Non-Muscle-Invasive Bladder Cancer unresponsive to BCG:

alpha therapy as compared to chemotherapy and immunotherapy including gene therapy.

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When non–muscle-invasive bladder cancer (NMIBC) fails bacillus Calmette-Guérin (BCG) therapy, the recommended treatment is radical cystectomy. This invasive procedure is rejected by many patients due to its significant impact on quality of life. As a result, the mean proportion of patients treated with radical cystectomy has been estimated to be 24.7% (1). This situation justifies the large number of therapeutic agents developed in recent years with the aim of effective bladder-sparing therapies in accordance with well-established recommendations (1, 2).

Since January 2020, four drugs have been approved by the FDA for the treatment of high-risk BCG-unresponsive NMIBC Carcinoma In Situ (CIS) with or without papillary tumors: pembrolizumab (Keytruda®) in Jan 2020, nadofaragene firadenovec (Adstiladrin®) in Dec 2022, nogapendekin alfa inbakicept-pmln (Anktiva®) in Apr 2024 and gemcitabine intravesical system (Inlexzo™) in Sep 2025. To date, none have been approved by EMA in that indication.

Pembrolizumab is administered intravenously every 3 weeks for up to 24 months or until recurrence, progression, or unacceptable toxicity. This has been shown necessary for an immune response durability.

The standard protocol with Adstiladrin® involves an initial dose followed by maintenance doses once every three months for up to 12 months (four total doses), or longer if there's no high-grade recurrence or unacceptable toxicity. This schedule continues indefinitely for responders to sustain cancer-free status, Adstiladrin® is a non-replicating adenoviral gene therapy that delivers a functional IFNa2b gene to bladder urothelium, enabling local interferon production to stimulate immune attack on cancer cells (3). Its effect is transient because the adenovirus does not integrate into the host genome and viral expression wanes over time, necessitating periodic re-administration to restore interferon levels and prevent relapse.

The dosing schedule of Anktiva® (nogapendekin alfa inbakicept) starts with weekly instillations for 6 weeks followed by maintenance which can extend to 37 months for responders. These prolonged instillations over several months are necessary to achieve and sustain durable complete responses. Maintenance therapy confers a 51% likelihood of sustaining complete response for at least 45 months, while discontinuation is associated with early recurrence.

Finally, gemcitabine intravesical system, recently approved, provides sustained release of gemcitabine directly into the bladder... This nucleoside analogue inhibits DNA synthesis and tumour cell proliferation, but sustained clinical benefit necessitates intravesical administration every 3 weeks for 6 months, followed by every 12 weeks through month 18.

Unlike the three previous drugs, which have an indirect effect on tumours by stimulating a long-term anti-tumour immune response, the intravesical gemcitabine system has a direct anti-tumour action, but its effectiveness also requires long-term repeated intravesical instillations.

Another technology involves directly targeting tumour cells with highly tumoricidal agents including Antibody Drug Conjugates (ADCs) and Antibody Radionuclide Conjugates (ARCs).

A first ADC has been developed to phase 3: oportuzumab monatox (Vicineum) is a locally instilled recombinant fusion protein (an antibody-toxin conjugate) targeting EpCAM and delivering a truncated Pseudomonas exotoxin A to tumour cells (4). The drug was evaluated in phase 2 on 134 patients. Patients were treated twice weekly for 6 weeks followed by once a week for 6 weeks. Then maintenance consisted in instillations once every other week up to 104 weeks. This prolonged treatment regimen was comparable to that of immunotherapy and gene therapy treatments. The results showed a 3-month complete response rate of 40% and a median duration of response of 9.4 months. Severe adverse events including grade 4 cholestatic hepatitis and grade 5 renal failure were observed presumably due to the toxin used.. Thus, despite its direct tumour-targeting mechanism, this ADC did not eradicate all tumour cells after a single or even multiple instillations.

In addition to ADCs, ARCs have significant advantages, particularly when using alpha-emitting radionuclides such as actinium 225, lead 212 or astatine 211... Owing to their markedly higher linear energy transfer (LET) compared with beta particles, alpha emitters produce intensely dense ionization tracks confined to a short range of 50–80 µm (a few cell diameters), resulting in highly localized energy deposition in targeted cells.

This results in double-strand breaks in DNA molecules that are virtually irreparable.

The clinical situation of NMIBC unresponsive to BCG corresponds well to the radio-physical characteristics of alpha particles. Tumour residues are small in size, corresponding to the path of alpha particles, and are located superficially in direct contact with a radiolabelled antibody (ARC) instilled into the bladder cavity.

A first academic clinical study was conducted in 12 patients with biopsy-proven CIS using a single intravesical instillation of an anti-epidermal growth factor receptor (EGFR) antibody labelled with bismuth-213, an alpha particle emitter with a short half-life of 45.6 minutes (5). Interestingly an excellent tolerance was observed without any sign of adverse effects. Three patients showed a complete response with, for two of them, no sign of recurrence 30 and 44 months after treatment. One patient had a partial response, and a second instillation was performed 4 months after the first instillation followed 4 months later by a complete response. This clinical study, although limited to 12 patients, showed, with a single instillation, an absence of toxicity and a complete response in four patients, including one after a second instillation. It is important to notice that, in this study, patients were not selected based on pre-treatment confirmation of tumour expression of the targeted EGFR antigen, whereas it is known to be expressed in 75% of the concerned population. It can therefore be estimated that at least one of the patients included in the study did not have EGFR tumour expression, which could explain the lack of response.

The results of this academic study, which was limited to a small number of patients, must of course be interpreted with caution, but it is interesting to note the absence of toxicity and the long-lasting responses (30 and 44 months) after a single instillation. The radionuclide chosen, which was available at the time of the study, is not suitable for practical use due to its short half-life. Other radionuclides, including actinium-225, lead-212, and astatine-211, have radio-physical characteristics that are more suitable for clinical applications.

Actinium-225 is currently the most widely used radionuclide in clinical studies because its half-life of 10 days allows it to be available at locations far from the production site. Lead-212, like astatine-211, has a short half-life of 10.6 and 7.2 hours, respectively, which is well suited for therapeutic applications, but the production of lead-212 is difficult to implement. The production of astatine-211 is simpler and requires a cyclotron with the appropriate energy for its production. The number of cyclotrons of this type is still limited but will increase in line with clinical applications.

The Institut de Cancérologie de l'Ouest (ICO, Nantes, France) has recently completed the PERTINENCE study (NCT04897763), which validated the safety of intravesical administration of a radiopharmaceutical (composed of the anti-CA-IX antibody, girentuximab, coupled to zirconium-89), both for the patient and clinical staff radioprotection(6). This trial showed by imaging that the product remained solely in the bladder, which is precisely what is sought in this type of cancer without metastatic spread. This suggests that bladder instillation of a therapeutic antibody labelled with astatine-211 would cause minimal or even non-existent toxicity throughout the body. Good efficacy was demonstrated in non-clinical studies and the Institut de Cancérologie de l'Ouest (ICO, Nantes, France) has been granted authorisation to launch the PERSEVERANCE EU Phase I clinical trial (NCT07260162), titled "A First In Human Phase I Trial Evaluating Safety, Tolerability and Response of [211At]At-Girentuximab (ATO-101™) in Patients With Non-Muscle-Invasive Bladder Cancer Refractory to Standard Treatment." This trial is in continuation of the PERTINENCE study, and a North American clinical trial is in planning phases.

This alpha-emitting radiopharmaceutical is expected to exert a profound cytotoxic effect on residual tumor cells, potentially achieving durable tumor control following a single administration. Moreover, the ability to select patients with tumors expressing CA-IX, an antigen present in approximately 70% of bladder cancers, could further enhance overall therapeutic efficacy, while maintaining a more favorable tolerability profile compared to regimens requiring repeated weekly administrations over several months.

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