Targeted approaches and innovative illumination solutions: A new era for photodynamic therapy applications in gynecologic oncology?

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Editorial

Targeted approaches and innovative illumination solutions: A new era for photodynamic therapy applications in gynecologic oncology ?

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HIGHLIGHTS

- PDT could be part of innovative management of gynecological cancer.
- Targeted photosensitizers may improve therapeutic index of intraperitoneal PDT.
- Intraperitoneal PDT requires having an expert knowledge of several parameters.

EDITORIAL

Different studies have been carried out to investigatethe potential application of photodiagnosisand photodynamic therapy (PDT) in the field of gynecological cancer treatment without finding a place in current standard clinical practice.

Photodiagnosis isbased on the principlethatabnormal tissues absorb light and fluoresce differentlyfrom normal tissues atspecificlight wavelengths. Autofluorescence takesadvantageof thisprinciple. Fluorescence canbeenhanced by the use of exogenous markers (photosensitizers)[1]. This technique, which has been evaluated in preclinical and clinical studies, has shown a good accuracy to detect peritoneal metastasis of ovarian origin, increasing the number of lesion detected by more than a third, and allowing easier detection of submillimericlesions. As a feasible application, photodiagnosis could be an efficientdecision-support technology to help the surgeon to take a decision during explorative laparoscopy before cytoreductive surgery for peritoneal carcinomatosis in ovarian cancer. Nevertheless, the therapeutic impact of fluorescence guided surgery remains uncertain as it is not possible to treat the entire peritoneal cavity surgically, even if more lesions are removed, and photodiagnosis will always be limited by optical detection device performances.

High peritoneal recurrence rate after optimal treatment of advanced ovarian cancer by the association of platinum-based chemotherapy and complete cytoreductive surgery raises the issue of peritoneal microscopic disease management and requires the development of additionallocoregional treatment strategies.

Photodynamic therapy is an efficient treatment already applied in other medical indications such as dermatology, thoracic surgery or urology. After administration of a photosensitizer (PS) which

accumulates in cancer cells, its illumination with a light of adequate wavelength may induce photochemical reaction with tissue oxygen which lead to reactive oxygen species production and cytotoxic phenomenon. Its ability to treat superficial lesions disseminated on large area makes it an excellent candidate to insure destruction of microscopic residual disease in complement of surgery and in addition of chemotherapy, even in prophylactic intent on apparently normal peritoneum, in early-stage ovarian cancer.

Development of intraperitoneal PDT has been confronted with a poor tolerance related to the lack of specificity of photosensitizers and the proximity of intraperitoneal organ. First generation photosensitizer porfimersodium is the only PS which has been clinically evaluated in intraperitoneal indication in phases I and II trials [2–4]. In these studies, the authors rapport high grade morbidity as digestive perforation, capillary leaks syndrome and no benefit has been observed neither on progression-free survival nor on global survival. This narrow therapeutic window[3] has been attributed to a narrow differential in drug selectivity betweentumor and normal tissues of the peritoneal cavity [5].As stated by Cengel et al., molecularly targeted photosensitizers have a strong clinical potential and are needed to improve therapeutic index of intraperitoneal PDT[6].

In this issue of *Photodiagnosis and Photodynamic Therapy*, we present our result regarding the preclinical evaluation of a new generation targeted photosensitizer and its specificity for ovarian peritoneal metastasis. We have used FRα which is a pertinent target to develop targeted therapy in gynecologic malignancies as stated by numerous recent publications which describe the high specificity of this receptor for tumour, its expression stability between primitive cancer and peritoneal metastasis, in case of recurrences, and after chemotherapy [7–12],

Other applications could be clinically relevant in gynecological cancer. In early stage endometrial cancer, it seems possible to propose conservative treatment with targeted PDT for young women who are eligible for fertility sparing treatment [13]. Folate targeted PDT could be developed in this indication as some serous endometrial cancer overexpress FRα [9,10]. Intracavitarian illumination of endometrial cancer would be much easier than intraperitoneal illumination without the risk of visceral injuries and could so be repeated if needed to enhance its efficacy. In early stage cervical cancer or cervical intra-

epithelial neoplasia, PDT could also be an effective fertility sparing treatment option in addition with conisation [14].

Another aspect of photodynamic therapy development is the illumination using an optimal scheme and a light administration monitoring. Innovative illumination solutions are available, as textile light diffusers which offer the possibility to apply a homogenous distribution of light on large surface area, as parietal peritoneum[15] or direct and cylindrical diffusing fibreswhich are easy to handle and allow reaching spaces that are difficult to attain.Homogeneity of light distribution inside the peritoneal cavity can be improved by filling it with a dilute intralipid solution which acts as an optical diffusing medium [16,17]. Oxygen depletion is the major reason of relative treatment failure. Besides fractionation of light, numerous studies have clearly demonstrated that PDT efficacy can be enhanced by instillation of hyperoxygenated fluids during light irradiation[18]. The fluence rate and the wavelength must be adapted to exposed organs to limit light penetration and to reduce the risk of deep visceral injuries. Light emission monitoring and source tracking are feasible to ensure a complete and homogenous illumination of any anatomical cavity as it is already performed for pleural mesothelioma treatment with promising results[19]. Moreover, the combination of this spatial tracking and imaging modalities allows a real-time feedback and display of the applied dose.

In conclusion, intraperitoneal photodynamic therapy requires having an expert knowledge of several parameters. It is essential to propose to the clinicians a device which allows a reproducible and efficient illumination procedure. With targeted photosensitizers and recent illumination innovations, photodynamic therapy could be part of innovative management in gynecological cancer care.

CONFLICT OF INTEREST STATEMENT

The authors declare that there have no conflicts of interest.

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