https://www.scientificarchives.com/journal/journal-of-cancer-immunology

Journal of Cancer Immunology Commentary

Aerosol Distribution Pattern of a Single-port Device: New Perspective Treatment for Peritoneal Carcinomatosis in Brazil

Rafael Seitenfus[1*], Lívia Brancher Gravina[2], Gustavo Andreazza Laporte[1]

[1]Surgical Oncology Service, Hospital Santa Rita, Santa Casa de Misericórdia, Porto Alegre, RS, Brazil
[2]Clinical Oncologist, Hospital Bruno Born, Lajeado, RS, Brazil

[*]Correspondence should be addressed to Rafael Seitenfus; rafasei@hotmail.com

Received date: March 25, 2020, **Accepted date:** April 28, 2020

Keywords: Peritoneal carcinomatosis; Aerosol; Medical device; Ultrasound; Pressurized intraperitoneal aerosol chemotherapy (PIPAC); Innovation

The local and peritoneal recurrence play a vital role in the natural history of the evolution of gastrointestinal and ovarian neoplasms. Different methods of applying intraperitoneal chemotherapy were used perioperatively to consolidate or control peritoneal carcinomatosis [1]. The use of chemotherapy directly in the peritoneal cavity allows the direct action of the therapeutic agent in the metastatic nodules, increasing the local concentration with a limited increase in the systemic concentration. [1] The use of chemotherapy directly in the peritoneal cavity allows the direct action of the therapeutic agent on the metastatic nodules, increasing local concentration with a limited increase in systemic concentration [2-4]. The use of hyperthermia (HIPEC), early application in the postoperative period (EPIC) and Hipec laparoscopic L-HIPEC are different methods of application that seek to explore advantages with hyperthermia, application timing and multiple applications as advantages in the control of peritoneal disease. With this same objective, Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) has led to a more efficient process of delivering intraperitoneal chemotherapy.

In a pioneering way, Gullino et al. evaluated the microenvironment of solid neoplasms suggesting that structural differences caused by neoplasms could be one of the mechanisms responsible for the resistance of tumors to the action of chemotherapeutic agents [5]. Unlike other metastases, peritoneal carcinomatosis has peculiar characteristics in its formation that enhance the effect described by Gullino et al. The process of free dissemination in the cavity, the formation of the cell entrapment and the free metastasis itself, not contained in an organ parenchyma, contribute to increasing the effect of this disarray on the vascular microenvironment and the interstitial matrix as factors that lead to the natural resistance of neoplasms to chemotherapeutic agents.

Videolaparoscopy presents itself as an opportunity to create a favorable environment for enhancing the action of chemotherapy applied directly in the peritoneal cavity. The pneumoperitoneum is no longer just an instrument for creating the surgical space for the performance of laparoscopy, but has a direct action role [6], contributing to the penetration of chemotherapy, receiving the name in this context of therapeutic pneumoperitoneum. [7]

The use of videolaparoscopy in each of the PIPAC applications has the advantage of direct monitoring of the peritoneal response to treatment with low morbidity. In the beginning, PIPAC emerged as an alternative for applying more homogeneous chemotherapy in the peritoneal cavity. This behavior was attributed to the fact that liquid chemotherapy transformed into aerosol starts to present the behavior of gas inside the closed peritoneal cavity, improving distribution in this anatomical space [8]. The low systemic toxicity of PIPAC, allowing its association with intravenous chemotherapy, was making this method of delivery of the therapeutic agent with a way to enhance the control of peritoneal dissemination without giving up systemic control in patients with advanced disease [9]. Alyami et al. reinforce the importance of this association

between the application of systemic chemotherapy regimens and the applications through PIPAC, especially in patients who have peritoneal metastases exclusively. Approximately 8% of these patients may experience a reduction in carcinomatosis to the point of becoming candidates for procedures with the potential for more definitive control of peritoneal carcinomatoses, such as surgical cytoreduction associated with intraperitoneal hyperthermic chemotherapy (HIPEC) [9].

Animal studies to assess the distribution of the aerosolized therapeutic cloud in the abdominal cavity showed an advantage in the distribution of PIPAC when compared to the use of liquid dialysis solutions [8]. However, Khosrawipour et al. showed that the greatest, more homogeneous, penetration and distribution of the drug is found in the area of direct action of the PIPAC spray treatment cone and in a more heterogeneous and less deep way in the therapeutic aerosol achieved [10]. Bellendorf et al. performed a scintigraphic analysis of the peritoneal distribution of a radiotracer in the abdomen of porcine models, identifying a tendency to concentrate in the central part of the abdomen (small intestine and parieto-colic leaks) and in the cul-de-sac [11]. Recently, Davigo et al. conducted a comparative study between the use of liquid intraperitoneal chemotherapy and aerosolized chemotherapy in two groups of animal models. In both techniques, they demonstrated a heterogeneous distribution with high concentrations of drugs at the application sites [12]. It is worth mentioning that the comparison is useful for measuring the performance of each method of delivery of the chemotherapeutic agent. However, HIPEC and PIPAC cannot be understood as competitors in the process of treating peritoneal carcinomatosis, but complementary methods that work in increasingly different scenarios.

Our team started the project called BhioQap with the objective of making the treatment of PIPAC feasible in Brazil. We evaluated the performance of aerosolization in animal models as to the intra-abdominal distribution of a 2% silver nitrate solution. Our findings are of a broad pattern of intra-abdominal distribution of the solution, although the delivery is not homogeneous [13]. This article was fundamental in the process of incorporating this new treatment in the country, culminating in the realization of the first cases of application of PIPAC in December 2017 at Hospital Santa Rita - Santa Casa de Misericórdia Complex in Porto Alegre. Today PIPAC has already become a reality in Brazil. It has already been successfully reproduced in other centres such as São Paulo and Bahia, and PIPAC represents an advance in the local treatment of peritoneal carcinomatosis in Brazilian territory with the monoportal technique. Although aerosolization behaves with a non-uniform distribution in the cavity, as shown in the article by our research team, it adequately affects both the upper, middle and lower abdomen [13].

The delivery of therapeutic agents in the peritoneal cavity still poses several different challenges. Mechanisms to increase performance both in the distribution and in the penetration of chemotherapeutic agents in the peritoneal cavity are just one of them. Our research team has already tested a new aerosolization method that is different from traditional methods that use mechanical energy to transform liquid chemotherapy. This new aerosolization method using ultrasonic energy seeks to produce a more homogeneous therapeutic mist, stable for longer periods and with a narrower droplet size spectrum at this early stage of the project. The scope of development foresees the first distribution tests for animal models later this year, so that we can evaluate the distribution performance of this new method of applying PIPAC by ultrasound.

References

1. Sugarbaker PH. Prevention and treatment of peritoneal metastases: a comprehensive review. Indian Journal of Surgical Oncology. 2019 Mar 6;10(1):3-23.

2. Solass W, Kerb R, Mürdter T, Giger-Pabst U, Strumberg D, Tempfer C, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Annals of Surgical Oncology. 2014 Feb 1;21(2):553-9.

3. de Bree E, Michelakis D, Stamatiou D, Romanos J, Zoras O. Pharmacological principles of intraperitoneal and bidirectional chemotherapy. Pleura and Peritoneum. 2017 Jun 27;2(2):47-62.

4. Alyami M, Hübner M, Grass F, Bakrin N, Villeneuve L, Laplace N, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. The Lancet Oncology. 2019 Jul 1;20(7):e368-77.

5. Gullino PM, Clark SH, Grantham FH. The interstitial fluid of solid tumors. Cancer Research. 1964 Jun 1;24(5):780-97.

6. Pierrre J, Stuart OA, Chang D, Sugarbaker PH. 1996 jacquetpressaodrogas.pdf 1996:597–603.

7. Reymond MA, Hu B, Garcia A, Reck T, Köckerling F, Hess J, et al. Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporisator. Surgical Endoscopy. 2000 Jan 1;14(1):51.

8. Solaß W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. Surgical Endoscopy. 2012 Jul 1;26(7):1849-55.

9. Alyami M, Gagniere J, Sgarbura O, Cabelguenne D, Villeneuve L, Pezet D, et al. Multicentric initial experience with the use of the pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the management of unresectable peritoneal carcinomatosis. European Journal of Surgical Oncology. 2017 Nov 1;43(11):2178-83.

10. Khosrawipour V, Khosrawipour T, Kern AJ, Osma A, Kabakci B, Diaz-Carballo D, et al. Distribution pattern and penetration depth of doxorubicin after pressurized intraperitoneal aerosol chemotherapy (PIPAC) in a postmortem swine model. Journal of Cancer Research and Clinical Oncology. 2016 Nov 1;142(11):2275-80.

11. Bellendorf A, Khosrawipour V, Khosrawipour T, Siebigteroth S, Cohnen J, Diaz-Carballo D, et al. Scintigraphic peritoneography reveals a non-uniform 99m Tc-Pertechnetat aerosol distribution pattern for Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) in a swine model. Surgical Endoscopy. 2018 Jan 1;32(1):166-74.

12. Davigo A, Passot G, Vassal O, Bost M, Tavernier C, Decullier E, et al. PIPAC versus HIPEC: cisplatin spatial distribution and diffusion in a swine model. International Journal of Hyperthermia. 2020 Jan 1;37(1):144-50.

13. Seitenfus R, Kalil AN, de Barros ED, Zettler CG, dos Santos GO, Glehen O, et al. Assessment of the aerosol distribution pattern of a single-port device for intraperitoneal administration of therapeutic substances. Surgical Endoscopy. 2019 Oct 15;33(10):3503-10.