Efficacy of HIVEC in patients with high-risk non-muscle invasive bladder cancer who are contraindicated to BCG and in patients who fail BCG therapy

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ABSTRACT

Purpose: To evaluate Hyperthermic-Intra-Vesical Chemotherapy (HIVEC) efficacy regarding 1-year disease-free survival (RFS) rate and bladder preservation rate in patients with High-risk Non-Muscle Invasive Bladder Cancer (NMIBC) who fail BCG therapy or are contraindicated to BCG.

Methods: Between June 2016 and October 2019, patients treated with HIVEC for mostly high-risk NMIBC who failed BCG or BCG-naive if BCG contraindicated have been included in our study. These patients had a theoretical indication for cystectomy but were ineligible for surgery or refused it. Results: Fifty-three patients, median age 72 \(\pm 24\) years, were included in this study \((n = 29\) BCG-failure and \(n = 24\) BCG-naive). The median follow-up was 18 months. The bladder preservation rate was 92.4\%. The 12-months-RFS rate was 60.5\%. The RFS rates for BCG-naive and BCG-failure groups were respectively 70\% and 52.2\% at 12 months. Three patients progressed to muscle infiltration, all in the BCG-failure group and all in the very high-risk EORTC group. Two of them developed metastatic disease and died from bladder cancer.

Conclusion: Chemohyperthermia using HIVEC achieved a RFS rate of 60\% at 1 year and enabled a bladder preservation rate of 92\%. Given the low risk of progression in the BCG-naive group, HIVEC could be a good alternative. Conversely, for patients with very high-risk tumors that fail BCG, cystectomy should remain the standard of care and HIVEC may be discussed cautiously for patients who are not eligible for surgery and well informed of the risk of progression to muscle-invasive disease.

Introduction

The incidence rates of bladder cancer increased in many European countries [1]. Non-muscle invasive bladder cancer (NMIBC) represents 75\% of bladder cancer. An adjuvant treatment with intravesical bacillus Calmette Guérin (BCG) is recommended for high-risk (HR) NMIBC. However, up to 50\% fail to maintain a response within 5 years [2].

Cystectomy is recommended in BCG-refractory or BCG-unresponsive tumors and should be upfront considered as an immediate option for patients at very-high-risk of progression according to the international guidelines [3]. The management of high-risk muscle invasive bladder cancer (HR-NMIBC) is a current challenge with the aim to enabling bladder preservation while avoiding progression to muscle infiltration, especially for patients suffering from recurrent disease after BCG. On another side, some patients are intolerant and contraindicated to BCG. Although radical cystectomy is recommended, some patients decline to undergo or are ineligible. Efficacious and safe therapeutic options are urgently needed for this challenging patient population.

Radiofrequency induced thermochemotherapeutic effect (RITE) is a microwave bladder heating technique having shown equivalent efficacy to BCG in a randomized trial for patients with intermediate and high-risk tumors [4]. The second technique, Hyperthermic-Intra-Vesical Chemotherapy (HIVEC), a recirculating conductive bladder heater evaluated in our study, has the advantage of being easier to use but is still poorly evaluated in the literature [5,6].

The objective of our study is to evaluate HIVEC regarding the disease-free survival (RFS) rate and bladder preservation in HR-NMIBC patients who fail BCG therapy or are contraindicated to BCG.
Methods

Patients

This is a multicenter, retrospective study, including patients treated with HIVEC between June 2016 and October 2019 in 5 French center (approved protocol number: THERMO-MMC-IPC 2019-019). The requirement for informed consent was waived.

The inclusion criteria were:

- Patients with high-risk or very high-risk NMIBC according to the European Organization for Research and Treatment of Cancer (EORTC) classification who have failed treatment with BCG (BCG-failure group) according to the definition of BCG-unresponsive from the International Bladder Cancer Group [7]. Patients with an intermediate risk tumor could be included in this group if the initial tumor was classified as high or very high-risk with early recurrence at the first cystoscopy after BCG therapy as low-grade tumor.
- Patients who have a theoretical indication of BCG therapy but who are contraindicated or intolerant to BCG (BCG-naive group). It could be an absolute contraindication, i.e., grade 3/4 adverse event during previous BCG therapy or it could be a relative contraindication: previous pelvic radiotherapy, immunosuppressive therapy or BCG shortage. Indeed, in 8 cases, the patients could not receive BCG due to national shortage and HIVEC has been proposed as an alternative to BCG.

These patients are in a therapeutic impasse, especially for highest risk tumors and BCG-refractory tumors where these patients may have a theoretical indication for cystectomy but are not eligible or refuse it. Patients included had recent urinary tract imaging (<6 months). Patients were classified into EORTC risk groups according to the recommendations of the EAU [3]. The ethics committees of each institution approved data collection and analysis.

Devices

Mitomycin C (MMC) was heated by the COMBAT BRS (Combat Medical, Wheathampstead, UK) device. This is a recirculating conductive bladder heating device which increases the temperature of the MMC at 43°C (±1°C) before instillation [8].

Instillation protocol

Chemohyperthermia was started 4–6 weeks after the first resection or after the second-look resection when recommended. The therapeutic plan consisted of 6 or 8 weekly instillations of 40mg of heated MMC. The standard protocol was to instill 40mg of mitomycin in 50 mL of 0.9% sodium chloride solution heated by the HIVEC system during one hour. The number of instillations planned was usually 6. Treatment was discontinued in case of severe (grade 3 or 4) side effects.

Monitoring protocol

Patients had cystoscopy and urinary cytology six weeks after the last instillation, then every three months during the two first years. A bladder resection was considered if a lesion was visualized by cystoscopy or in case of high-grade positivity of the cytology.

Endpoints

Co-primary endpoints were recurrence-free survival time (RFS) and bladder preservation rate (defined as the proportion of patients who did not have a cystectomy among those who did not progress). The secondary endpoints were, time to recurrence, MIBC progression rate, progression-free survival (PFS), time to muscle infiltration, time to a metastatic disease, disease specific survival (DSS), overall survival (OS), and adverse events according to the CTCAE v5.0 classification. The complete response rate at 6 months for BCG-failure with carcinoma in situ was also analyzed. For RFS, a sub-group analysis was performed for BCG-naive and BCG-failure patients separately.

Tolerance was evaluated prospectively using patients reported outcomes questionnaires. At the same time, physician-reported grade 3/4 side effects were collected retrospectively for each patient.

Statistical analysis

Data were collected and analyzed using SAS software version 9.3 (SAS Institute, Cary, NC, USA) and R software version 3.0.3. Clinical and histopathological correlations were tested, using, for continuous (quantitative) variables, the Student’s t-test, and for qualitative variables, the Chi2 test with or without Yates correction depending on the expected numbers. RFS and OS analyses were performed using Kaplan-Meier curves and were compared using the log-rank test with a univariable Cox regression model used to determine unadjusted hazard ratios. The data were considered statistically significant at the 95% confidence interval (p < .05).

Results

Patients characteristics

A total of 53 patients were included in this study, including 24 patients in the BCG-naive group and 29 patients in the BCG-failure group. The median age of the patients was 72 years (39–93) for the BCG-failure group. The characteristics of the population are summarized in Table 1.

Oncological outcomes

Median follow-up in our study was 18 months. A total of 22 patients recurred, with a mean time to recurrence of 18 months [5–43], 20 months [5–43] for the BCG-naive group and 15 months [5–31] for the BCG-failure group.
19 patients had a NMIBC recurrence. Treatments in case of NMIBC recurrence included (Table 3): radical cystectomy \( (n = 3) \), rechallenge intravesical therapy because the recurrence occurred more than one year after the end of HIVEC therapy \( (BCG \ n = 6, \text{or} \ HIVEC \ n = 4) \), abstention for patients who were not eligible to another treatment \( (n = 5) \) and intravenous pembrolizumab \( (n = 1) \).

Three patients progressed to muscle infiltration with a mean time to progression of 7 months \([5–12]\). Two of them developed a metastatic disease and died from bladder cancer whereas one had a cystectomy for an organ-confined disease.

At the end of the follow-up, a total of 5 patients died: 2 from bladder cancer, 1 from a myocardial infarction, 1 from a pulmonary embolism and 1 from head and neck cancer. Overall survival rate was 90.6%.

The RFS rates for the whole population at 3-, 6-, 12- and 18 months were respectively 94.3%, 80.4%, 60.5% and 46.2%. For the BCG-naive group of patients, the RFS rates at 3-, 6-, 12- and 18 months were respectively 100%, 95.7%, 70% and 61.1%. For the BCG-failure group, the RFS rates at 3-, 6-, 12- and 18 months were respectively 89.7%, 67.9%, 52.2% and 33.3% (Figure 1).

In the BCG-failure group, in case of presence of Cis, complete response rates at 6 months were 75%.

The bladder preservation rate was 92.4%.

### Predictive factors of recurrence and progression after HIVEC

In univariate analysis, only the tumor grade was associated with RFS (Table 2), 0% (0/6) low grade recurred and 46.8% (22/47) recurred \( (p = .028) \) while the presence of Cis was not a predictive factor of recurrence in our series. Pure Cis (without papillary tumor associated) recurred in 66.7% of cases versus 36.4% for papillary tumors, but this difference was not significant \( (p = .09) \).

None of the different clinicopathological factors was predictive of progression to muscle-invasive disease in univariate analysis. The three patients who progressed had a very high-risk tumor according to the EORTC classification. However, the EORTC classification was not significantly associated with the risk of progression \( (p = .058) \). It is also noteworthy that the three patients who progressed were in the BCG-failure group \( (10.3% \text{ of patients in the BCG-failure group progressed during follow-up whereas none of the BCG-naive patients have progressed}) \).

### Safety

No severe side effect (grade 3 or 4) has occurred. Grade 1 or 2 side effects consisted of: 29.4% positive urine culture, 38.2% pain, 14.7% hematuria, 52.9% urgency, 8.8% myalgia, 26.5% bladder spasm, 2.9% skin allergy. The percentage of delivered/theoretical instillations was 93.7%. Five patients received less than 5 instillations with early treatment discontinuation due to minor side effects (grade 1 or 2).

### Discussion

Management of HR-NMIBC is a challenge to allow bladder preservation while avoiding progression toward a muscle-invasive disease. Second-look resection and adjuvant BCG therapy have been shown to decrease the risk of recurrence.
and progression [9,10]. For patients who failed BCG, radical cystectomy remains the standard [3]. However, cystectomy is associated with a high morbidity and some patients are ineligible for surgery, due to their comorbidities. For these reasons, some patients will attempt bladder preservation therapies.

One of them is chemohyperthermia. By increasing the intracellular concentration of mitomycin and thereby its effectiveness, hyperthermia seems to have a synergistic effect with chemotherapy [11]. In terms of safety, it has already been shown that heated MMC is at least equivalent to BCG whether with RITE [12] or with HIVEC [13]. Our study confirms these data since we did not have any major side effects.

In terms of efficacy, thermo-chemotherapy with HIVEC is still poorly evaluated. Regarding RITE (Synergo® device), the first results are encouraging suggesting a superior efficacy of RITE compared to passive MMC and an efficacy at least equivalent to that of the BCG in terms of RFS for intermediate- or high-risk NMIBC [4]. There is only one randomized phase III study assessing RITE efficacy in patients who fail BCG [13]. This study included 104 patients treated with either RITE or BCG. At 1 year, RFS in the RITE group was 49%, which is close to our results (52.2% in the BCG-failure group). RFS at 2 years was close to BCG in the overall cohort (35% versus 41%, \( p = .49 \)), with a non-significant improvement in the subgroup of patients without cis (53% versus 24%, \( p = .11 \)). Conversely, in the group of patients with cis, BCG was significantly better in terms of recurrence-free survival at 2 years (49% versus 26%, \( p = .01 \)).

With a median follow-up of 18 months, we were able to show a RFS rate at 1 year of 60% with HIVEC with a bladder preservation rate was 92.4%. However, it is noteworthy that the RFS rate differs between BCG-naive and BCG-failure sub-groups.

For BCG-naive patients, it is established that the risk of recurrence after a first line of BCG therapy is 20% at 6 months and 25% at 12 months, while the risk of progression is 3% at 6 months and 5% at 12 months [7]. In our series, RFS rate in the BCG-naive group was 70% at 12 months signifying that less than a third of the patients recurred at 1 year. These results are favorable since HIVEC seems to have an efficacy similar to that of BCG, suggesting that HIVEC could be a good alternative, especially for patients contraindicated to BCG.

The BCG-failure group had a worse prognosis in terms of recurrence and progression risk. Indeed, in our series, a half of patients recurred within the first year. According to the recommendations for clinical trials in BCG unresponsive NMIBC [7], and taking in account the fact the placebo-controlled arm is not ethical, single arm trials with new agents are now being conducted with the objective of achieving a RFS rate of at least 30% at 12 months. For BCG unresponsive Cis, the objective of at least 50% of complete response at 6 months is considered as clinically meaningful. With a RFS rate of 52.2% at 12 months in our BCG-failure whole population and with a complete response rate of 75% at 6 months (and 60% at 12 months) for BCG unresponsive Cis in our study, chemohyperthermia could therefore be considered as a valid option for patients who fail BCG.

In our study, Cis was not a predictive factor of recurrence after HIVEC, even if pure CIS seem to have a distinct profile with two third of patients who recur early after HIVEC. Conversely, the outcomes seem favorable in the group of patients with papillary tumors without associated CIS, with a recurrence rate at 1 year of 3% at 6 months and 5% at 12 months [7]. In our series, the RFS rate differs between BCG-naive and BCG-failure sub-groups.

Table 3. Salvage therapy for NMIBC recurrence after HIVEC treatment.

| Salvage therapy | n = 19 |
|-----------------|-------|
| Radical Cystectomy | 3 |
| Abstention/No curative treatment | 5 |
| Rechallenge intravesical therapy* | 10 |
| CHT | 6 |
| BCG | 4 |
| Pembrolizumab IV | 1 |

*Rechallenge intravesical therapy in case of recurrence > 1 year after HIVEC. BCG = Bacillus Calmette-guérin, CHT: intravesical chemohyperthermia with Mitomycin C.

BCG: Bacillus Calmette-guérin; cis: carcinoma in situ; MMC: mitomycin C; CHT: intravesical chemohyperthermia with Mitomycin C.

Table 2. Predictive factors of recurrence after HIVEC.

| Characteristics | Recurrence | No recurrence |
|----------------|------------|--------------|
| Age, median [min–max] | n = 22 | n = 31 | .58 |
| Sex, n (%) | | | |
| Male | 4 (40) | 6 (60) | .92 |
| Female | 18 (41.9) | 25 (58.1) | |
| Previously treated by MMC, n (%) | | | |
| Yes | 3 (50) | 3 (50) | .65 |
| No | 19 (40.4) | 28 (59.6) | |
| Previously treated by BCG*, n (%) | | | |
| Yes | 17 (44.7) | 21 (55.3) | .45 |
| No | 5 (33.3) | 10 (67.7) | |
| Indication, n (%) | | | |
| BCG-naive group | 14 (48.3) | 15 (51.7) | .27 |
| BCG-failure group | 8 (33.3) | 16 (66.7) | |
| Papillary tumors, n (%) | | | |
| Papillary | 16 (36.4) | 28 (63.6) | .09 |
| Pure cis | 6 (66.7) | 3 (33.3) | |
| T-stage, n (%) | | | |
| Ta | 8 (38.1) | 13 (61.9) | .69 |
| T1 | 8 (34.8) | 15 (65.2) | |
| Tis | 6 (66.7) | 3 (33.3) | |
| Tumor grade, n (%) | | | |
| Low Grade | 0 (0) | 6 (100) | .028 |
| High Grade | 22 (46.8) | 25 (53.2) | |
| Associated, Cis n (%) | | | |
| Yes | 12 (50) | 12 (50) | .25 |
| No | 10 (34.5) | 19 (65.5) | |
| Tumor size, n (%) | | | |
| <3cm | 17 (39.5) | 26 (60.5) | .54 |
| ≥3cm | 5 (50) | 5 (50) | |
| Multifocality, n (%) | | | |
| Yes | 16 (43.2) | 21 (56.8) | .69 |
| No | 6 (37.5) | 10 (62.5) | |
| EORTC recurrence risk group n (%) | | | |
| Intermediate | 0 (0) | 3 (100) | .31 |
| High | 14 (45.2) | 17 (54.8) | |
| Very high | 8 (42.1) | 11 (57.9) | |
| Time interval Diagnosis-CHT, n (%) | | | |
| <2 months | 7 (31.8) | 15 (68.2) | .22 |
| >2 months | 15 (48.4) | 16 (51.6) | |

Salvage therapy

- Pembrolizumab
- Radical Cystectomy
- Abstention/No curative treatment
- Rechallenge intravesical therapy
- CHT
- BCG
- Pembrolizumab IV

*Rechallenge intravesical therapy in case of recurrence > 1 year after HIVEC. BCG = Bacillus Calmette-guérin, CHT: intravesical chemohyperthermia with Mitomycin C.
early recurrence rate of 30% at 3 months in this subpopulation.

Risk of progression is also an important endpoint in this bladder preservation approach. The progression rate is also very different between the two sub-groups in our study. Indeed, 3 patients (10.3%) had a disease progression to muscle infiltration in the BCG-failure group, all of very high-risk according to the EORTC, while no progression was observed in the BCG-naive group after a median follow-up of 20 months. It should be noted that among the 3 patients who progressed to muscle infiltration, 2 patients presented upfront distant metastases and one patient was operated on with N⁺ status on final pathological specimen, underlying the poor prognosis of these progressive patients. Therefore, patients with very high-risk tumors who fail BCG should be well informed of the risk of undertreatment and putative progression to muscle-invasive disease despite treatment with HIVEC, with the possibility of rapid lymph node involvement and/or metastatic spread due to the aggressive profile of this type of tumors.

Other drugs are being studied for BCG-unresponsive population. Recently, pembrolizumab (monotherapy intravenous) has been evaluated in this indication [14]. De Wit et al. reported the results of the CIS cohort and showed a complete response rate at 3 months of 38.8%, with a recurrence within one year for almost half of the responder patients (54% of responders remain free from recurrence at 1 year, i.e., 21% of the whole population). In a recent meta-analysis on bladder sparing therapies, Kamat et al. reported a pooled 12-mo response rate of 36% for trials with one or more prior BCG courses, with a lower response in case of inclusion of ≥50% of patients with CIS [15]. However, there is a great heterogeneity and variability regarding the treatment strategies. Emerging treatments currently in development, such as IFN-based gene therapy [16] or reverse thermal gel [17], show promising efficacy.

Our study has several limitations. First, this is single-arm study, with two different populations (BCG-naive and BCG-failure) with different prognosis and profile. No comparative design is acceptable for patients who fail BCG (since randomization versus cystectomy is not ethically conceivable) but this could be considered a weakness for the BCG-naive patients’ sub-population. Second, even if the data were collected prospectively, the outcomes were assessed retrospectively with some patients for whom follow-up was carried out in another center. Then, there are two distinct sub-populations with different prognosis and therefore with therapeutic objectives, ultimately justifying being studied separately in larger cohorts. Finally, there is no maintenance after the induction courses; although monthly maintenance MMC decreases the recurrence rate with an indication of 1 year of maintenance for intermediate-risk NMIBC [18], the role of MMC maintenance in a chemohyperthermia protocol has not been investigated.

Despite these limitations, our cohort is one of the largest retrospective series of patients treated with HIVEC, and the preliminary results are encouraging. Prospective and comparative studies with homogeneous populations are awaited. These studies will have to answer two different questions: the efficacy of HIVEC in patients with high-risk NMIBC (compared to BCG therapy) and the place of HIVEC among bladder preservation strategies in the population of BCG-refractory or BCG-Unresponsive tumors.

In conclusion, chemohyperthermia using HIVEC achieved a RFS rate of 60% at 1 year and enabled a bladder preservation rate of 92%. Given the low-risk of progression in the BCG-naive group of patients, chemohyperthermia could be a good alternative to early cystectomy, in particular for patients contraindicated to BCG. Conversely, for patients with very high-risk tumors that fail BCG, cystectomy should remain the standard of care and HIVEC may be discussed cautiously for patients not eligible for surgery and well informed of the risk of progression to muscle-invasive disease. The results of prospective trials are needed to confirm this.

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