line with evidence from basic research showing that statins influence the rate of PCa development and progression by several mechanisms involving the synthesis of cholesterol [1]. Yet, observational studies that examined the association of statin use with biochemical failure after definitive local therapy for PCa reported conflicting results, with a recent meta-analysis including eight cohort studies showing no significant difference [2]. In contrast, the study of Yo et al. showed a large statin-related benefit in terms of overall and PCa mortality. Two potential biases, the misclassifications in the primary cause of death and the known healthy-statin-user bias, were both supposed to be minimal, according to the authors; however, this claim is dubious. In the group using statins, of the 1229 men that died during study observation, 541 (44%) died from PCa; in the group not using statins, of the 2270 men that died, 1250 (55%) died from PCa. Two remarkable results are the high percentage of PCa deaths in a group of men that were diagnosed with nonmetastatic PCa [3] and the relatively lower percentage of PCa deaths in the group of statin users, most likely influenced by the higher incidence of comorbidities in this group (sensitive for cause-of-death misclassification).

For these reasons, we need results from more robust clinical trials. The ongoing prospective randomized statin clinical trial (REALITY) is designed to assess the impact of statin therapy on the progression of PCa [4]. In this study, men meeting specific criteria are enrolled in an active surveillance protocol and randomized to receive either a cholesterol-lowering agent or a placebo. The study end point is disease progression. Until then, it is too early to prescribe a statin to all your PCa patients, despite the promising report by Yo et al.

Conflicts of interest: The author has nothing to disclose.

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Re: Comparative Efficacy and Safety of Medical Treatments for the Management of Overactive Bladder: A Systematic Literature Review and Mixed Treatment Comparison

Maman K, Aballea S, Nazir J, et al.

Eur Urol 2014;65:755–65

Experts' summary:

A systematic review of medical treatments of overactive bladder (OAB) compared efficacy and safety of mirabegron, a new β3-adrenergic agonist, with anticholinergic agents. Analysis of 44 randomized controlled trials (RCTs) suggests a comparable effect of anticholinergic drugs and mirabegron on the frequency of micturition and urgency urinary incontinence episodes with the exception of solifenacin 10 mg, which appeared to be more efficacious. Incidence of dry mouth, the most common adverse event associated with anticholinergic agents, was similar to placebo in mirabegron arms of RCTs, whereas an incidence of 21% was observed with anticholinergic agents.

Experts' comments:

After a 30-yr monopoly by anticholinergic agents, we finally have an innovative drug [1,2]. Research in this area has been intense over the years, with a number of drugs failing during their development phase, including potassium channel openers, phosphodiesterase type 5 inhibitors, and neurokinin-1 receptor antagonists.

Do we really need a new drug for OAB? We definitely need a new class of drugs but certainly not another anticholinergic agent. Adherence to drug treatment of chronic conditions is known to be low, and in real-life practice, about 90% of patients are off treatment within 2 yr from treatment start [3]. In a study by Benner et al., this was mainly due to lack of efficacy (46%), but side effects of anticholinergic agents also played a major role (21%) [4]. Dry mouth is the most prevalent adverse event associated with this family of drugs, although constipation, blurred vision, and cognitive impairment have been reported. The American Society of Geriatrics recommends considering the total anticholinergic load before treatment is initiated with a new agent with a similar activity [5].

Will mirabegron or other β3 agonists change the game? We do not know yet how many patients who do not respond or tolerate anticholinergic drugs will benefit from mirabegron. We do not know whether the use of mirabegron as first-line treatment will improve adherence because of its good safety profile. We do not know whether urologists will finally stop treating urgency with α-blockers and start using mirabegron, which has no adverse event on detrusor function. We do not know whether patients with urgency due to multiple sclerosis will tolerate mirabegron better than they do anticholinergic agents. The number of questions we do not have answers for is still larger than the few things we know about β3 agonists. This is why research in functional urology remains an exciting area.

Conflicts of interest: A. Tubaro has served as an advisory board member for Allergan and Bayer; as an investigator for AMS, Astellas, and GSK; and as a paid speaker for Astellas and Ferring.

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Re: Transurethral Surgery and Twice-daily Radiation Plus Paclitaxel-Cisplatin or Fluorouracil-Cisplatin with Selective Bladder Preservation and Adjuvant Chemotherapy for Patients with Muscle Invasive Bladder Cancer (RTOG 0233): A Randomised Multicentre Phase 2 Trial

Mitin T, Hunt D, Shipley WU, et al.

Lancet Oncol 2013;14:863–72

Expert's summary:
In a randomized phase 2 trial, two chemotherapeutic regimens were compared before cisplatin-based chemoradiotherapy and adjuvant chemotherapy for muscle-invasive urothelial cancer of the bladder. Induction chemoradiotherapy with paclitaxel plus cisplatin, followed by cisplatin consolidation chemoradiotherapy and adjuvant chemotherapy with cisplatin, gemcitabine, and paclitaxel, was completed by 67%, whereas in the group that received 5-fluorouracil (5-FU) plus cisplatin induction chemoradiotherapy, 53% completed the entire protocol. When the tumor was stage T1 or worse after induction chemoradiotherapy, cystectomy was recommended. T1 or worse disease after induction was present in 2 of 45 patients that completed the induction chemoradiotherapy in the paclitaxel group and in 5 of 45 patients in the 5-FU group. Overall survival and retained-bladder survival was similar for both groups after a median follow up of 5 yr. Grade 3–4 toxicity was slightly more frequent in the paclitaxel group (35%) versus the 5-FU group (19%), and more patients discontinued treatment due to toxicity in the paclitaxel group (13%) compared with the 5-FU group (6%).

Expert's comments:
This study illustrated continued interest in chemoradiotherapy regimens for muscle-invasive bladder cancer management. The good 5-yr overall survival data can be partly explained by the >90% T2-staged tumors in their population. Of note is the fact that although the recommendation of cystectomy after induction chemoradiotherapy for persistent T1 or worse bladder cancer was relatively low (7 of 90 patients, 8%), the 5-yr bladder retention rate was highest in the 5-FU group (71%), indicating that around 20% required cystectomy after consolidation radiotherapy. Also of note is the observation that of 93 patients enrolled in the study, only 58% completed induction, consolidation chemoradiotherapy, and adjuvant chemotherapy.

Muscle-invasive bladder cancer is classically treated by radical cystectomy. A meta-analysis containing 439 patients from three randomized studies showed a slight benefit of radiotherapy plus cystectomy compared with radiotherapy alone [1]. In these trials, no chemotherapy treatment was included. Despite the fact that several trials address the use of chemoradiotherapy in bladder cancer [2], no randomized trial data are available in a comparison of chemoradiotherapy and cystectomy. Several radiosensitizing chemotherapeutic modalities have been studied. Cisplatin is widely considered a potent radiosensitizer and has been combined with several other agents.

Mitin et al. present data from a randomized phase 2 study comparing two cisplatin-based chemotherapy combinations. Similar to the data presented by James et al. [3] on mitomycin–5-FU chemoradiotherapy, the majority of cases had cT2 disease. This does not necessarily indicate that chemoradiotherapy cannot be considered effective in larger bladder cancers; understaging in bladder cancer is common. A substantial number of patients in both studies will have had undetected extravesical disease and still respond favorable to the chemotherapy regimens. The 5-yr overall survival rate for the two regimens presented by Mitin et al. (>70%) was considerably higher than that reported by James et al. (48%) [3]. The fact that the latter study contained more cT3 disease may account for this difference. Another important difference between the two studies was the use of a primary tumor evaluation after induction chemoradiotherapy. In the BC2001 study [3], only three patients (0.8%) underwent early cystectomy before protocol treatment was completed, whereas in the RTOG 0233 study reported by Mitin et al., seven patients (8%) underwent early cystectomy for not obtaining at least less than T1 disease after induction chemoradiotherapy.

Selection of patients for chemoradiotherapy regimens requires a multistep, multidisciplinary approach in which close collaboration between medical oncology, radiotherapy, and urology is required. The role of urologists starts with