cancer centres, is that this paradigm will change to one in which a sample of every patient’s tumour will be characterised by DNA sequencing and other means. Therapy will then be selected to target the specific pathways that drive cell proliferation and other malignant properties in that patient’s tumour.

By demonstrating extensive intratumour heterogeneity, the studies by Gerlinger et al. and Xu et al. explain why resistance to current therapy occurs invariably and should curb enthusiasm for selection of individualised therapy. Heterogeneity in properties of individual tumour cells will include those determining sensitivity to any anticancer drug, so resistant cells present in the tumour will be selected by treatment, as has been shown for colorectal cancer [1]. Spatial variation in genetic and phenotypic properties can also explain mixed responses to treatment. Moreover, personalised therapy can only be expected to generate markedly improved effectiveness if the analysed sample is characteristic of the whole tumour. In contrast, the noted studies indicate that different biopsies will reveal different properties, and even single cells within a biopsy will have different genetic characteristics. Emerging studies in other cancers, including bladder and prostate cancer, suggest that intratumour heterogeneity is common, implying similar limitations for the outcomes of personalised medicine.

Conflicts of interest: The author has nothing to disclose.

Reference

Expert’s summary:
This large multicenter prospective and randomized trial included 1355 patients with non–muscle-invasive bladder cancer who were at intermediate and high risk. The primary objective of this trial was the duration of the disease-free interval (DFI), and secondary objectives were progression, survival, and toxicity. The trial was designed as a noninferiority study, and two comparisons were foreseen for each of the two null hypotheses, thus being randomly allocated in four groups. The primary objectives were evaluated comparing the following: (1) The efficacy of a one-third dose (1/3D) of bacillus Calmette-Guérin (BCG) is inferior to the full dose (FD) of BCG (1/3D compared with FD BCG with 1-yr maintenance [1 yr] and 1/3D compared with FD BCG with 3-yr maintenance [3 yr]) and (2) the efficacy of 1-yr maintenance is inferior to 3-yr maintenance (1-yr compared with 3-yr maintenance with 1/3D BCG and 1-yr compared with 3-yr maintenance with FD BCG).

The prespecified decrease of 10% in the 5-yr DFI rate was not reached in primary and secondary objectives or in the preplanned stratification. Only a 10% decrease in the 5-yr DFI was observed in the non–preplanned stratification comparing 1/3D–1 yr and FD–3 yr, absolute difference of 9.8% (hazard ratio [HR]: 0.75, p = 0.01).

According to the sample heterogeneity, a new non–planned stratification was carried out taking into account risk groups. In the intermediate-risk group, the 5-yr DFI for patients receiving FD–1 yr was not statistically significant compared with FD–3 yr (HR: 0.88, p = 0.4380). The authors conclude that these patients should be treated with FD–1 yr BCG, as this group showed the lowest percentage of events. In high-risk patients, the lowest percentage of events occurred in patients receiving FD–3 yr, resulting in a higher 5-yr DFI compared with FD–1 yr patients (HR: 1.61, p = 0.0087), without increasing toxicity. Therefore, the authors conclude that high-risk patients should be treated with FD–3 yr BCG.

Expert’s comments:
The authors of this large randomized trial give us two practical recommendations: to administer the FD of BCG with 1-yr maintenance for patients included in the intermediate-risk group and the FD with 3-yr maintenance in high-risk patients. The authors prudently suggest that “the benefit of the two additional years of maintenance should be weighed against its added costs and inconvenience.”

Although this large randomized trial underwent a very scrupulous statistical analysis, some concerns remain. First, a 1/3D of BCG was not inferior to an FD in either primary and secondary objectives or in preplanned stratifications. As a whole, these data are in agreement with the Club Urológico Español De Tratamiento Oncológico’s (CUETO’s) conclusion in a randomized study, but without a maintenance schedule [1]. Only 1/3D–1 yr BCG was significantly inferior to FD–3 yr BCG (HR: 0.75, p = 0.01) in a non–preplanned stratification. Also, there was no difference when both groups had the same maintenance duration. This trend was also observed with 1 yr compared with 3 yr of maintenance. All these data as a whole suggest a therapy equivalence between the 1/3D and the FD, as well as 1 yr and 3 yr of maintenance.

Second, regarding the intermediate-risk group, the CUETO trial [1] suggests that a 1/3D is equally as effective as an FD without maintenance. However in the European Organization for Research and Treatment of Cancer (EORTC)
trial, FD-1 yr was the most effective schedule for these patients, as there was no significant difference compared with FD-3 yr, saving 2 yr of BCG. Although there were no comparisons between the 1/3D with 1 or 3 yr of maintenance and the FD with 1 or 3 yr of maintenance, the benefit of FD-1 yr was due to the high percentage of events (55.2%) recorded in the subgroup of patients receiving 1/3D–1 yr compared with the remaining subgroups (37.7% for FD-1 yr; 44.4% for 1/3D–3 yr; 43.0% for FD-3 yr). It is surprising to note that this high percentage of events is superior to that of high-risk patients receiving the same schedule of FD-1 yr (40.2%). These contradictory findings put into question the results of this non–prespecified stratification. Whether the different BCG strains used—the TICE strain in the EORTC trial and the Connaught strain in the CUETO trials—have some impact on the better results of the CUETO trial with 1/3D remains to be seen. Indeed, according to a recent communication from colleagues at Bern University, the Connaught strain appeared to be more effective in reducing recurrence than the TICE strain (p < 0.002) [2].

Third, in high-risk patients, the results of this trial confirm the findings of the CUETO trials [1,3], suggesting that the FD of BCG was superior to the 1/3D without maintenance. The present trial enlarged this information, suggesting that the maintenance should be for 3 yr. However, the compliance for 3-yr maintenance was only 36.4%. This finding also suggests that the maintenance should be >1 yr but not necessarily 3 yr; therefore, the suitable duration of maintenance remains to be defined in other trials. Another contradiction of these groups is the higher percentage of events in patients receiving FD-1 yr (50%) than in patients receiving 1/3D–1 yr (40.2%), a potentially less effective schedule.

The most relevant conclusions of the EORTC trial arise from the non–preplanned stratification, with controversial results related to the percentage of events recorded in the four groups considered. Data suggest that these results should be taken cautiously when formulating recommendations for patients with non–muscle-invasive bladder cancer who are about to undergo treatment with BCG.

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References


Eduardo Solsona
Service of Urology, Instituto Valenciano de Oncología, Valencia, Spain
E-mail address: solsona@pulso.com.

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