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Maintenance BCG for Ta, T1 bladder tumors is not associated with increased toxicity and side effects do not predict efficacy of BCG

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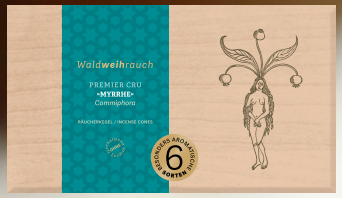

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R. Sylvester, A. v. d. Meijden and Members of the EORTC-GU Group

MAINTENANCE BCG FOR TA, T1 BLADDER TUMORS IS NOT ASSOCIATED WITH INCREASED TOXICITY AND SIDE EFFECTS DO NOT PREDICT EFFICACY OF BCG

Before intravesical Bacillus Calmette-Guérin (BCG) was introduced a quarter of a century ago by Morales, patients with Ta, T1 papillary tumors and carcinoma in situ (CIS) were treated after transurethral resection (TUR) of biopsy with intravesical cytotoxic drugs. Thiotepa, epodyl, adriamycin, epirubicin and mitomycin C are all able to delay the time to first recurrence and to reduce the number of recurrences (recurrence rate). A meta-analysis comprising over 2,500 patients showed that while intravesical chemotherapy delays the time to first recurrence as compared to TUR alone, it has no influence on the time to progression to muscle invasive disease. With the use of BCG over the past 25 years, a number of questions have arisen, most of which, but not all, have now been answered:

1. How does BCG exert its anti-tumor effect?
2. Is there an optimal route of BCG administration?
3. Is BCG superior to chemotherapy for preventing recurrences?
4. Which patients should be treated with BCG and which should not?
5. Can BCG delay or prevent progression to muscle invasive bladder cancer?
6. Is maintenance BCG necessary for optimal efficacy?
7. Is maintenance therapy associated with increased toxicity?
8. Is there a relationship between BCG efficacy and toxicity?
9. What is the optimal schedule and dose of BCG?
10. Is there an optimal BCG strain?

In this extended abstract we intend to answer questions 7 and 8.

Is maintenance therapy associated with increased toxicity?

Assuming that maintenance therapy is necessary for optimal efficacy, the issue of BCG toxicity becomes more relevant. Because of the more pronounced side effects of BCG compared to intravesical chemotherapy, reluctance still exists about its use. Early publications reporting deaths due to BCG sepsis, and indicating that BCG induced cystitis occurs in up to 90 % of the patients, have strongly influenced fears over the use of BCG. However with increasing experience in applying BCG, the side effects now appear to be less prominent and few if any deaths due to BCG therapy have been reported in the recent literature. Serious side effects are encountered in less than 5 % of the patients and can be effectively treated in virtually all cases.

The assessment of side effects remains subjective, strongly associated with the personal opinion of the investigator towards BCG. Some urologists strongly believe that BCG only works if side effects are observed. Others stop treatment immediately to protect their patients from severe adverse events. In a large randomized study from the SWOG, only 16 % of the patients fulfilled the complete maintenance schedule of 3 years, suggesting that completing maintenance therapy is not a realistic objective. But if so many patients stop BCG treatment, is this really due to increasing toxicity?

In an EORTC randomized phase III study, 520 patients who received BCG were assessed to determine whether BCG toxicity increased over time. The maintenance schedule used was identical to the scheme used in several SWOG studies: a six week induction course followed by three weekly maintenance courses at 3, 6, 12, 18, 24, 30 and 36 months. The treatment period was divided into 5 periods:

- the six week induction course (6 instillations)
- months 3 and 6 (6 instillations)
- month 12 (3 instillations)
- the second year of maintenance (6 instillations)
- the third year of maintenance (6 instillations)

In each of the periods local and systemic side effects were assessed. Details will be provided in a separate publication but the conclusions were: About one third of the patients completed the maintenance schedule, 17 % stopped due to inefficacy, 19 % stopped due to adverse events and 31 % stopped due to "other reasons". Local side effects of BCG therapy did not increase during maintenance. Systemic side effects were more frequent during the first 6 months of treatment after which time they decreased. Two thirds of all patients who stopped BCG due to side effects did so during the first 6 months of treatment (table 1).

Bohle et al concluded that while BCG associated cystitis was more frequent than with mitomycin C, it did not differ between the BCG maintenance (at least 1 year of BCG) and BCG non-maintenance groups (6 months of less of BCG). Saint et al and Morgia et al also included that the side effects of BCG were more prominent during the induction and early maintenance instillations. Therefore the assumption that BCG induced side effects increase with time during maintenance does not appear to be correct.

Is there a relationship between BCG efficacy and toxicity?

Previous reports have indicated that there may be a relationship between the presence and severity of BCG side effects and its efficacy. It has been suggested that patients with a local inflammatory reaction fever and leukocyturia have a better clinical outcome than those without. However the prognostic importance of side effects should be investigated using a proper statistical model: the landmark method. For instance patients with multifocal tumors who are at high risk of recurrence will recur and drop out earlier than patients with single tumors. Such high risk patients will, because of the nature of their disease, receive fewer BCG instillations and thus may have fewer side effects than the good prognosis patients, who will recur later or not at all and receive more BCG instillations.

Table 1: Time of stopping BCG due to side effects in 101 of 520 patients

Time period	Stop BCG for side effects
Six week induction	30 (29.7 %)
Months 3 and 6	39 (38.6 %)
Month 12	6 (5.9 %)
Second year	12 (11.9 %)
Third year	14 (13.9 %)
Total	101

In the EORTC trial reported above, the relationship between BCG side effects and efficacy was also studied. The prognostic importance of local side effects and systemic side effects (including fever) within the first 6 months of BCG treatment on subsequent recurrences was investigated using the landmark method. There was no relationship between the occurrence of local side effects, and systemic side effects or fever within the first 6 months and the subsequent time to first recurrence. This analysis will be published separately.

Similarly, Saint et al found no difference in efficacy between patient with and without adverse events. Thus while controversial, the most recent evidence suggests that BCG toxicity is not a prognostic factor for treatment efficacy.

Conclusions

The majority of local and systemic side effects are seen already during the induction course in the first 6 months of maintenance. After 6 months BCG toxicity does not increase and instillations are generally well tolerated. While a correlation between BCG toxicity and efficacy exists, our results do not confirm that BCG toxicity is actually responsible for an improved outcome.

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