definition, a reliable and specific biomarker should help and promote an early diagnosis, monitor the disease progression, and predict the response to a specific treatment, thus supporting the selection of the most appropriate therapeutic option. This approach leads to patient stratification and paves the way to some forms of precision medicine. In this context, EVs would offer a novel perspective in the search for accurate cancer biomarkers by providing a protected reservoir of circulating molecules. The identification of EVs typical cargoes, holding biomarkers of otherwise undetectable amounts, can be eventually translated into clinically relevant information. Thereof, a continuous implementation in terms of EVs isolation will shape the potential future pipelines. For instance, relevant to the urological fields, is the quite recent findings that a small group of miRNAs extracted from EpCAM-positive exosomes allowed the differentiation between clear-cell renal carcinoma and healthy controls [4,5]. Why is urology such a lucky field? Because we may consider at least two unique biofluids: urine and semen. Indeed, the great advantage of monitoring urological tumors is the possibility to exploit urine samples, which are easy to retrieve and are actually enriched in cancer cells-derived molecules due to the direct contact with the tumor itself. That noninvasive diagnostic method is well accepted by patients, thereby improving their adherence to the surveillance programs. This is not only true for the most intuitive condition of bladder cancers [6] but a diagnostic potential has also been identified in urinary exosomes purified from patients with prostate cancer [7,8]. Even of greater translational interest, a study has been also conducted to validate the performance of a novel urine exosome gene expression assay to discriminate a benign disease toward clinically significant prostate cancers in men with a prostate-specific antigen value between 2 and 10 ng/ml on initial biopsy. Why is this clinically important? The test may improve the identification of patients with high-grade disease while avoiding unnecessary biopsies more efficiently than existing risk calculators and standard clinical data [9]. The field for semen analysis is then extremely open and innovative.

Even if EVs were mostly considered as a biomarker source, they received renewed attention over the past few years when they were used for the first time as a drug delivery system [10]. Indeed, their biological compatibility, the ability to overcome biological barriers and to localize at tumor sites, while simultaneously protecting a therapeutic cargo and increasing its circulation time, make them suitable carriers for therapeutic interventions. Various cargoes such as cytotoxic drugs (doxorubicin and paclitaxel) or RNAs (miRNA and siRNA) have been inserted in EVs; shuttled molecules maintain their biological activity and are capable of modulating and reprogramming recipient cells. The targeting behavior of EVs can be tuned via genetic engineering of producing cells or direct chemical addition of specific ligands