Statement concerning the shortage of BCG vaccine from the EAU Guidelines Panel on non-muscle invasive bladder cancer

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The current situation

The company Sanofi Pasteur has announced a suspension of the production of the BCG Connaught strain in June 2012. Because of the ongoing renovation of its manufacturing facility, production is not expected to resume before the end of 2013. As the Connaught strain supplies a significant segment of the world market, the suspension of its production may result in a global shortage of BCG in the treatment of non-muscle invasive bladder cancer. Although the situation is different in individual countries depending on the BCG strain on the market, it represents potential danger for patients and requires the attention of urologists.

Each urologist has an obligation to provide optimal treatment according to the current evidence for individual patients with non-muscle invasive bladder cancer. This statement summarizes information which can help the urologist with treatment decisions in the absence of BCG Connaught or with a suboptimal supply of BCG on the market.

Current role of BCG in the treatment of non-muscle invasive bladder cancer and EAU guidelines recommendations

BCG intravesical immunotherapy is the most effective conservative management for bladder carcinoma *in situ* (CIS) and for Ta T1 tumours at intermediate and high risk of recurrence and progression (EORTC risk calculator) after complete TURB (transurethral resection of the bladder), where it significantly reduces the recurrence rate and has an impact on the early progression rate.

According to EAU guidelines on non-muscle invasive bladder cancer, BCG intravesical instillations are indicated in patients with bladder CIS and in patients with Ta T1 tumours at intermediate and high risk of recurrence and/or progression. For optimal efficacy, the induction course (6 weekly instillations) should be followed by at least one year of maintenance.

Is the efficacy of different BCG strains comparable?

Only a small number of published studies have compared different BCG strains when used as induction treatment. The publication of a prospective randomized comparison of induction BCG Connaught and induction BCG TICE is expected soon. No head-to-head comparisons of the clinical efficacy of different BCG strains when used as maintenance therapy have been published in the literature.

The published meta-analysis of prospective randomized trials did not suggest any difference in efficacy of the BCG strains (Pasteur, Frappier, Connaught, TICE, RIVM).

There are no data which provide information on whether switching from one BCG strain to another during the treatment schedule can have an impact on antitumor efficacy.

How long should the optimal BCG schedule be? When can BCG instillations be terminated without compromising efficacy?

For optimal efficacy, BCG should be given with a maintenance schedule. Many maintenance schedules have been used with a maximum of 27 instillations over 3 years. The optimal length of maintenance is, however, not known. According to meta-analyses, BCG should be given for at least one year to be superior to intravesical chemotherapy. With the current BCG shortage, instillations can be safely terminated when the patient has completed one year of BCG treatment.

References about the use of only an induction course (6 weekly instillations without maintenance) are controversial. A recently presented cohort study showed promising results, however meta-analyses have shown induction only BCG to have inferior efficacy compared to intravesical chemotherapy.

Can be BCG instillations be replaced by another treatment?

In patients with Ta and T1 tumours at intermediate or high risk of recurrence and intermediate risk of progression, intravesical chemotherapy (multiple instillations for up to 12 months) represents an alternative treatment option to BCG immunotherapy. It has a higher risk of recurrence but a lower risk of side effects.

In Ta and T1 tumours at high risk of progression and in CIS, EAU guidelines provide two treatment options, intravesical BCG immunotherapy and radical cystectomy. Cystectomy represents an oncologically safe but more invasive treatment which should be discussed, particularly with younger and fit patients.

Some promising data have been presented about device assisted chemotherapy (Synergo or EMDA) which might replace BCG instillations in patients with high risk tumors who are not fit for cystectomy. The current evidence however is limited and this treatment is considered to be experimental.

Conclusions and recommendations:

1. The efficacy of different BCG strains seems to be comparable
2. There is no information about the consequences of switching from one BCG strain to another. This seems, however, to be a reasonable solution during the first year of maintenance in the situation where BCG Connaught is no longer available, but another strain can be obtained.
3. In the current situation of BCG shortages, instillations can be safely terminated when the patient has completed one year of BCG.

4. In patients with Ta and T1 tumours at intermediate or high risk of recurrence and intermediate risk of progression, adjuvant BCG treatment can be replaced by intravesical chemotherapy, which represents an alternative treatment option.

5. In younger and fit patients with Ta T1 tumours at high risk of progression and with CIS, an immediate radical cystectomy should always be considered. This should be underlined, particularly in the current situation with BCG shortages.

6. In patients with Ta T1 tumours at high risk of progression or with CIS who are unfit to or unwilling to undergo a cystectomy, there is no scientifically proven alternative to BCG treatment. Thus every effort should be made to obtain an available BCG strain. As an alternative, device assisted chemotherapy seems to provide promising results and could be considered. Passive intravesical chemotherapy can achieve some responses in CIS, influence the recurrence rate in TaT1 tumours and thus provide some benefit for the patient. Urologists should not forget, however, that the effect of passive intravesical chemotherapy on tumour progression has never been confirmed.

7. It should be emphasized that the most important modality in the treatment of non-muscle invasive bladder cancer remains a complete and precisely performed TURB, independent of the availability of BCG on the market.