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ORIGINAL ARTICLE

The role of device-assisted therapies in the management of non-muscle invasive bladder cancer: A systematic review

Efficacité des dispositifs médicaux pour le traitement endovésicale des tumeurs de vessie non infiltrant le muscle: revue de la littérature

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KEYWORDS
NMIBC;
Urothelial carcinoma;

Summary
Objective. — Despite optimal treatment, patients affected by non-muscle invasive bladder cancer (NMIBC) suffer from high risk of recurrence and progression. Intravescical

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TURBT;
EMDA;
RITE;
Synergo

device assisted therapies such as radiofrequency induced thermochemotherapeutic effect (RITE) and electromotive drug administration (EMDA) have shown promising effect in enhancing the effect of intravescical chemotherapies. The aim of the study was to assess clinical outcomes of these two devices in non-muscle invasive bladder cancer.

Methods. — A systematic literature review was performed in December 2019 using the Medline, Embase, and Web of Science databases. Only articles published in the last 10 years were considered (2009—2019). The articles were selected using the following keywords association: ''bladder cancer'' AND ''EMDA' AND ''synergo'' AND ''hyperchemotherapy'' AND ''electromotive drug administration'', AND ''radiofrequency induced thermochemotherapeutic'' AND ''RITE''.

Results. — We found 16 studies published in the last ten years regarding the efficacy of RITE (12 studies) and EMDA (4 studies) in the treatment of NMIBC. Both RITE and EMDA showed promising results in the treatment of intermediate and high risk NMIBC as well as in patients affected by recurrent BCa after BCG failure. In high-risk BCG naïve NMIBC patients treated with EMDA recurrence and progression rates were 68% and 95%, respectively. Considering RITE, recurrence and progression range rates were 43%—88% and 62%—97%, respectively. Discordance results were reported regarding its effect on patients with carcinoma in situ. However, only few studies could be compared since differences exist regarding inclusion criteria with high patients' heterogeneity. Considering recurrence after BCG, recurrence and progression range rates were 29%—29.2% and 62%—83% for RITE and 25% and 75% for EMDA, respectively.

Conclusion. — Delivery of intravescical hyperthermia seems to enhance the normal effect of intravescical chemotherapy instillation. Although prospective trials supported its effect on both BCG naïve and BCG failure patients, data are urgently required to validate these findings and to understand its effect on patients with carcinoma in situ.

Level of proof.— 3.

MOTS CLÉS
NMIBC, Carcinome de la vessie, TURBT, EMDA, RITE, Synergo

Résumé Objectif Malgré un traitement optimal, les patients présentant une tumeur de vessie non infiltrant le muscle (TVNIM) sont à haut risque de récidive et de progression. Les dispositifs médicaux pour le traitement endovésicale des TVNIM comme la thermochimiothérapie ont montré des résultats prometteurs potentialisant l'efficacité des instillations endovésicales. L'objectif de cette étude était d'évaluer les résultats cliniques des deux dispositifs médicaux les plus etudiés dans le traitement des TVNIM.

Matériel et méthode. — Une revue systématique de la littérature a été réalisée en décembre 2019 en utilisant les bases de données Medline, Embase, et Web of Science. Seuls les articles publiés entre 2009 et 2019 étaient retenus. Les articles étaient retrouvés en utilisant les mots clés «bladder cancer» ET «EMDA» ET «synergo» ET «hyperchemotherapy» ET «electromotive drug administration», ET «radiofrequency induced thermochemotherapeutic» ET «RITE».

Résultats. — Nous avons retenu 16 études qui évaluaient l'efficacité du *radiofrequency induced thermochemotherapeutic effect* (RITE) (12 études) et de *electromotive drug administration* (EMDA) (4 études) dans le traitement des TVNIM. Les deux techniques ont montré des résultats prometteurs pour le traitement des TVNIM de haut risque et de risque intermédiaire, ainsi que chez les patients présentant une récidive après BCG. Chez les patients présentant une tumeur à haut risque sans BCG préalable, les taux de récidive et de progression étaient de 68% et 95%. Concernant le RITE, les taux de récidive et de progression étaient respectivement de 43% à 88% et de 62% à 97%. Néanmoins, peu d'études ont pu être comparées car les critères d'inclusions étaient très hétérogènes selon les études. Les taux de récurrence ou de progression après BCG étaient respectivement de 29% et 62—83% avec RITE et 25% avec EMDA.

Conclusion. — La thermothérapie semble pouvoir améliorer l'effet des chimiothérapies endovésicales. Néanmoins, bien que ces effets soient démontrés chez des patient BCG naïfs ou après échec du BCG, des études avec un niveau de preuve suffisant sont nécessaires pour valider ces données ainsi que son efficacité en cas de CIS.

Niveau de preuve.— 3.

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Introduction

In 2018, 81,190 estimated new bladder cancer (BCa) cases and 17,240 related deaths were recorded in the United States only [1]. Overall, 75% of new diagnosed BCa are non-muscle invasive affected by an average recurrence and progression rates of 60—80% and 10—30%, respectively [2]. The gold standard treatment for non-muscle invasive BCa is represented by a complete transurethral resection of bladder tumour (TURBT) with adjuvant intravescical instillations on the bases of the pathology results [3]. In this regard, intravescical chemotherapeutical agents after TURBT have shown to be effective on reducing the risk of recurrence and progression during the follow-up. However, despite an adequate treatment, a consistent percentage of patients incur in recurrence or progression of the disease [2]. Risk groups have been developed to accurately predict recurrence and progression risk and to determine the best therapeutic management [4—7] and new technologies to improve the efficacy of chemotherapy are under investigation.

Among these, increasing the delivery and the effect of chemotherapy by using device to deliver hyperthermia to the bladder wall or circulating chemotherapy and ionisation of chemotherapy to improve drug tissue penetration [8] have been tested in the last years. The most used devices are the electromotive drug administration (EMDA) and the radiofrequency induced thermochemotherapeutic effect (RITE). In this systematic review, we describe the current evidence and highlighting the potential clinical application of these two devices.

Methods

A systematic literature review was performed in December 2019 using the Medline, Embase, and Web of Science databases. Review articles, editorials and congress abstracts were excluded. Search terms included ''bladder cancer'' in combination with the terms ''bladder cancer'' OR ''EMDA'' OR ''synergo'' OR ''hyperchemotherapy'' OR ''electromotive drug administration'' AND ''radiofrequency induced thermochemotherapeutic'' AND ''RITE''. Only articles published in the last 10 years were considered (2009—2019). The search was limited to the English literature. References cited in selected articles and in review articles retrieved in our search were also used to identify manuscripts that were not included in the initial search. The articles that provided the highest level of evidence were then evaluated. When existing, prospective studies were preferred to retrospective designs. A list of articles judged to be highly relevant by the first and senior authors was circulated among the co-authors and a final consensus was reached on the structure of the review and the articles included. The systematic review was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9] (Fig. 1).

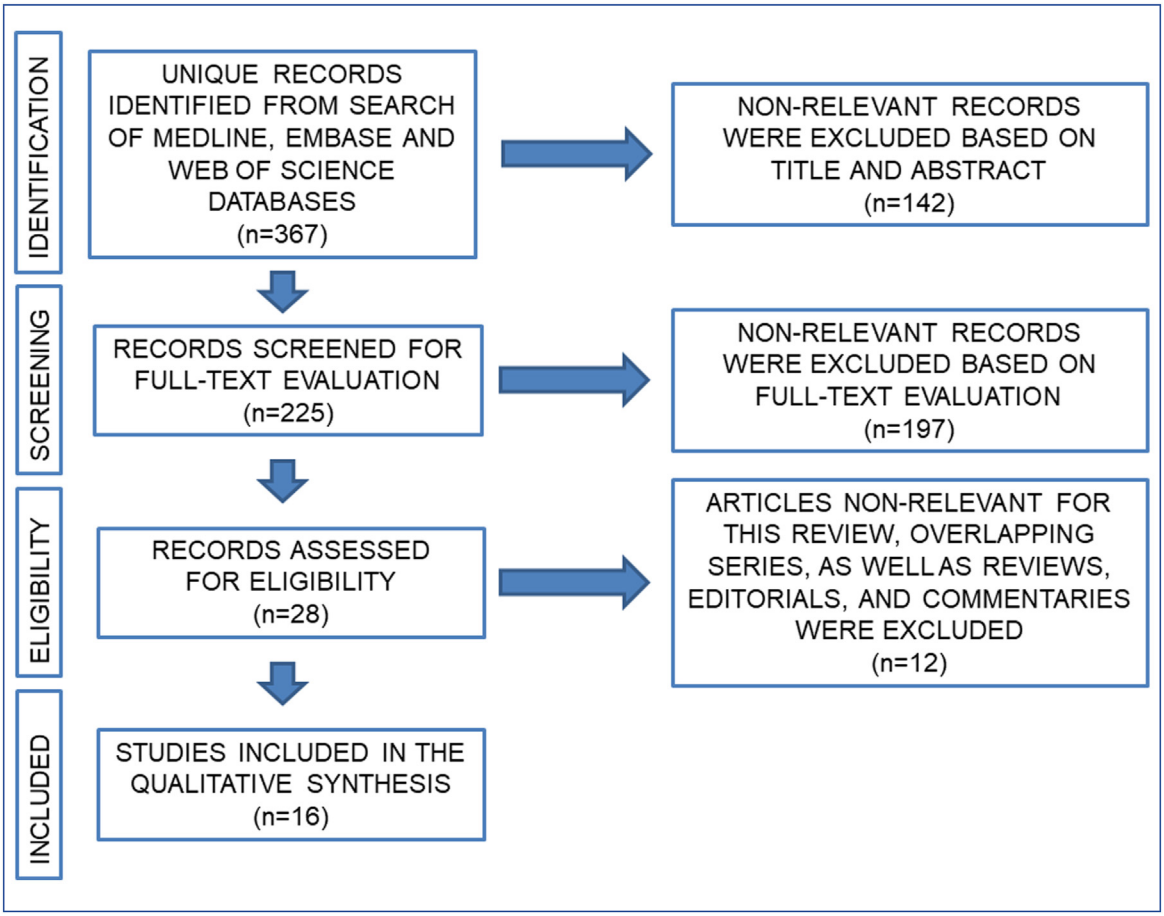

Figure 1. Flow diagram of the search results.

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The rationale of hyperthermia in the treatment of bladder cancer

Hyperthermia has been proposed as a treatment for several type of cancers including bladder, stomach and liver [10]. The idea beyond this treatment is that hyperthermia can potentiate and enhance the effect of chemotherapy, immunotherapy or radiotherapy [11]. In vitro studies demonstrated the effect of hyperthermia consists in the degradation of cytoplasmic structures, inducing cell death by apoptosis [12]. On the other hand, the high temperature enhances cell membrane permeability, resulting in increased drug absorption [13]. Hyperthermia cause also the release of heat shock proteins, which stimulates an immune response, potentially increasing the effect of immunotherapy [14]. In vitro studies demonstrated synergism of hyperthermia plus chemotherapy than the combine additive effect [15]. Considering these elements, hyperthermia has been proposed for the treatment of non-muscle invasive BCa in different settings:

- to potentiate the effect of intravesical chemotherapy in BCG naïve patients or;
- as a therapy in BCG refractory patients (high-grade relapse after a BCG treatment) in patients that otherwise should be treated with radical cystectomy.

We identified using medline, embase and web of science databases, a total of 367 studies potential related to this topic. A total of 142 records were excluded as non-relevant for this systematic review and a total of 225 full texts were evaluated. However, after the full text evaluation, only 16 studies were evaluated eligible for our outcomes evaluation.

In this regard, several questions have been raised to understand the real efficacy of these therapies, such as its potential effect in papillary disease compared to the efficacy in patients affected by carcinoma in situ where a treatment with BCG, even repeated in case of recurrence after BCG treatment still seems the treatment of choice. Different type of delivery of hyperthermia in the context of non-muscle invasive BCa has been proposed. An intravesical radiofrequency induced hyperthermia or conductive heat via energy transfer from heated circulating fluid are two of the most studied mechanisms proposed [16].

Radiofrequency induced thermochemotherapeutic effect (RITE)

The RITE technology has been developed to induce hyperthermia using microwave radiation, which does not require conductive delivery of energy. This modality of energy delivery has been used for the treatment of different cancers, including breast [17] and lung [18]. This type of technology allows the delivery of heat energy directly to the tissue to enable on bladder wall thickness using a 915 MHz intravescical microwave applicator heating. This application is made through a transurethral catheter containing a lumen for fluid introduction and a lumen for fluid outflow. Thermocouples are positioned tangentially from the catheter tip to measure the temperature of the bladder neck, the dorsal and the lateral bladder walls. In vitro studies showed that the application of RITE with mitomycin for 60 minutes increase the concentration in bladder cancer tissue 10 fold higher than passive intravescical mitomycin administration [19]. The RITE system for the treatment of bladder cancer has been developed by the Synergo and was first reported in 1995 [20]. An overview of the studies analysing outcomes of RITE published in the last 10 years is reported in Table 1.

Arends et al. [21] randomised 190 NMIBC patients to 1 year chemo hyperthermia versus 1 year of therapy with BCG. They found a significant reduced risk of recurrence in patients treated with chemo hyperthermia at 2 months in the per protocol analyses. They conclude that chemo hyperthermia represents a safe and secure option in patients affected by intermediate and high grade NMIBC. Colombo et al. [22] randomised 83 intermediate and high-risk NMIBC patients following complete TURBT to receive RITE or intravescical chemotherapy alone. After a median follow up of 91 months, the 10-year disease free survival rate for thermochemotherapy and chemotherapy alone were 53% and 15%, respectively ($P < 0.001$). Bladder preservation rates were similar for the two procedures. Similar results were found in retrospective cohorts [23–27]. RITE was tested in patients with different characteristics. Mostly of the reports focused on patients affected by intermediate-high risk NMIBC not previously treated with BCG. However, some authors evaluated the effects of RITE in patients who experience high-grade recurrence after BCG treatment. Tan et al. [28] in an open label, phase III randomised controlled trial across 14 centres between 2010 and 2013 enrolled 104 patients to RITE or control following stratification for carcinoma in situ status, therapy history and treatment centre. After a median follow up of 31 months, they found no differences in disease free survival (DFS) or 3-month clinical recurrence rates between the two treatment arms. DFS rates were significantly lower in RITE than in control in patients with CIS with or without concomitant papillary tumours. Similar results were described in retrospective series investigating recurrent NMIBC [29–31]. On the other hand, Kiss et al. [32] reported data of 21 patients treated between 2003 and 2009 with RITE in patients with recurrent NMIBC. They found that only 29% of the patients remained free of disease at a median follow up of 50 months, while adverse effects were recorded in half of the patients. The use of this technology in BCG refractory patients is of extreme interest in the urological community especially considering the paucity of data regarding therapeutical option in this setting [33,34] and the BCG shortage recorded in several countries.

Electromotive drug administration (EMDA)

With the EMDA technology, an electrical charge is generated between a cutaneous electrode and a catheter electrode to increase the transport of drug molecules into tissue [35]. This effect is mediated by electro osmosis, electroporation and iontophoresis. Previous research demonstrated that this technology increases the delivery of mitomycin six fold greater concentration of mitomycin compared to the bladder wall than passive diffusion and reaching a peak concentration of mitomycin within 15 minutes [36]. This concentration was different in all the layers of the bladder, but mitomycin was found in concentration of 30-fold

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Table 1 Studies reporting results of radiofrequency induced thermochemotherapeutic effect (RITE) between 2009 and 2019 on patients affected by non-muscle invasive bladder cancer.

Study	Publication Year	Study design	Patients, number	Year	Population	Median follow-up, months	Type of treatment, induction	Type of treatment, maintenance	Recurrence free rates (%)	Progression free rates (%)
(Tan et al.) [28]	2019	Prospective, randomised trial	104, (RITE: 48, 56 control)	2010–2013	Intermediate or high risk with recurrence following BCG (48 RITE vs. 56 control)	36	six once-weekly with 20 plus 20 mg MMC in 50 mL water for 60 min	20 plus 20 mg MMC in 50 mL water once every 6 weeks (year 1) and then once every 8 weeks (year 2)	Overall 2-year DFS: RITE: 29.2 Similar compared to control	83 Similar compared to control
(Arends et al.) [21]	2016	Prospective, Randomised control	190, (RITE:92 vs. BCG 98)	2002–2011	Intermediate or high-risk BCG naïve	24	six once weekly 20 plus 20 mg MMC in 50 mL water for 60 min	20 plus 20 mg MMC in 50 mL once weekly at 6-week intervals	81.8 RITE BCG	100 No differences with BCG group
(Kiss et al.) [32]	2015	Prospective, no comparative group	21	2003–2009	Intermediate high-risk recurrent NMIBC	50	Ablative: twelve once-weekly 40 plus 40 mg MMC in 50 mL saline over 60 min Adjuvant: six once-weekly 20 plus 20 mg MMC in 50 mL saline over 60 min	NA	Overall RFS: 29	Overall: 62
(Sooriakumaran et al.) [23]	2016	Retrospective, no comparative group	97	2009–2013	High-risk NMIBC	27	Six-to-eight once-weekly 40 mg MMC in 50 mL saline for 60 min	20 mg MMC in 50 mL saline six once- weekly (year 1) and then once eight-weekly (year 2)	NA	61.9
(Erturhan et al.) [24]	2015	Retrospective, no comparative	26	NA	High-risk NMIBC	16	Six once weekly 20 plus 20 mg in 50 mL saline for 60 min	Six once monthly 20 plus 20 mg in 50 mL saline	RFS: 88.4	NA
(Maffezzini et al.) [25]	2014	Retrospective, no comparative group	42	2006–2010	High-risk NMIBC	38	Four once weekly then six two weekly 40 plus 40 mg of MMC in 50 mL water for 60 min	Four once monthly 40 plus 40 mg MMC in 50 mL water	RFS: 57.1	88
(Volpe et al.) [29]	2012	Retrospective, no comparative	30	2006–2009	High-risk NMIBC	14	Ablative: eight once-weekly 40 plus 40 mg MMC in 50 mL water over 60 min	Ablative: six once-monthly 40 plus 40 mg MMC in 50 mL water	Ablative CR: 42.9	Ablative: 82.4

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Table 1 (*Continued*)

Study	Publication Year	Study design	Patients, number	Year	Population	Median follow-up, months	Type of treatment, induction	Type of treatment, maintenance	Recurrence free rates (%)	Progression free rates (%)
							Adjuvant: six once-weekly 20 plus 20 mg MMC in 50 mL water over 60 min	Adjuvant: six once-monthly 20 plus 20 mg MMC in 50 mL water	Adjuvant RFS: 43.8	Adjuvant: 0
(Moskovitz et al.) [26]	2012	Retrospective, no control group	92	2001–2011	Intermediate or high-risk NMIBC	23	Ablative: eight once-weekly 40 plus 40 mg MMC in 50 mL water over 60 min	Adjuvant: six once every 6 weeks 20 plus 20 mg MMC in 50 mL water	Ablative CR: 79	Ablative: NA
							Adjuvant: six once-weekly 20 plus 20 mg MMC in 50 mL water over 60 min		Adjuvant RFS: 72	Adjuvant: 95.3
(Colombo et al.) [22]	2011	Prospective, no control group	83	1994–1999	Intermediate or high-risk NMIBC	91	Eight once- weekly 20 plus 20 mg MMC 50 mL water over 60 min	Four once- monthly 20 plus 20 mg MMC in 50 mL water for 60 min	RFS: 60	RITE: 95.1
(Halachmi et al.) [27]	2011	Retrospective, no control group	56	2000–2007	High-risk NMIBC	18	Six once-weekly 20 plus 20 mg MMC over 60 min	Four-to-six once-weekly 20 plus 20 mg MMC for six treatments	RFS: 64.7	92.9
(Nativ et al.) [30]	2009	Retrospective, no comparative group	111	2001–2008	High-risk NMIBC	16	Six once-weekly 20 plus 20 mg MMC in 50 mL over 60 min	Four-to-six once-weekly 20 plus 20 mg MMC for six treatments	12 months RFS: 85	97
									24 months RFS 56	
(Alfred Witjes et al.) [31]	2009	Retrospective, no comparative group	51	1997–2005	High-risk NMIBC	22	Ablative (papillary lesion and/or widespread CIS): eight once-weekly 40 plus 40 mg MMC in 50 mL water over 60 min	Ablative: six once-monthly 40 plus 40 mg MMC in 50 mL water	All-patient RFS: 55	90
							Adjuvant: six once-weekly 20 plus 20 mg MMC in 50 mL water over 60 min	Adjuvant: six once-monthly 20 plus 20 mg MMC in 50 mL water	All-patient CR at 4 months: 92	

NMIBC: Non-muscle invasive bladder cancer; MMC: Mitomycin; BCG: Bacillus Calmette Guerin; TURBT: Transurethral resection of the bladder tumour.

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Table 2 Studies reporting results of electromotive drug administration (EMDA) between 2009 and 2019 on patients affected by non-muscle invasive bladder cancer.

Study	Publication Year	Study design	Patients, number	Population	Median follow-up, months	Type of treatment, Induction	Type of treatment, maintenance	Recurrence free rates, %	Progression free rates, %
(Racioppi et al.) [39]	2018	Prospective, single centre, single arm Phase II study	26	BCG refractory NMIBC	36 months	40 mg of MMC diluted in 100 mL of sterile water retained in the bladder for 30 min with 20 mA pulsed electric current	6 monthly instillations	TaG3, T1G3, Cis, TaT1G3 + Cis 75, 71.4, 50 and 25, respectively	61% (cystectomy free patients at 3 years)
(Di Stasi et al.) [37]	2011	Multicentre, randomised, parallel group study	374 (124 neoadjuvant EMDA MMC vs. 124 TURBT alone vs. 126 passive diffusion mytomicin)	Low-risk (6%), intermediate risk (66%) or high-risk (28%) (no previous intravescical treatment)	86	TURBT versus TURBT plus immediate postoperative 40 mg MMC versus neoadjuvant EMDA plus TURBT 40 mg MMC in 100 mL water (20 mA for 30 min)	Intermediate risk: six once weekly 40 mg MMC in 50 mL water High risk: six once weekly 81 mg BCG (ImmuCyst) in 50 mL saline for 120 min	Neoadjuvant EMDA MMC plus TURBT: 62	Neoadjuvant EMDA MMC plus TURBT: 94
(Carando et al.) [38]	2019	Retrospective, no comparative group	65	Low, intermediate and high risk NMIBC naïve or refractory to other treatments	Follow up: 62 subjects at 3 months and 45 at 6 months	30-min treatment with EMDA/MMC (Physion Mini 30N2, 20—23 mA, 40% [w/v] MMC in distilled water).	88% received maintenance therapy	84	Not reported
(Gan et al.) [40]	2016	Retrospective, no comparative group	107	High risk NMIBC	24	BCG weekly for week 1 and 2 plus EMDA MMC for week 3. Repeated 3 times.	Three once weekly BCG 3 months after induction and every 6 months for 3 years	68	95.3

NMIBC: non-muscle invasive bladder cancer, MMC: mitomycin, BCG: bacillus Calmette Guerin; TURBT: transurethral resection of the bladder tumour.

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greater than passive diffusion in the urothelium. Technically, a catheter is placed, and 40 mg of mitomycin in 100 mL are instilled with a current of 20 mA. The duration treatment is usually of 15 minutes per treatment. An overview of the studies published in the last 10 years reporting results of EMDA is presented in Table 2.

Di Stasi et al. [37], in the only randomised trial assessing the effect of EMDA in the last 10 years, included 372 patients treated between 1994 and 2003. Patients were randomised to receive TURBT alone, immediate post TURBT instillation of mitomycin or immediate pre TURBT instillation of mitomycin with the EMDA technology. After a median follow- up of 86 months, patients who received EMDA before TURBT had a lower recurrence rate than those assigned to TURBT and mitomycin. Carando et al. [38] reported the data of 65 patients affected by NMIBC with a complete TURBT of all visible tumour followed by EMDA. They found that complete TURBT and EMDA was effective at 6 months in intermediate (83%) and high risk (83%) patients. Racioppi et al. [39], in a prospective, single centre, single arm phase II study, evaluate the efficacy and the safety of EMDA treatment in BCG refractory NMIBC on a 3-year follow-up. At the end of follow-up, 61% patients reserved their native bladder. At the end of follow-up, DFS rates were 75, 71.4, 50 and 25% in TaG3, T1G3, CIS, and TaT1G3 + CIS patients, respectively. Gan et al. [40] reported results of sequential BCG EMDA of mitomycin C as the treatment of high risk NMIBC. Authors treated 107 patients with an induction dose of BCG at week 1 and 2, followed by mitomycin administered with EMDA in week 3 and repeated thrice for a total of 9 weeks. A maintenance scheme was offered with 3 doses of BCG given 3 months after induction and every 6 months for 3 years. 87% of patients were free of disease at the first control cystoscopy. The effect of EMDA has been tested in different population and no articles share the same inclusion criteria. In fact, one study included high risk NMIBC, one patient without previous intravesical treatment regardless of risk class, one naïve and BCG refractory patients regardless of risk class and one BCG refractory patients. In this regard, no definitive comparison can be made.

Future perspective and limitations of the current studies

Several new technologies are under investigation for the optimal treatment of BCG refractory patients. In this regard, promising data are coming regarding the use of pembrolizumab in neoadjuvant setting with its recent approval by the FDA. However, still this approach is not available in Europe and should be considered in the context of clinical trials.

Several open questions remain regarding the optimal use of RITE and EMDA technology. First, as highlighted during this systematic review, the technology behind these two approaches is different and differences in oncological and safety outcomes might exist. In fact, RITE technology uses radiofrequency-induced hyperthermia that might show differences in tissue perfusion. Second, inclusion criteria varied consistently between studies, with a mixture of intermediate and high-risk BCG naïve and BCG refractory patients. In this regard, only limited comparison can be made. Contrasting results exist regarding the role of RITE in the treatment of patients affected by CIS [23,28,31]. In fact, although some series suggest a possible lack of efficacy of RITE in patients affected by CIS, other data reported excellent tumour responses. In this regard, data are required to validate the utility of RITE and hyper chemotherapy in general in this patient's settings. Until this time, BCG therapy should be considered the standard of care in this particular clinical scenario. Fourth, no data exists regarding the role of thermochemotherapy in the treatment of NMIBC patients affected by histological variants. Immunotherapy does not represent an option for many of these variants [41] and early cystectomy has been considered the standard of care if an histological variants has been diagnosed at the time of TURBT [42,43]. Fifth, data are required regarding toxicity and side effects of these treatments in real world setting. In fact, sparse data exists regarding this aspect and toxicity and the possibility to finish the treatment is an important aspect to consider in the administration of this therapy.

Finally, it is important to remark that radical cystectomy with concomitant bilateral pelvic lymph node dissection represents the current standard of care for the treatment of BCG failure patients and other treatment strategies should be considered only in the setting of a clinical trial or in patients who refused radical cystectomy or are unfit to receive it. In this regard, performing an early cystectomy might improve the possibility of recovering functional outcomes [44].

Conclusion

Device assisted intravescical hyperthermia therapies appear as a promising tool for enhancing the effect of chemotherapy in the treatment of non-muscle invasive BCa. Level 1 evidence supported its effect on both BCG naïve and BCG failure cohorts. However, further data are urgently required to validate these findings in patients diagnosed with primary or concomitant CIS and to analyse the potential effect of hyperthermia on immunotherapy. These results are of utmost importance for offering an alternative to candidates to BCG, especially in consideration of the issue of BCG supply in some countries.

Ethical standards

All persons gave their informed consent to use their data for this retrospective study.

Disclosure of interest

The authors declare that they have no competing interest.

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