Jorge Huguet. Clinical Head in the Uro-Oncology and Renal Transplantation Unit. Fundació Puigvert (Barcelona) @jorhuguet1

POSSIBLE SITUATIONS AFTER BCG TREATMENT OF HIGH-RISK NON-MUSCLE-INVASIVE BLADDER TUMORS

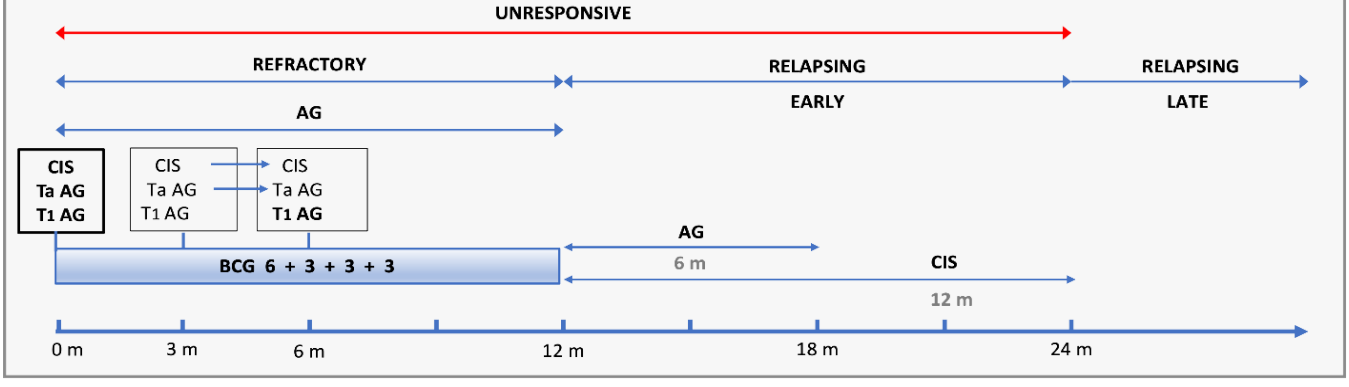
3 POSSIBLE SITUATIONS:

1. **RESPONSE TO BCG:**
   BCG is the treatment for **intermediate and high-risk non-muscle invasive tumors (NMIBC).** It achieves **response rates close to 70%, which approach 80% in CIS.**
   It may reduce progression, and as such, it is the drug with which to compare new therapies under study (1,2).

2. **PROGRESSION DURING TREATMENT WITH BCG (:≥ T2)**
   It occurs in **9.5%-21%** of cases (3). It results in **poorer patient prognosis.** A worse survival has been described in invasive tumors resulting from progression of a NMIBC (progressive), compared to those that are invasive at the outset (4).
   In progressive tumors, genomic changes associated with a poorer response to neoadjuvant chemotherapy have also been observed (5). In high-risk NMIBC, cystectomy should not be delayed until progression. Progression also falls under the definition of BCG failure.

3. **NO RESPONSE TO BCG OR BCG FAILURE (high-grade recurrence during or after BCG):**
   Since approximately 2015 to the present, the need to reach a consensus on the definition of non-response to BCG has been evident. This need has become even greater with the appearance of numerous clinical trials with new drugs to treat BCG failure. Each urological society has created its definitions of non-response to BCG, but they are all very similar.
   Since 2018, the European Association of Urology (EAU) guidelines have defined the different types of BCG failure (6). We present the **Table** in which a diagram helps to better understand the definitions (7). According to the EAU, **unresponsive tumors** are those that will not benefit from further BCG treatment. They will require cystectomy, clinical trial or other options different from BCG. They will be divided into:
   a. **Refractories:** High-grade recurrences during BCG treatment, specifically high-grade T1 at 3 and 6 months and Ta and CIS with recurrence at 3 and 6 months.
   b. **Early relapsing**: High-grade papillary recurrences during the 6 months following the end of BCG maintenance or CIS during the year following BCG termination.
   c. **Late Relapsing**: high-grade recurrences beyond the post-BCG year.

   Some authors consider BCG Refractories and Early Relapsing to have equal risk of progression, although there is no evidence. Late Relapsing tumors have a better prognosis than Refractories (8) and therefore can be offered BCG again or cystectomy.
   The EAU guidelines also add that low-grade recurrences during or after BCG are not considered BCG failure and recommend appropriate treatment with BCG, having received at least 5 out of 6 induction doses, plus at least 2 out of 6 of the second induction or 2 out of 3 of maintenance.



1. Lamm DL et al. Mantainance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000;163:1124-9.
2. Sylvester R et al. Intravesical bacillus Calmette-Guerin reduces de risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomiced clinical trials. J Urol 2002;168:1964-70.
3. Van den Bosch S et al. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. Eur Urol 2011;60:493-500.
4. Scherier B Ph et al. Prognosis of muscle-invasive bladder cancer: difference between primary and progressive tumours and implications for therapy. Eur Urol 2004;45:292-6.
5. Pietzak EJ et al. Genomic differences between "primary" and "secondary" muscle-invasive bladder cancer as a basis for disparate outcomes to cisplatin-based neoadjuvant chemotherapy. Eur Urol 2019;75:231-39.
6. EAU Guidelines in non-muscle-invasive bladder cancer v 2022 (consultado en noviembre 2022). Disponible en http:uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/
7. Huguet J et al. Actas Urol Esp . In press. doi.org/10.1016/j.acuro.2023.01.00.
8. Gallager BL et al. Impact of previous bacille Calmette-Guerin failure pattern on subsequent response to bacille Calmette-Guerin plus interferon intravesical therapy. Urology 2008;71:297-301.