shortreport

Regione Emilia-Romagna
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
osservatorio regionale per l'innovazione

n. 2

The report

A brief presentation of a technology, providing sufficient information to decide whether to undertake a comprehensive assessment process.

The reported information derives from:

› the consultation of web materials supplied by the producer and of current national and/or regional registries

› the search of secondary studies on HTA databases and of primary studies, indexed on Medline.

! The report does not represent a definitive assessment of the technology.

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Technology

Medical device for intravesical microwave hyperthermia in the treatment of superficial bladder cancer

Commercial technology name

Synergo®

Producer / supplier

Medical Enterprise Europe B.V., The Netherlands

Use

■ therapeutic
☐ diagnostic
☐ other .....

Category

Medical device

Therapeutic or diagnostic field of application

Oncological (urological)

Patients / clinical condition

Patients with Superficial Transitional Cell Carcinoma of the Bladder (STCCB) at stage Ta and T1, Carcinoma In Situ (CIS), recurrent after surgery, chemotherapy or immunotherapy treatments.

Technology description

Synergo® is a system that allows to combine the administration of intravesical chemotherapy with an hyperthermic treatment to the bladder wall. The system has a catheter, inserted into the bladder through the urethra, with multiple functions:

- heating the wall through an antenna emitting microwaves
- instilling intravesical chemotherapic drugs
- monitoring the temperature reached

Intake of the cytostatic drug by tumor cells and its distribution would be improved because of the increased cell permeability induced by heat (*1*).

The therapy is performed as an outpatient treatment with weekly sessions lasting 40-60 minutes, repeated 4-8 times and followed by 4-6 maintenance sessions every 4-8 weeks.

Target patients

Synergo® is proposed as a second-line treatment following the failure of previous instillations of chemotherapy or immunotherapy.

From the databases of specialist outpatient service and Hospital Discharge Records relative to the year 2008, it has been estimated that the number of patients eligible for such treatment would be about 250 per year.

Standard treatment / method

Patients with recurrent Superficial Transitional Cell Carcinoma of the Bladder undergo endoscopic resection followed by postoperative intravesical instillation of chemotherapic drugs or immunotherapic treatment with the Bacillus Calmette-Guerin vaccine (BCG). In cases of recurrence or progression, subsequent instillations of chemotherapy and immunotherapy are given. Cystectomy may be required in some patients. (*2*).

Main expected benefits

A reduction of the risk of tumour progression or subsequent recurrence.

Available evidence and results

N° and type of studies

- One overview published by NICE (*3*) where 2 RCTs, 2 non-randomised comparative studies and 2 case series are included.
- 12 primary studies published from 1991 to 2009, identified through PubMed:
  - ¬ 3 RCT:
    - * 52 patients, follow up: 36-38 months (*4*);
    - * 83 patients, follow up: for a minimum of 2 years (*5*);
    - * 51 patients, follow up: few hours after instillation (*6*);
  - ¬ 1 non-randomised controlled study (80 patients, follow up: 7-10 days after the last treatment) (*7*)
  - ¬ 9 case series (12-111 patients; follow up: 3 - 35.3 months) (*8* - *16*)

Outcomes

- EFFICACY

  According to the NICE overview (*3*):
  - ¬ Neo-adjuvant treatment before re-intervention in patients with recurrence already treated with chemotherapy or immunotherapy: one RCT evaluating efficacy outcomes and a controlled study showing a greater efficacy of the hyperthermic treatment when compared to chemotherapy alone, in terms of complete response to treatment and/or recurrence rate (complete response: 66% vs. 22% [RCT], 66% vs. 28% [controlled study] and recurrence 28% vs. 39% at 36-38 months [RCT]).
  - ¬ Postoperative adjuvant therapy in patients at medium and high risk: the only RCT identified indicates a higher recurrence rate in the group of patients treated with chemotherapy alone (56% vs. 14% at 2 years).

- SAFETY

  Most studies evaluating safety outcomes reported that all or nearly all patients experienced symptoms of cystitis, that usually resolved within a few days. Other reported findings (range) were: urethral stenosis (4-7%), reduced urinary capacity (2-11%), bladder contracture, minor tissue reactions of the bladder wall to hyperthermia (24-64%) with spontaneous recovery after 2-3 days, skin rashes (2-7%), pain during the session, extravasation and chemical peritonitis.

  In the controlled trials, some adverse effects, usually transient such as pain and reaction of the wall to hyperthermia, were more frequent in the group treated with hyperthermia and chemotherapy than in the group treated with chemotherapy alone.

Notes

In most of the primary studies identified, some of the co-authors are the same. Authors from the centre that developed the device contributed to almost all studies.

Only two studies reported elements related to possible conflict of interest (confirmed in one case, denied in another one).

Costs

Cost/year per patient: € 11 000 (including costs for depreciation, materials, drugs and personnel).

Presumed impact

Clinical issues

Should the results of earlier studies on recurrence reduction be confirmed, improved survival and quality of life of patients could be expected, together with a reduction of the number of resections and cystectomies.

Economic issues

The technology is expensive, compared to standard treatment. Any savings associated with a reduction in the number of repeated resections and cystectomy can be assessed only if the clinical efficacy can be demonstrated.

Organisational issues

The technology is in use in outpatient settings where existing treatments of endoscopic resection of bladder tumour are carried out, so it does not lead to significant changes in the diagnostic and therapeutic pathway already planned for the patient. However, the procedure carried out with Synergo takes considerably longer and the device requires additional space.

Ethical-social issues

Not evaluated.

Ongoing studies

1 registered multicentre RCT, sponsored by the producer, started in 2002 (*17*).

STUDY	PATIENTS / CONDITIONS	STUDY DESIGN	PRIMARY ENDPOINTS	END OF STUDY
NCT00384891	Superficial bladder cancer (N = 300)	Synergo + Mitomycine versus BCG	» recurrence-free survival at 2 years » time to complete remission of the CSI » rate of progression (to stage of disease > T1 and/or metastatic disease)	2013

Authorisations

FDA authorisation: not found.

CE mark: 2001 - Medical Devices Repertoire number (Italian Dept. of Health): 69997.

Diffusion / diffusion prediction

The technology was developed in the late Eighties at the San Raffaele Hospital in Milan (Italy) and is now diffused in some countries (Austria, Belgium, The Netherlands, UK, Germany, Korea, Switzerland, Turkey, Italy, Israel), limited to some centres. In Italy it is/has been used at: San Raffaele Hospital in Milan, Polyclinic of Palermo, IEO in Milan, Galliera Hospital in Genoa, Hospital of Treviglio, Hospital of Magenta, Humanitas Gavazzeni in Bergamo, Sant'Anna Hospital in Como, Gemelli Polyclinic in Rome.

It is not present in any public or private hospital of the Emilia-Romagna Region.

Brief summary

The technology has been proposed for nearly 20 years. Nevertheless, the quality and quantity of evidence produced by the low number of studies conducted so far do not allow to draw concluding remarks on the clinical efficacy and safety of the technology. Its indication of use is for second-line treatment following the failure of previous therapies and additional studies, independent and of good methodological quality, are desirable to provide conclusive data on clinical efficacy.
The high cost of the technology makes these studies impractical at present.

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References

1. Basi scientifiche per la definizione di linee-guida in ambito clinico per i Tumori della Vescica. CNR. 2005. http://progettooncologia.cnr.it
2. M. Babjuk, W. Oosterlinck, R. Sylvester, et al. Guidelines on TaT1 (Non-muscle invasive) Bladder Cancer European Association of Urology. 2009.
3. NICE. Interventional procedure overview of intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer. IP 395, 2007. http://www.nice.org.uk/
4. Colombo R, Da Pozzo LF, Lev A, et al. Neoadjuvant combined microwave induced local hyperthermia and topical chemotherapy versus chemotherapy alone for superficial bladder cancer. J.Urol. 1996; 155:1227-32.
5. Colombo R, Da Pozzo LF, Salonia A, et al. Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. J.Clin.Oncol. 2003; 21:4270-6.
6. Paroni R, Salonia A, Lev A, et al. Effect of local hyperthermia of the bladder on mitomycin C pharmacokinetics during intravesical chemotherapy for the treatment of superficial transitional cell carcinoma. Br.J.Clin.Pharmacol. 2001; 52:273-8.
7. Colombo R, Brausi M, Da Pozzo L, et al. Thermo-chemotherapy and electromotive drug administration of mitomycin C in superficial bladder cancer eradication. a pilot study on marker lesion. Eur.Urol. 2001; 39:95-100.
8. Rigatti P, Lev A, Colombo R. Combined intravesical chemotherapy with mitomycin C and local bladder microwave-induced hyperthermia as a preoperative therapy for superficial bladder tumors. A preliminary clinical study. Eur.Urol. 1991; 20:204-10.
9. Gofrit ON, Shapiro A, Pode D, et al. Combined local bladder hyperthermia and intravesical chemotherapy for the treatment of high-grade superficial bladder cancer. Urology. 2004; 63:466-71.
10. Colombo R, Da Pozzo LF, Lev A, et al. Local microwave hyperthermia and intravesical chemotherapy as bladder sparing treatment for select multifocal and unresectable superficial bladder tumors. J.Urol. 1998; 159:783-7.
11. Colombo R, Lev A, Da Pozzo LF, et al. A new approach using local combined microwave hyperthermia and chemotherapy in superficial transitional bladder carcinoma treatment. J.Urol. 1995; 153:959-63.
12. van der Heijden AG, Kiemeney LA, Gofrit ON, et al. Preliminary European results of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma of the bladder. Eur.Urol. 2004; 46:65-71.
13. Moskovitz B, Meyer G, Kravtzov A, et al. Thermo-chemotherapy for intermediate or high-risk recurrent superficial bladder cancer patients. Ann.Oncol. 2005; 16:585-9.
14. Halachmi S, Moskovitz B, Maffezzini M, et al. Intravesical mitomycin C combined with hyperthermia for patients with T1G3 transitional cell carcinoma of the bladder. Urol Oncol. 2009 Apr 21.
15. World J Urol. 2009 Jun; 27(3):319-24.
16. Nativ O, Hendricksen K et al Combined Thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette-Guerin J. Urol 2009; 182:1313-1317.
17. http://www.clinicaltrials.gov

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