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What is the Optimal Treatment Strategy for T1 Bladder Tumors?

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1. Introduction

Approximately 20–30% of non–muscle invasive bladder urothelial carcinomas invade the lamina propria and are staged as T1. They represent a therapeutic challenge because of their highly malignant potential. Their individual clinical behavior is difficult to predict, and despite recent developments, their molecular profile and position in pathogenic pathways remain enigmatic.

Patients with T1 urothelial carcinoma are at risk of tumor recurrence and, more important, at risk of disease progression. Without bacillus Calmette-Guérin (BCG) treatment, the progression into muscle-invasive disease threatens 18–40% of patients with T1 urothelial carcinoma. In 848 BCG-treated patients from Club Urológico Español De Tratamiento Oncológico (CUETO) trials, the progression to muscle invasion appeared in 15% of T1 cases (Luis Martinez-Piñeiro, personal communication, September 2009) [1].

Despite this unfavorable prognosis, I believe that outcomes can be improved by utilization of current clinical experience and technical progress. The data from the prospective randomized trial managed by the Urothelial Cancer Group of the Nordic Association of Urology (NAU) and published in this issue offer the perfect opportunity to consider and discuss some options and critical points [2].

The management of T1 bladder urothelial tumors is based on three milestones: complete transurethral resection (TUR), effective intravesical treatment, and early detection of treatment failure and timely indication of radical cystectomy.

2. Discussion

2.1. Complete transurethral resection

The aim of TUR of the bladder (TURB) is to establish the histologic diagnosis and grade of the tumor, to determine the extent of the disease (depth of invasion, number of tumors, presence of carcinoma in situ [CIS]), and to achieve its complete removal.

Although TURB is a procedure familiar to all urologists, its results, particularly in T1 tumors, are far from optimum. Indeed, significant numbers of tumors persist or are even understaged. Moreover, the chance to detect associated CIS with conventional equipment is limited, but there are some measures that could improve the outcomes.

The procedure should be performed systematically and meticulously by a relevantly trained urologist. It was shown recently that the establishment of a systematic, dedicated teaching program can improve the results of TURB [3], and I am personally persuaded that the quality of TURB performed nowadays is much higher than it was decade ago.

The procedure should be performed with modern equipment, including a video system. Broad perspective has been opened with the introduction of new imaging technologies, such as fluorescence cystoscopy (FC) and narrow-band imaging. FC increased the detection rate of T1 tumors from 86% to 95% in one study [4]. It was shown that better detection rate of T1 tumors with FC-guided TURB results in a lower recurrence rate, although its effect on disease progression has not been confirmed yet [5]. FC is particularly valuable in detection of associated CIS. The outcomes of the NAU study presented in this issue demonstrate the benefit of BCG in patients with associated CIS [2]. This observation underlines the value of precise CIS detection.

The European Association of Urology (EAU) guidelines strictly recommend the second endoscopic resection (re-TUR) in all T1 tumors [6]. The outcomes presented by Duchek et al provide clear support for this recommendation. There is no doubt that persistent tumors in 39% of

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patients after initial resection are a strong argument for routine repeat procedure [2]. Presented with these data, it is not a great surprise that the re-TUR was able to reduce the early recurrence rate in T1 tumors from 63% to 26% in a randomized study from Turkey [7]. An even more important argument for re-TUR in all T1 tumors is correction of staging error in about 4–10% of cases.

2.2. *Effective intravesical treatment*

According to patient stratification recommended by EAU guidelines, T1 tumors are classified mostly as high-risk or, in some cases, as intermediate-risk tumors. Intravesical immunotherapy or chemotherapy instillations comprise an integral part of their treatment [6]. Two questions, however, should be considered and discussed.

The first question is, what is the role of early chemotherapy instillation before BCG immunotherapy? The European Organization for Research and Treatment of Cancer (EORTC) meta-analysis confirmed that an immediate chemotherapy instillation after TURB reduces the risk of recurrence in TaT1 tumors. Of 1476 patients, 475 (32%) had T1 carcinoma [8]. This observation was a basis for the EAU's guidelines and its recommendation to utilize early instillation after resection of all clinical TaT1 cases, even in those where further intravesical treatment is expected [6].

To be honest, we must admit that there are no statistically relevant data addressing the role of early instillation in patients with further BCG treatment. It should be considered, however, that the immediate instillation is effective through the destruction of circulating tumor cells and through prevention of their implantation. This principle also should hold for high- and intermediate-risk tumors, although for a definitive conclusion, we need an adequately powered, prospective, randomized trial.

The second question is, which intravesical treatment is the most beneficial in T1 tumors? There is no doubt that patients with intermediate- and high-risk tumors need further instillations. The selection of the optimal tool was addressed by several trials and meta-analyses.

A recently published individual patient data meta-analysis by Malmström et al (2820 patients, 1139 of them with T1 disease) confirmed that in intermediate-risk tumors (74% of patients) and high-risk tumors (23% of patients), BCG with maintenance schedule was more effective than mitomycin C (MMC) in prevention of tumor recurrence [9]. In trials with BCG maintenance, a 32% reduction in the risk of recurrence for BCG compared to MMC was found ($p < 0.0001$), while there was a 28% increase in the risk of recurrence for BCG without maintenance ($p = 0.006$). The same conclusion was possible for intermediate- and high-risk groups.

It was shown by the EORTC meta-analysis of 24 randomized trials that BCG with maintenance provides a reduction of 27% in the odds of progression [10]. The conclusion, however, must be cautiously considered because of short follow-up (median: 2.5 yr) and low number of progressions (6.4% between papillary tumors). Nonsignificant trends in favor of BCG maintenance for progression and survival were observed in the aforementioned Malmström et al meta-analysis. The meaningful comparison for progression and death was not possible because of short follow-up (median: 4.4 yr) and low number of events (12% of patients progressed and 7% died of bladder cancer) [9].

The NAU Urothelial Cancer Group study published in this issue is unique in its evaluation of a homogenous group of patients with T1 tumors. Its primary limitation is the short follow-up, which prevents any definitive conclusion, particularly for disease progression. In the prospective randomized study, authors compared the results of maintenance BCG to combination treatment with 50 mg epirubicin and 10 million units of interferon α2b. The short-term data support, to an extent, maintenance BCG over chemotherapy [2]. Although one can admit that the potential could be improved by device-assisted instillation in chemotherapy or by dose escalation in interferon immunotherapy, these options would increase the economic burden of the treatment dramatically and are, in my opinion, not realistic for daily practice—at least in the near future.

2.3. *Early detection of treatment failure and timely indication of radical cystectomy*

The prognosis of patients who progress to muscle-invasive disease despite BCG treatment is extremely poor. In one study, the 5-yr disease-specific survival after cystectomy decreased to 28% in such patients [11]. Optimally, we should switch to radical cystectomy before muscle-invasive progression. There is no reason to continue with BCG in patients who do not respond until they have had 6 mo of treatment [6]. The unreasonable delaying of radical surgery through intravesical treatment can have a negative impact on patient survival [12].

In conclusion, the authors from Sweden, Norway, and Finland should be applauded for this trial that included a homogenous group of patients. Moreover, most treatment steps were performed exactly according to current recommendations. Long-term evaluation of the data will be anticipated with great interest.

Conflicts of interest: The author has received honoraria from GE Healthcare for lectures at meetings on bladder cancer.

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