CIRURGIA CITORREDUTORA E QUIMIOTERAPIA INTRAPERITONEAL HIPERTÉRMICA NO TRATAMENTO PRIMÁRIO DOS TUMORES EPITELIAIS DE OVÁRIO: PROJETO TERAPÊUTICO PILOTO PARA PACIENTES DO SUS/PE

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Tese apresentada ao Programa de Pós-Graduação Interinstitucional em Oncologia da Fundação Antônio Prudente em parceria com o Hospital de Câncer de Pernambuco, para obtenção do título de Doutor em Ciências
Área de Concentração em Oncologia

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São Paulo
2018

FICHA CATALOGRÁFICA

Preparada pela Biblioteca da Fundação Antônio Prudente

Batista, Thales Paulo

Cirurgia citorredutora e quimioterapia intraperitoneal hipertérmica no tratamento primário dos tumores epiteliais de ovário: projeto terapêutico piloto para pacientes do SUS/PE / Thales Paulo Batista. São Paulo; 2018.

41p.

Teses (Doutorado)-Programa de Pós-Graduação Interinstitucional em Oncologia da Fundação Antônio Prudente em parceria com o Hospital de Câncer de Pernambuco

Curso de Pós-Graduação em Ciências - Área de concentração: Oncologia.

Orientador: Levon Badiglian Filho

Descritores: 1. Neoplasias Ovarianas/Ovarian Neoplasms. 2. Cavidade Peritoneal/Peritoneal Cavity. 3. Quimioterapia do Câncer por Perfusão Regional/Chemotherapy, Cancer, Regional Perfusion. 4. Hipertermia Induzida/Hyperthermia, Induced. 5. Sistema Único de Saúde/Unified Health System. 6. Procedimentos Cirúrgicos de Citorredução/Cytoreduction Surgical Procedures.

“*Nossa tarefa é aprender, tornamo-nos divinos através do conhecimento.*”

Anônimo. Citado por Weiss (1944)

A meu tio, **Prof. Albert Mente**,
pelo exemplo de vida e dedicação à ciência.
A meu pai, **Prof. Rui Bezerra Batista**,
pelo persistente incentivo.

AGRADECIMENTOS

À **Profa. Dra. Leuridan Torres**, pela exemplar dedicação à coordenação deste projeto cooperativo de pós-graduação;

Ao **Dr. Levon Badiglian Filho**, pela oportunidade de tê-lo como orientador;

A **Direção Geral do HCP e IMIP**, pelo apoio à realização do projeto;

À **Diretoria de Pesquisa do HCP**, pela oportunidade de participar deste programa cooperativo de pós-graduação;

Aos **Coordenares dos Serviços de Cirurgia Geral e Oncologia do IMIP**, **Dr. Cristiano Souza Leão** e **Dra**. **Jurema Teles**, pelo imensurável apoio ao projeto;

Aos **Residentes de Cirurgia Geral, Aparelho Digestivo e Cirurgia Oncológica do IMIP**, pela dedicação aos pacientes do estudo e excelente condução dos casos, em especial no período pós-operatório;

À **Anestesiologista Dra. Ana Lígia Bezerra Teles,** pelo empenho e dedicação ao desenvolvimento deste projeto;

Aos **Colegas Cirurgiões do Serviço de Cirurgia Geral do IMIP**, pelo excelente apoio à condução clínica dos casos;

Aos **Colegas Cirurgiões do Departamento de Oncoginecologia do HCP**, pelo auxílio à condução clínica dos casos e rastreamento de novos casos para o estudo;

Aos **Colegas dos Serviços de Oncologia Clinica do IMIP e HCP**, em especial **Dr. Radrigo Tancredi**, **Dr. Felipe Marinho** e **Dra. Caroline Matias**, pela excelente condução clínica e proservação das pacientes envolvidos no estudo;

Às **Enfermeiras-Chefes do Bloco Cirúrgico Adriana Pernambuco e Viviane Santos**, pelo excelente suporte à realização dos procedimentos de experimentais;

Ao **Dr. Fernando Figueira**, pelo apoio logístico e estimulo a realização do projeto;

À **Enfermeira Perfusionista Grabriela Henriques**, pela dedicação e excelente manuseio dos dispositivos de perfusão intraperitoneal hipertérmica de fuídos;

À **Farmacêutica Camila Castelo Branco**, pelo manuseio dos quimioterápicos;

Às **Instrumentadoras Gilvanilda Luna** e **Christiane Valentin**, pelo auxílio aos procedimentos operatórios;

Aos **Amigos Vandré Carneiro, Mario Rino** e **Rogério Santos**, pelo incentivo e sugestões;

Ao **Prof. Eduardo Miranda Brandão**, por apresentar-me ao tema da "HIPEC";

Aos **Chefe do Departamento de Ginecologia do AC Camargo Cancer Center**, **Dr. Glauco Baiocchi Neto**, pelo apoio científico, críticas e sugestões;

Aos **Cirurgiões Dr. Ademar Lopes**, **Dr. Eduardo H. Akaishi** e **Dr. Cláudio A. Quadros**, por compartilhar suas experiências para a condução deste estudo;

Aos **Colegas do Comitê de Neoplasias Peritoneais e *HIPEC* da SBCO – Sociedade Brasileira de Cirurgia Oncológica**, pela troca de experiências, muito pertinentes à condução deste estudo.

Aos **Colegas Pós-Graduandos deste Programa Cooperativo de Pós-Graduação**, pelo incentivo, críticas construtivas e pertinentes sugestões;

Ao estudante **Victor de Andrade Siqueira**, por sua contribuição à coleta dos dados;

Aos meus **familiares**, pela compreensão nos momentos de ausência e perene estímulo;

À amada **Ana Carolina C. Erhardt**, pela revisão dos textos;

Ao pequeno **Davi Erhardt Batista**, por servir de estímulo nos momentos de fadiga.

RESUMO

Batista TP. **Cirurgia citorredutora e quimioterapia intraperitoneal hipertérmica no tratamento primário dos tumores epiteliais de ovário: projeto terapêutico piloto para pacientes do SUS/PE**. São Paulo; 2018. [Tese de Doutorado-Programa de Pós-Graduação em Oncologia da Fundação Antônio Prudente, em Parceria com o Hospital de Câncer de Pernambuco].

Contexto: O câncer ovariano representa a mais letal das neoplasias ginecológicas. Dada a predileção pela via peritoneal na disseminação desta neoplasia maligna (i.e.: carcinomatose peritoneal), a utilização de quimioterapia intraperitoneal hipertérmica (i.e.: *HIPEC* – hyperthermic intraperitoneal chemotherapy; sigla mantida em inglês) representa promissora opção de tratamento para seu manejo multidisciplinar. Assim, a adoção de um protocolo simplificado de *HIPEC* poderia incrementar os resultados de seu tratamento às custas de reduzida morbimortalidade. **Objetivos**: Avaliar a eficácia e a segurança de um protocolo de *HIPEC* para tratamento do câncer epitelial avançado de ovário em pacientes da rede pública de saúde – SUS, em Pernambuco. **Métodos**: Estudo transversal (análise interina) de dados oriundos de ensaio clínico prospectivo fase II, de braço único e aberta, ainda em curso. O protocolo em estudo envolve o tratamento multidisciplinar do câncer de ovário com quimioterapia sistêmica perioperatória (i.e.: neoadjuvante e adjuvante) associado à citorredução ciurgica com *HIPEC*. O protocolo de *HIPEC* utilizou o dispositivo *Performer HT* (RanD S.r.l., Medolla – MO, Itália) e envolveu o uso de cisplatina (25mg/m²/L) perfundida em solução glicosada de diálise peritoneal por 30 minutos, sob temperatura de 41 a 43°C. O estudo foi aprovado pela CONEP (CAAE: 04016212.5.0000.5201) e registrado no *ClinicalTrial.gov* (NCT02249013). Recebeu financiamento do Decit/SCTIE/MS – CNPq/FACEPE/SES-PE (APQ:0187-4.01/13) e do FAPE/IMIP. **Resultados**: Entre março de 2015 e junho de 2017 foram realizados nove procedimentos de HIPEC em nove pacientes portadoras de neoplasia epitelial de ovário em estádio FIGO IIIB (n=1) ou IIIC (n=8), dos sub-tipos histológicos

endometrióide (n=1) e seroso (n=7) e misto (n=1), e com idade mediana foi de 43 (Min – Max: 19 – 63) anos. O valor mediano do marcador tumoral CA125 antes do início do tratamento foi de 692U/mL (Min – Max: 223,7 – 6550), o qual foi reduzido para 35,78U/mL (Min – Max: 18,5 – 374,6) após tratamento sistêmico com 3 (Min – Max: 2 – 4) ciclos de quimioterapia neoadjuvante baseada em platina, o que resultou em *PCI* (i.e.: índice de disseminação peritoneal) de 9 (Min – Max: 3 – 18) ao tempo do procedimento de HIPEC, realizado após 29 dias (Min – Max: 26 – 43) do último ciclo de quimioterapia pré-operatória. Oito procedimentos de citorredução associada à HIPEC resultaram em citorredução macroscópica completa, isto às custas de ressecção colônica em três pacientes – exenteração pélvica posterior (n=2) e colectomia parcial (n=1). O com tempo cirúrgico mediano foi de 395 minutos (Min – Max: 235–760), com tempo mediano de internamento hospitalar de 4 dias (Min – Max: 3 – 10). Todos os pacientes deixaram a UTI na manhã seguinte aos procedimentos, ao passo que 91% das morbidades compreenderam complicações menores grau I e II, de acordo com a classificação de Clavien-Dindo. Segundo a Common Terminology Criteria for Adverse Events – Versão 4 (CTCAE v4.03), as complicações mais comuns foram vômitos G1/G2 (n=2) e anemia G3 (n=2). Apenas uma paciente requereu re-operação ao quarto dia de pós-operatório devido hemorragia intraperitoneal sem foco de sangramento específico (complicação grau IIIB) e não houve registro de óbitos ou complicações tardias relacionadas aos procedimentos. O tempo mediano para reinício do tratamento sistêmico foi de 37 dias (Min – Max: 33 – 50) e todas as pacientes completaram tratamento sistêmico previsto no protocolo do estudo (i.e.: 6 ciclos de quimioterapia). **Conclusões**: Este protocolo de tratamento multidisciplinar parece ser factível e seus dados preliminares apontam para curto tempo de internação e baixa morbidade. Este é um ensaio clínico pioneiro no Brasil e também o primeiro a usar o dispositivo *Performer HT*.

SUMMARY

Batista TP. **[Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for treatment of epithelial ovarian cancer: a therapeutic pilot study for patients from SUS/PE]**. São Paulo; 2018. [Tese de Doutorado-Programa de Pós-Graduação em Oncologia da Fundação Antônio Prudente, em Parceria com o Hospital de Câncer de Pernambuco].

Context: Ovarian cancer is the main lethal gynecologic malignance. Due to its predilection for peritoneal route of spreading (i.e.: peritoneal carcinomatosis), the use of HIPEC-Hyperthermic Intraperitoneal Chemotherapy emerged as a promising treatment option for the comprehensive management of this malignancy. Thus, the adoption of a simplified protocol of HIPEC could increase the results of treatment with reduced morbidity and mortality. **Objectives**: To evaluate the efficacy and safety of a HIPEC protocol for treatment of advanced epithelial ovarian cancer patients from the Public Health System – SUS in Pernambuco. **Methods**: A cross-sectional study (interim analysis) was carried out on the women enrolled in our ongoing single-arm, open label, phase 2 clinical trial. The study involved the multidisciplinary treatment with perioperative systemic chemotherapy associated cytoreductive surgery (CRS) plus HIPEC. The HIPEC protocol used Performer HT device (RAND Srl, Medolla - MO, Italy) and involved the use of cisplatin (25mg/m²/L) perfused into dextrose peritoneal dialysis for 30 minutes under temperature of 41-43°C. The study was approved by CONEP (CAAE: 04016212.5.0000.5201) and recorded in ClinicalTrial.gov (NCT02249013). It received funding from Decit/SCTIE/MS - CNPq/FACEPE/SES-PE (APQ: 0187-4.01/13) and FAPE/IMIP. **Results**: From March 2015 to August 2016, nine patients with stage IIIB (n=1) or IIIC (n=8) epithelial ovarian carcinoma were enrolled into our trial, with sub-types endometrioid (n=1), serous (n=7) or mixed (n=1) adenocarcinoma, and median (range) age of 43 years (range: 19 – 63). The median preoperative

serum CA125 levels at diagnosis was 692U/mL (range: 223.7–6550), which was reduced to 35.78U/mL (Min – Max: 18,5 – 374,6) after a median of 3 (range: 2 – 4) cycles of neoadjuvant chemotherapy, and peritoneal cancer index scores (PCI) of 9 (range: 3 – 18) at the time of CRS/HIPEC, developed after 29 days (range: 26 – 43) from the last neoadjuvant course of chemotherapy. Eight procedures resulted in no visible disease, and three patients required bowel resection as rectosigmoidectomy (n=2) or partial colectomy (n=1). Median operation time was 395 minutes (range: 235 – 760), with a length of hospital stay of 4 days (range: 3–10). All patients left the ICU on the morning after the procedure, whereas about 91% of postoperative complications were minor grade I and II complications, according to the Clavien–Dindo classification. The most common morbidities were minor G1/G2 vomiting (n=2) and G3 anemia (n=2), according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI/CTCAE) classification version 4.0. Only one patient experienced reoperation at the fourth postoperative day because of G3 postoperative hemorrhage, but no deaths or long-term complications were recorded. Time to re-starts systemic chemotherapy (i.e.: adjuvant chemotherapy) was 37 days (range: 33 – 50) and all patients completed the systemic treatment protocol (i.e.: 6 cycles of chemotherapy). **Conclusions**: Our comprehensive multimodal protocol seems to be feasible and safe, with low rates of complications and a short length of hospital stay in this preliminary report. This is a pioneering clinical trial in Brazil and also the very first to use the Performer HT device.

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INTRODUÇÃO

1 INTRODUÇÃO

O câncer ovariano tem figurado como a mais letal das neoplasias ginecológicas, em muito devido a seu caráter insidioso e à ineficiência de programas de rastreamento e detecção precoce aplicáveis à população em geral. Neste contexto, grande parte das pacientes acaba sendo diagnosticada em estádios avançados, ao passo que 2/3 dos tumores malignos ovarianos são descobertos em estádios III ou IV[4,8]. Imersas neste cenário, 80-90% das pacientes terminarão por apresentar recorrências neoplásicas, a despeito das altas taxas de resposta inicialmente observadas com a utilização de esquemas quimioterápicos baseados em platinas[4].

O tratamento desta neoplasia habitualmente envolve a realização de cirurgia e a utilização de quimioterapia antineoplásica. A cirurgia, por sua vez, implica no acurado estadiamento operatório em casos de doença limitada e na citorredução tumoral, em casos de doença avançada ou metastática. Nesta última situação, mais frequente, a ressecção cirúrgica é focada em remover o sítio primário da doença e em reduzir ao máximo o volume tumoral residual, uma vez que a resposta terapêutica às drogas antineoplásicas é inversamente proporcional à carga tumoral remanescente[5,7-8]. Esta abordagem citorredutora foi inicialmente descrita por MEIGS em 1934[42] e tem sido mantida como importante componente do tratamento do câncer ovariano desde os primeiros relatos de Griffiths, reportados em meados da década de 70[24].

Mais recentemente, a extirpação de todo o componente tumoral macroscópico tem sido adotada meta cirúrgica após operações citorredutoras[9,21]. Felizmente, graças à padronização de técnicas de citorredução ultrarradicais envolvendo ressecções multiviscerais e peritoniectomias parietais[16,53,55], esta premissa tem sido alcançada com aceitáveis taxas de morbimortalidade cirúrgica, equiparáveis a outras cirurgias gastrintestinais de grande porte [12]. Por outro lado, apesar destes avanços técnicos propiciarem maiores taxas de citorredução completa, a sobrevivência de pacientes com câncer ovariano ainda têm se mantido muito baixa nas últimas décadas[28], o que tem estimulado a utilização de outras modalidades de tratamento multidisciplinares, como quimioterapia neoadjuvante[23,33,44,59,64], quimioterapia adjuvante por via intraperitoneal (por meio de cateter abdominal)[1,56,65], tratamentos sistêmicos com drogas-alvo[14,20] ou imunoterapia,[47] e quimioterapia intraperitoneal hipertérmica (*HIPEC-hyperthermic intraperitoneal chemotherapy*; sigla mantida em inglês)[2,6,17-19,22,32,34,45,49].

Devido a camada epitelial do ovário e do peritônio apresentarem origem comum a partir do epitélio celômico, esta representa a via predominante de disseminação das neoplasias ovarianas[67]. Desta maneira, a utilização de quimioterapia por via intraperitoneal tem sido reconhecida como importante medida para incrementar os resultados do tratamento multidisciplinar do câncer de ovário[1,56,65]. No entanto, a morbidade deste tipo de abordagem, sobretudo aquelas relacionadas ao cateter abdominal de infusão, têm limitado a tolerância dos pacientes a esta modalidade de

tratamento, impedindo sua aplicação prática mais ampla[1,60,65]. Neste sentido, protocolos de *HIPEC* aplicados apenas no transoperatório representam alternativa promissora e mais simples de utilização da via peritoneal para a administração de quimioterápicos, somando ainda diversas vantagens sobre o uso de drogas por meio de cateteres intra-abdominais[6,41],

A associação de cirurgia citorredutora e *HIPEC* representa uma inovadora modalidade terapêutica para pacientes com disseminação peritoneal neoplásica[36]. Este método de tratamento se baseia na tríade de citorredução, calor e quimioterapia loco-regional, na qual a hipertermia agrega o efeito citotóxico direto sobre as células neoplásicas, além de atuar em sinergismo com os agentes quimioterápicos, potencializando sua ação antineoplásica[63]. Atualmente, apesar de não contar com o embasamento de ensaios clínicos randomizados e controlados, esta modalidade representa o tratamento padrão para as neoplasias mucinosas do apêndice cecal com disseminação peritoneal[11,54] e para o mesotelioma peritoneal maligno[27,66], mas também tem sido utilizada, com resultados animadores, em pacientes portadores de diversos outros tipos de cânceres, principalmente de cólon, estômago e ovário[45]. Neste contexto, representa uma alternativa promissora de tratamento para o câncer de ovário, principalmente se considerando a predileção pela disseminação peritoneal nesta neoplasia[67], a veemente aplicabilidade dos princípios de citorredução cirúrgica[5,7-8] e a importância da utilização da via intraperitoneal para incremento da sobrevivência dos pacientes com este tipo de câncer[1,56,65]. Estes aspectos corroboram o

grande entusiasmo em se adicionar *HIPEC* ao tratamento do câncer de ovário.

Além dos benefícios supracitados relacionados à *HIPEC*, outras vantagens específicas da técnica incluem evitar a hipotermia induzida pela quimioterapia intraperitoneal por cateter, aumentar o contato do quimioterápico com a superfície peritoneal, permitir a remoção de células tumorais flutuantes e aumentar o desprendimento das células aderidas às superfícies viscerais, antes de se formarem bridas e aderências pós-operatórias que poderiam servir de abrigo aos remanescentes tumorais pós-operatórios, protegendo-os do efeito citotóxico local da quimioterapia intraperitoneal[6,41]. Ainda, protocolos de quimioterapia intraperitoneal aplicados apenas sob a forma de *HIPEC* durante os procedimentos operatórios são considerados mais simples para a equipe cirúrgica, corpo de enfermagem e para os próprios pacientes, evitando-se a necessidade de cuidados específicos para manuseio dos cateteres peritoneais e a morbidade relacionada a estes dispositivos[35,41]. Alguns estudos, ainda, revelam que hipertermia pode reduzir os mecanismos de resistência celular às platinas[30] e induzir uma eficiente resposta imune antineoplásica[46,68].

Por outro lado, apesar das potenciais vantagens atribuídas à utilização de *HIPEC*, sua crescente utilização fora do contexto de estudos clínicos têm sido muito criticada pela escassez de evidências científicas robustas baseadas em ensaios clínicos controlados[3,10,25-26,29,34,39] e pelo potencial aumento da morbimortalidade atribuível a um procedimento abrangente que combina cirurgia radical, hipertermia e quimioterapia

locorregional[13]. Desta forma, este projeto tem se desenvolvido como um ensaio clínico terapêutico piloto (ensaio clinico de fase II) na tentativa de somar algumas evidências ao tema; em especial, focado na avaliação de um protocolo simplificado de *HIPEC* factível ao âmbito do SUS – Sistema Único de Saúde, com potencial de incrementar a sobrevivência das pacientes com câncer ovariano às custas de reduzida morbidade e baixo custo financeiro. As publicações ora apresentadas no corpo desta tese contemplam a revisão de seus resultados preliminares, após exploração de parâmetros técnicos do procedimento e análise interina planejada para a monitorização da morbidade do protocolo experimental em estudo.

ARTIGO I

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ORIGINAL RESEARCH

Neoadjuvant chemotherapy followed by fast-track cytoreductive surgery plus short-course hyperthermic intraperitoneal chemotherapy (HIPEC) in advanced ovarian cancer: preliminary results of a promising all-in-one approach

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Purpose: Hyperthermic intraperitoneal chemotherapy (HIPEC) has been considered a promising treatment option for advanced or recurrent ovarian cancer, but there is no clear evidence based on randomized controlled trials to advocate this approach as a standard therapy. In this study, we aim to present the early outcomes and insights after an interim analysis of a pioneering clinical trial in Brazil.

Methods: This study was a cross-sectional analysis of early data from our ongoing clinical trial – an open-label, double-center, single-arm trial on the safety and efficacy of using HIPEC for advanced ovarian cancer (ClinicalTrials.gov: NCT02249013). A fast-track recovery strategy was also applied to improve patient outcomes.

Results: Nine patients with stage IIIB (n=1) or IIIC (n=8) epithelial malignancies were enrolled until February 2017. The median (range) serum CA125 level at diagnosis was 692 (223.7–6550) U/mL. The median number of preoperative cycles of intravenous (i.v.) chemotherapy was 3 (2–4), resulting in peritoneal cancer index scores of 9 (3–18) at the time of HIPEC. Time of restarting i.v. chemotherapy was 37 (33–50) days with all patients completing 6 cycles as planned. The median operation time was 395 (235–760) minutes, the length of hospital stay was 4 (3–10) days, and all the patients left the ICU on the morning after the procedure. Two patients experienced no postoperative complications, whereas 91% of the complications were minor G1/G2 events. Preliminary assessment also suggested no impair ment of the patient's quality of life.

Conclusion: Our comprehensive protocol might represent a promising all-in-one approach for advanced ovarian cancer. The patient recruitment for this trial is ongoing.

Keywords: hyperthermia, peritoneal neoplasms, peritoneal surface malignancy, peritoneal carcinomatosis, ovarian neoplasms

Introduction

Ovarian cancer is a peritoneal disease, and most patients will ultimately die of tumor progression in the natural history of this gynecologic malignancy. The disease tends to disseminate early into the peritoneal cavity and often remains confined to the peritoneum, which is also the preferred site of recurrence. In these settings, the treatment of the peritoneal cavity has been considered an important point for making a difference in the outcome of ovarian cancer patients, and several studies have assessed the role of intraperitoneal (i.p.) chemotherapy in debulking surgery.[1–3] Usually delivered through a catheter directly into the abdominal cavity, i.p. chemotherapy has demonstrated survival

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http://dx.doi.org/10.2147/CMAR.S153327

advantages over intravenous (i.v.) chemotherapy that extends beyond 10 years of follow-up.[1] However, this approach has not been widely accepted in clinical practice mainly due to its higher toxicity, inconvenience, and catheter-related complications,[2,4] as well as the impairment of the patient's quality of life (QoL) when compared with patients receiving conventional i.v. chemotherapy alone.[5]

Recently, hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a main comprehensive treatment of malignancies on the peritoneal surface in association with advanced cytoreductive surgery (CRS), and thus has been considered a promising treatment option for advanced or recurrent ovarian cancer.[6–13] The rationale for using HIPEC is based on the direct cytotoxicity of hyperthermia for malignant cells, the enhancement of this cytotoxicity by anticancer drugs, and the pharmacokinetic advantages of the i.p. route for chemotherapy.[12] Some studies have also revealed that hyperthermia can reduce the mechanisms of cellular resistance to platins[7,8,14] and induce an efficient anticancer immune response via exposure to cell surface heat shock proteins.[15,16] This technique is delivered intraoperatively, avoiding the need for implantation of peritoneal access devices and thereby reducing catheter-related morbidity and tolerance issues.[17] Despite the potential advantages of HIPEC, there is no clear evidence from randomized controlled trials to advocate this approach as a standard therapy for patients suffering from ovarian cancer. The absence of these solid evidences supports a lot of criticism directed at the increasing use of HIPEC outside of clinical trials.[18–23]

Following the skepticism surrounding HIPEC in ovarian cancer, we considered it important to present early outcomes after the interim analysis of a pioneering clinical trial in Brazil. This trial explores the safety and efficacy of a short course of the HIPEC protocol in patients from the Brazilian public health system (i.e., Sistema Único de Saúde [SUS]) under the hypothesis of low morbidity and improved progression-free survival (PFS). Some insights regarding our experience with CRS/HIPEC procedures are also discussed.

Patients and methods

Study design and population

A cross-sectional study (interim analysis) was carried out on the women enrolled in our ongoing Phase II trial. This trial was an open-label, double-center, single-arm clinical trial exploring safety and efficacy of neoadjuvant chemotherapy (NACT) followed by CRS plus short-course HIPEC as a comprehensive treatment for patients suffering from advanced epithelial ovarian cancer (EOC). A fast-track recovery strategy was also applied to improve patient outcomes. This trial was conducted under the hypothesis of low morbidity and improved PFS for this all-in-one treatment, and recruited patients from the Brazilian public health system (i.e., SUS) in Pernambuco State since February 2015. The primary end point for this trial is PFS, and the secondary end points are morbidity/mortality, patient-reported QoL, time of restarting systemic chemotherapy after CRS/HIPEC, the length of the ICU and hospital stay, and the overall survival (OS). Calculation of the sample size was based on our preliminary hypothesis that the expected 12-month PFS previously reported with the use of NACT alone[24,25] could be doubled by our comprehensive management involving the HIPEC procedure.[9,26] With both accrual time and a minimum follow-up period of 2 years, 20 patients were required for analysis considering a one-sided type I error rate of 0.05 and a power of 80%. For safety monitoring, an interim analysis was also planned after completing the predefined trigger of recruiting 50% of patients.

The eligibility criteria for patients for inclusion in the study were that the patients were fit for major surgery and chemotherapy as well as having a biopsy-proven diagnosis of EOC with a clinical stage of IIIB–IV (abdominal only). Additionally, the patients need to be aged 18–70 years, have a performance status of 0–2 (Eastern Cooperative Oncology Group) and/or >70 points on the Karnofsky scale, and should have signed the consent form. We excluded patients who showed evidence of extensive retroperitoneal lymph node involvement or unresectable disease (i.e., massive involvement of the small bowel, mesentery, or hepatic pedicle, and ureteral or biliary obstruction), as well as disease progression, infection, or health impairment during NACT; limiting visceral obesity for surgical purposes; and residual disease after CRS that was ≥2.5 mm (i.e., CC-2 and CC-3).

The study protocol was approved by the Ethics Research Committees of Instituto de Medicina Integral Professor Fernando Figueira (IMIP) and the Brazilian National Ethics Research Committees – CONEP (CAAE: 18388113.4.0000.5201), and registered on ClinicalTrials.gov under the identifier NCT02249013. Written informed consent was obtained from all patients, and the procedures complied with the standards set by the Declaration of Helsinki and the current Brazilian ethical guidelines.

Variables and outcomes

Clinical data on the patients enrolled in our trial were prospectively assessed and recorded by electronic spreadsheets. Follow-up scheduling for patient monitoring included clinical

pelvic/general examination, and assessment of CA125 every 3 months for 2 years, every 6 months for the next 3 years, and then, annually. Imaging exams were also performed every 6–12 months or when clinically required, for at least 2 years and annually, thereafter.

Response to chemotherapy and progression were defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) and the Gynecologic Cancer Intergroup (GCIG) criteria. We defined PFS as the time from the start of NACT until the date of first progression or death and the OS as the time until death; however, the data on patient survival were not explored at the time of this interim analysis. We measured the QoL using the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30 v.3.0. This health-related questionnaire was completed at baseline just before the CRS/HIPEC procedure (i.e., at the time of hospital admission), after the CRS/HIPEC (i.e., at the time of restarting the systemic chemotherapy), and after completion of the entire protocol (i.e., at 3–6 weeks after the last systemic chemotherapy cycle). The scales and items of the questionnaire were linearly transformed and analyzed according to the EORTC QoL group procedures.

For descriptive analyses, we summarized the continuous variables as medians (interquartile range) and categorical variables as frequencies (percent). Statistical analyses were not necessary for this interim analysis, and charts were created using Microsoft® Office for Mac 2011 (v.14.2.1).

Treatment protocol

At screening, all women received a comprehensive assessment of the risk factors for suboptimal cytoreduction based on clinical, radiological, and surgical findings (i.e., previous laparotomy or staging laparoscopy/laparotomy), as well as the concentrations of serum tumor markers.[27–29] Patients with a high tumor burden were then assigned to receive 2–4 cycles of NACT followed by fast-track CRS, plus a short course of HIPEC for all patients who had a response or stable disease, which was then followed by 2–4 cycles of postoperative chemotherapy. Systemic chemotherapy was scheduled in a total of 6 cycles of the standard combination of carboplatin (AUC 6) and paclitaxel (175 mg/m^2) administered every 21 days, adopting the usual criteria for dose modification or delay, as appropriate.

Standard CRS comprises total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and maximum debulking of metastatic tumors. Systematic pelvic and/or aortic lymphadenectomy was performed at the surgeon's discretion in patients with clinically suspicious nodal involvement. Whenever needed, advanced CRS procedures also involved parietal peritonectomies and visceral resections, as previously standardized.[30] However, a more conservative policy using high-voltage electrocoagulation, traditional scissors or knife resections, and other minor procedures was adopted as much as possible to reduce morbidity, confining complete peritonectomy to where there is evidence of a more bulky or confluent disease.

HIPEC was performed according to the closed-abdomen technique, using cisplatin (25 mg/L of perfusate/m^2, total limit of 240 mg) for 30 minutes, with an intra-abdominal target temperature of 41°C–43°C. The perfusate (2 L/m^2, ranging from a minimum of 4 L to a maximum of 6 L) was circulated using an extracorporeal circulation device called the Performer HT (RanD, Medolla, Italy) at a flow rate of 700 mL/min. This HIPEC protocol was named "short course" based on its 30-minute length.

Fast-track recovery strategy

A comprehensive fast-track program was planned to accelerate recovery, reduce morbidity, and shorten convalescence for patients enrolled in our trial. All patients were admitted 1 day before surgery. A soft diet was permitted until late at night, and a chlorhexidine shower was recommended. We do not routinely recommend the systematic mechanical preparation of the colon, but patients with a previous history of constipation were provided with a single dose (500 mL) of a 12% glycerin solution administered rectally for bowel preparation.

Anesthetic management included the positioning of a low thoracic epidural catheter in association with the inhalational and i.v. general anesthesia and strict monitoring to maintain the temperature and i.v. fluid needs of the patient. The fluid therapy regimen was used to maintain a mean arterial pressure ≥65–75 mmHg, a central venous pressure from 8 to 12 mmHg, and central venous oxygen saturation ≥70%. The patients were transfused with a concentrated red cells with Hb values <8 mg/dL. The empiric use of prophylaxis antibiotics (i.e., ampicillin/sulbactam) was initiated at the time of operation and continued postoperatively for 24 hours. The preemptive prophylaxis of postoperative nausea and vomiting included administration of metoclopramide (10 mg, 1 hour before surgery), dexamethasone (10 mg, at the time of induction of anesthesia), and ondansetron (8 mg, immediately after surgery). During the HIPEC phase, fresh-frozen plasma was administered (1 U/15 min), and diuresis was maintained at values ≥120 mL/15 min by optimization of the hemodynamic parameters and/or using a low dose of diuretics (i.e., furosemide), as appropriate. At this period, we

also started an i.v. infusion of 10% $MgSO_4$ (2 g over 2 hours, starting ~1 hour before HIPEC) to prevent cisplatin-induced nephrotoxicity. Abdominal drains and colostomies were avoided as much as possible, and the nasogastric tube was removed after the intervention. Following surgery, patients were extubated in the operating room when possible and were transferred to the ICU.

Postoperative treatments included analgesia using epidural and venous nonopioid drugs and i.v. drip therapy adjusted according to individual needs. Venous thromboembolism prophylaxis with low-molecular-weight heparin was only administered after 12–24 hours when its safety was confirmed by laboratory test. Urinary catheters were removed on the first postoperative day unless contraindicated, and the patients required early mobilization out of bed. Early oral feeding was also introduced on the first day, and bowel stimulation with 30 mL/day of oral magnesium hydroxide and prokinetics (i.e., metoclopramide 10 mg q8 h, i.v.) was applied for 48 hours (or presence of flatus) to prevent postoperative paralytic ileus. Criteria for hospital discharge included tolerance to regular diet and satisfactory pain control with oral agents alone.

Results

Twenty-seven patients were screened for eligibility, and finally, nine patients with stage III EOC were allocated to the HIPEC procedure from February 2015 to July 2017. These include four patients who met some exclusion criteria but ultimately underwent HIPEC, as shown in the flow diagram (Figure 1). Because of slow accrual, the planned interim analysis was anticipated, and the patient's data were explored according to the intention-to-treat principle focus-

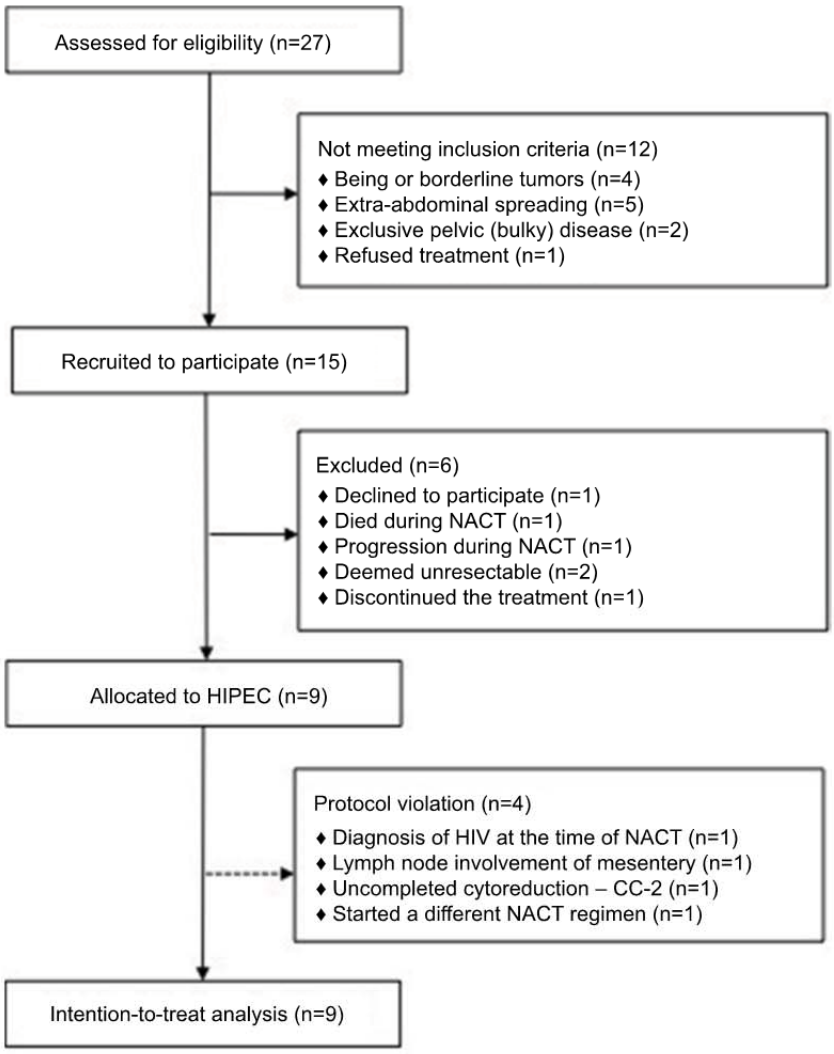

Figure 1 Flow diagram summarizing the number of patients who were assessed for eligibility, recruited to participate, assigned to HIPEC, and included in the analyses.
Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; NACT, neoadjuvant chemotherapy.

ing on the HIPEC procedures. The baseline demographic and preoperative clinical characteristics of the enrolled patients are presented in Table 1. The median (range) CA125 serum levels at diagnosis, after NACT, after CRS/HIPEC, and at the end of protocol were 692 (223.7–655.0), 35.7 (18.5–374.6), 34 (11.6–146.5), and 14.2 (7.8–57.8) U/mL, respectively. All the patients completed a total of 6 cycles of perioperative i.v. chemotherapy, as planned, in association with CRS/HIPEC.

The same surgical team performed all CRS/HIPEC procedures in the same participating hospital (i.e., IMIP). Systematic lymphadenectomies were not routinely performed in five of the nine patients, while four underwent para-aortic lymph node dissection with (n=2) or without (n=2) pelvic lymphadenectomy. As part of the CRS, four patients required bowel resection, such as rectosigmoidectomy (n=3) or partial colectomy (n=1), but no ostomies were performed and only one patient received pelvic drainage. All patients left the ICU on the morning after the procedure, whereas about 91% of postoperative complications were minor G1/G2 complications, according to the Clavien–Dindo classification. The most common morbidities were minor G1/G2 vomiting (n=2) and G3 anemia (n=2), according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI/CTCAE) classification version 4.0. Only one patient experienced reoperation at the fourth postoperative day because of G3 postoperative hemorrhage, but no deaths or long-term complications were recorded. Tables 2 and 3 summarize most of the operative characteristics and the postoperative complication rates.

A baseline EORTC QLQ-C30 questionnaire and at least one follow-up questionnaire were received from all the

Table 1 Baseline demographic and preoperative clinical characteristics

Variable	Median (range) or n (%)
Age (years)	46 (19–63)
Body mass index	21.5 (16.5–29.1)
Performance status (ECOG)[a]	
0	1 (11.1)
1	6 (66.7)
2	2 (22.2)
ASA classification	
I	4 (44.4)
II	5 (55.6)
Charlson comorbidity index	
0–2	2 (22.2)
3–5	5 (55.6)
>5	2 (22.2)
Prior surgical score	
0	4 (44.4)
1	4 (44.4)
2	1 (11.2)
FIGO staging	
IIIB	1 (11.1)
IIIC	8 (88.9)
Histology (WHO)	
High-grade serous	6 (66.7)
Endometrioid	1 (11.1)
Mixed epithelial	1 (11.1)
Serum CA125 (U/mL) at diagnosis	692 (223.7–6550)
Number of cycles of neoadjuvant chemotherapy	3 (2–4)
Number of cycles of adjuvant chemotherapy	3 (2–4)

Note: [a]Performance status at the time of CRS/HIPEC (after NACT).
Abbreviations: ASA, American Society of Anesthesiologists; CRS, cytoreductive surgery; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HIPEC, hyperthermic intraperitoneal chemotherapy; NACT, neoadjuvant chemotherapy; WHO, World Health Organization.

Table 2 Operative and postoperative clinical characteristics

Variables	Median (range) or n (%)
Peritoneal cancer index	9 (3–18)
Completeness of cytoreduction	
CC-0	8 (88.9)
CC-2	1 (11.1)
Operative time (minutes)	395 (235–760)
Time of perfusion[a] (minutes)	50 (43–58)
Mean temperature (°C)	42.1 (41.2–42.5)
Chemotherapy dose (mg)	170 (140–220)
Hospital stay (days)	4 (3–10)
Time to CRS/HIPEC after NACT (days)	29 (26–43)
Time to chemo after HIPEC (days)	37 (33–50)

Notes: [a]Total time after the "patient-filling phase", while waiting for stable temperatures. The "drug circulation phase" (i.e., HIPEC) was 30 minutes in all cases.
Abbreviations: CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; NACT, neoadjuvant chemotherapy.

Table 3 Postoperative complication rates[a]

Variables	Median (range) or n (%)
Number of complications[b] (per patient)	1 (0–3)
Patients with no complications (G0)	2 (22.2)
Minor complications (G1/G2)	
Vomiting[c]	2 (22.2)
Abdominal distension (G1)	1 (11.1)
Wound infection (G2)	1 (11.1)
Catheter-related infection (G2)	1 (11.1)
Hypokalemia (G1)	1 (11.1)
Lymphocele (G1)	1 (11.1)
Major complications (G3/G4)	
Anemia (G3)	2 (22.2)
Vomiting (G3)	1 (11.1)
Postoperative hemorrhage (G3)	1 (11.1)
Postoperative death (G5)	0 (0)

Notes: [a]According to both the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI/CTCAE), version 4.0. [b]A total of 11 complications were recorded. [c]One case was ranked as G1, and the other one as G2.

patients. Seven of the nine patients completed follow-up questionnaires "after HIPEC", and five completed "after protocol". The preliminary data on the QoL of the patients were assessed only as functioning scales and are summarized in Figure 2.

Discussion

Upfront CRS followed by platinum-based chemotherapy is the mainstay of treatment for advanced disease and has been our preferred multimodal treatment for patients eligible for the oncologic surgical procedure. However, ovarian cancer is often diagnosed at a later stage and in elderly patients who are then referred to specialists at a high perioperative risk profile or a low likelihood of achieving cytoreduction, especially in the context of the SUS public health system. In these settings, NACT may offer rapid symptomatic improvement and reduction in tumor burden, which helps in the selection and preparation of patients for aggressive treatment options, such as advanced CRS. This approach may also contribute to reducing the invasiveness of treatment and perioperative morbidity with noninferior outcomes with respect to PFS and OS.[24,25,31–33] Some pieces of evidence also suggested the effectiveness of NACT followed by interval debulking surgery and i.p. chemotherapy (delivered by means of abdominal catheters).[34,35] We thus considered NACT as an important component for our study protocol involving HIPEC.

Despite the established rationale and encouraging results favoring the use of NACT, this approach has also been related to a higher risk of developing platinum resistance.[36] Accordingly, we reinforced the concept of early and complete removal of all macroscopic tumors in the therapeutic sequence of EOC, and thus, we limited NACT to 2–4 cycles before surgery with the intention of minimizing the risk of chemoresistance.[37] Our protocol additionally adopted a more flexible policy regarding the number of preoperative cycles of chemotherapy to allow for a more individualized decision in terms of the best moment to proceed with the CRS/HIPEC procedures, which accounts for a balance of variables such as the improvement of health status, tumor response (i.e., CA125 response by GCIG and at least stable disease according to RECIST), and operating room scheduling. At this point, HIPEC also appears complementary to NACT in reducing the mechanisms of cellular resistance to platins,[7,8,14] while some clinical studies revealed its protective value against chemoresistance.[7,8]

Recent literature has supported the hypothesis of improvement in the survival associated with HIPEC for advanced and recurrent ovarian cancer.[6–9,13,38,39] For example, Spiliotis et al[7] presented a pioneering Phase III trial exploring the use of HIPEC for recurrent disease and demonstrated a survival advantage favoring the use of HIPEC. A main interesting finding of this study was the similar rate of survival observed in both the platinum-sensitive and platinum-resistant subgroups, which is in line with the previous report by the FROGHI (French Oncologic and Gynecologic HIPEC) group of a multicenter retrospective cohort study of 474 patients with

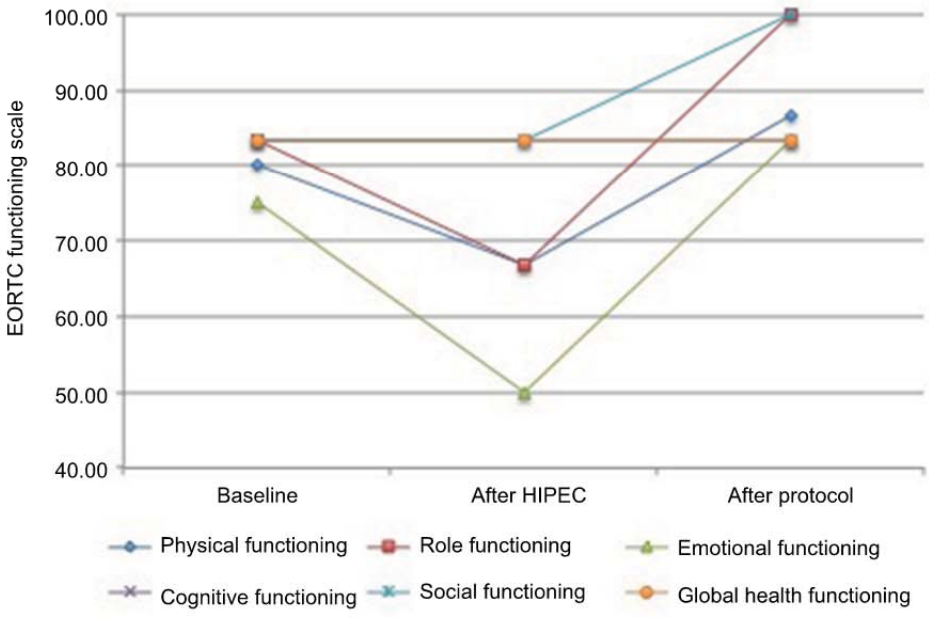

Figure 2 Course of the patient-reported health-related quality of life over time, according to EORTC QLQ-C30 functioning scales. All subscale responses were converted to 0–100 scales (according to the EORTC guidelines).
Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; HIPEC, hyperthermic intraperitoneal chemotherapy.

recurrent EOC.[8] Despite the merit of this pioneering study, it has been criticized because of the many drawbacks in its presentation and methods.[19,21] The role of HIPEC in advanced EOC was also explored in three European Phase II trials. In the study conducted by Deraco et al involving upfront CRS/HIPEC,[9] all the patients, except one who died postoperatively, started adjuvant systemic chemotherapy after a median of 46 (29–75) days, which represents a relative delay compared to our results (37 [33–50] days). In the strategy adopted by Gouy et al[38] combining 6 cycles of NACT, CRS/HIPEC, and postoperative maintenance bevacizumab, the median interval between the last cycle of NACT and the CRS/HIPEC was 41 (24–81) days, which contrasts with our better results (29 [26–43] days) in these settings. In the study by D'Hondt et al exploring interval CRS plus HIPEC after 3–4 cycles of NACT,[26] the time to starting the adjuvant systemic chemotherapy was 42 (14–89) days. In all these trials, the addition of HIPEC seemed to be a promising strategy for the treatment of advanced EOC in terms of survival, whereas our approach initially suggested some advantages favoring toxicity and postoperative outcomes, especially the length of the hospital stay – our postoperative hospital stay was only 4 (3–10) days, compared to 21 (13–67), 18.5 (10–69), and 15 (10–69) days in the cited trials. Accordingly, our approach could be presented as a promising all-in-one approach if some survival advantage could be confirmed in the final analysis, including survival outcomes for this trial.

More recently, Van Driel et al[39] and Lim et al[40] presented preliminary data from their Phase III trials (NCT00426257 and NCT01091636, respectively). In the former study, patients who showed at least stable disease after three cycles of NACT, and who had no residual mass greater than 2.5 mm, were randomly assigned to receive intervals of CRS with or without HIPEC using cisplatin (100 mg/m^2) for 90 minutes. Three additional cycles of i.v. chemotherapy were also given postoperatively. The time of restarting chemotherapy was 33 days, with a hospital stay of 10 days. HIPEC was associated with a longer recurrence-free survival and a significant improvement in the OS (48 vs. 34 months; HR, 0.64; 95% CI, 0.45–0.91; P=0.01), whereas the number of patients with G3/G4 adverse events was also similar in both treatment arms (28% vs. 24%; P=0.61). In the second trial, the HIPEC regimen comprised cisplatin at the dose of 75 mg/m^2 for 90 minutes and NACT was allowed, but not systematically applied. The eligibility criteria for intraoperative randomization were based on residual tumors <1 cm. With this study design, the authors found no statistical superiority for HIPEC in terms of the survival, but the subgroup of women who received NACT showed a gradual distinction trend favoring the HIPEC group, where the 5-year OS was 47.9% in the HIPEC arm and 27.7% in the control arm. In summary, these early results highlight the clinical importance of combining HIPEC with NACT, including the role of HIPEC for patients with residual tumors no greater than 2.5 mm. This is probably linked to the potential effect of hyperthermia in modifying factors of cancer growth, the microenvironment, immune response, vascularization, and oxygen supply that could serve to improve the outcomes in ovarian cancer.[41]

Despite the fact that CRS/HIPEC practices are widely variable,[12,42] the majority of HIPEC studies on ovarian cancer have used i.p. cisplatin,[8,12,42,43] which could also be employed in routine clinical practice as a single agent according to most experts.[42] The duration of perfusion with this drug may reach 160 minutes (usually ranging from 30 to 120 minutes) in line with the investigator's experience and the protocol to be used,[8,12,42] but consequently, a higher procedure length may also imply major morbidity.[43] Additionally, some data have supported an increased drug concentration in the instillation with a shorter bathing duration would probably give similar pharmacokinetic results to those with a longer bathing duration and decreased drug concentration.[44,45] In these settings, we proposed a short-course (i.e., 30 minutes), high-dose (i.e., 25 mg/m^2/L) cisplatin schedule as the drug protocol for our study, supposing that it could be a low-morbidity but equally effective regimen to be applied to our comprehensive approach. At the time of this interim safety analysis, the lower morbidity of this regimen can be based on our low rates of complication and short length of hospital stay.

Our study was limited by the slow accrual, which led us to anticipate this interim analysis and to work inviting other Brazilian cancer centers to participate in this trial. With these efforts, we hope to complete our targeted accrual in the following years, while waiting for the results of many ongoing trials addressing the issue of HIPEC in ovarian cancer. Another point is that the study protocol lacks the ability to provide routine laparoscopic estimation of tumor burden at diagnosis for all our patients, as previously published.[33] Because of our initial interest in including patients who were referred to our tertiary-care centers after some surgical exploration by a general gynecologist, the selection of patients with a low likelihood of achieving an upfront complete cytoreduction was planned based on comprehensive evaluation of the clinical status, serum CA125 levels, CT scan findings,[27,28] and reports of

the first exploratory surgery, whereas an initial staging laparotomy or laparoscopy was not performed by our team in one of the nine cases. Accordingly, only one patient with Federation of Gynecology and Obstetrics (FIGO) stage IIIB at laparotomy staging was recruited due to disease spreading into the upper abdomen and diffusing in the mesentery, while all other patients were considered as having bulky stage IIIC disease. Since the tumor load remains an independent and poor prognostic factor despite the completeness of cytoreduction,[46,47] we sincerely believe that preoperative measurement plays a role in clinical trials exploring new strategies for advanced EOC patients. Additional criticisms of our protocol might involve the lack of baseline QoL measurements just before starting NACT because our focus in this sub-analysis was directed at the CRS/HIPEC component of our protocol. On the other hand, the strengths of this study include the fact that it is a former clinical trial involving HIPEC procedures in Brazil and the first trial to use the Performer HT device (RanD). This includes efforts for conducting this kind of study in the context of the public health system from a developing country, and finally, the pioneering exploration of a comprehensive strategy combining perioperative chemotherapy (i.e., NACT plus adjuvant chemotherapy), advanced CRS, fast-track recovery procedures, and a short-course HIPEC for advanced EOC.

Conclusion

Because most of the criticism surrounding the use of HIPEC in ovarian cancer involves the inherent potential morbidity of this approach,[48] we considered it important to present an interim analysis of our trial that suggests the low morbidity and lack of impairment of the patient's QoL with the adoption of comprehensive treatment involving HIPEC. Although this current paper does not yet focus on the efficacy of HIPEC (data about PFS and OS are not matured and recruitment is ongoing), the issue could be potentially interesting. In our opinion, this is a promising approach that should be evaluated in the management of EOC, especially when other combined i.p. chemotherapy regimens and sophisticated target therapies failed to demonstrate an advantage for patients with advanced disease.[3] Herein, our all-in-one protocol seems to be feasible, safe, and simple for the patient, surgeon, and nursing caregivers. It has advantages in combining the early i.p. route of chemotherapy without the need for abdominal catheters, the synergism of hyperthermia, and the benefits of NACT and the fast-track recovery procedures allowing for earlier patient mobility, recovery, and hospital discharge.

Acknowledgments

This study was supported by grants from Decit/SCTIE/MS – CNPq/FACEPE/SES-PE (APQ:0187-4.01/13) and FAPE/IMIP. The authors would like to thank the medical student Victor A Siqueira and the perfusionist, Gabriela Henriques for helping them with data collection, the RanD Company (Medolla, Italy) for the excellent technical assistance, and Dr. Fernando Figueira and the nurses-in-chief Adriana Pernambuco and Viviane Santos for their logistic efforts. They also wish to thank the residents in general surgery and the fellows in digestive surgery and surgical oncology. Some technical support to their protocol was also provided by AC Camargo Cancer Center (São Paulo, Brazil). Important help was provided in the development of their trial by the Research Director Leuridan Torres, as well as the entire office of the General Hospital Directors of both institutions (i.e., IMIP and Hospital de Câncer de Pernambuco), the head of their clinical oncology team Jurema Teles, and the pharmaceutical Camila Castelo Branco. Finally, they would like to thank Arthur Krause, Luciana Câmara, and Gustavo Carvalho for polishing the English language after the professional copyediting services.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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ARTIGO II

DOI: 10.1590/0100-69912016006014 Technical Note

Exploring flow rate selection in *HIPEC* procedures

Explorando parâmetros de fluxo em procedimentos de HIPEC

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A B S T R A C T

Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a main comprehensive treatment of peritoneal malignancies. However, current data on the literature are very heterogeneous in terms of its technical particularities, which require some efforts to standardization of practices. In these setting, we present some early data from a pioneering clinical trial in Brazil (ClinicalTrials.gov Identifier: NCT02249013) to explore the dynamic relationships between flow rates and temperature parameters in the first cases of our study, which may help in selecting better technical parameters during HIPEC procedures.

Keywords: *Injections, Intraperitoneal. Hyperthermia, Induced. Drug Therapy. Peritoneal Neoplasms.*

INTRODUCTION

Cytoreductive surgery (CRS) plus hypertermic intraperitoneal chemotherapy (HIPEC) has emerged as a main comprehensive treatment of peritoneal malignancies. The rationale of combining heat with intraperitoneal chemotherapy is the synergistic effect of heat with the cytotoxic drugs. Heat has a direct cytotoxic effect, potentiates the action of certain antimitotic agents, as well as increasing their penetration into tumor tissue. Similarly, hyperthermia can also reduce the mechanisms of tumoral resistance to chemotherapy and induce an efficient anticancer immune response[1]. In summary, these arguments have highlighted HIPEC as a promising oncological approach.

Many HIPEC techniques have been described and the current data are heterogeneous in terms of technical procedures, which require some standardization of practices that might permit systematic comparisons. The technical particularities of HIPEC include instillation circuit, timing of parietal closure, length of perfusion, target temperatures, and choice and dosage of antimitotic agents. Herein, flow rate is an important variable in achieving and maintaining goal temperatures during HIPEC, whereas a minimal temperature threshold is also critical to improve chemotherapy effects and survival outcomes[2,3]. In this setting, we aimed to explore the dynamic relationship between flow rates and temperature parameters during HIPEC procedures to help selecting a target flow rate set up.

TECHNICAL NOTE

This note involves a cross-sectional analysis of early data from our ongoing clinical trial (ClinicalTrials.gov Identifier: NCT02249013) regarding HIPEC procedures – the very first Brazilian clinical trial on this matter. This study is testing a short-term protocol of cisplatin-based HIPEC for treatment of peritoneal carcinomatosis of ovarian origin. Details of the study design are available at https://clinicaltrials.gov/ct2/show/NCT02249013?term=HIPEC+AND+ovarian+cancer&rank=4. Shortly, HIPEC was held immediately after cytorreduction according to the closed-abdomen technique. Our protocol involves the use of cisplatin (25mg/L of perfusate/m^2, total limit of 240mg) for 30 minutes with an intra-abdominal target temperature of 41-43°C. Perfusate (2L/m^2, ranging from 4L to 6L) circulated using an extracorporeal circulation device named *Performer HT* (RanD, Medolla, Italy – Figure 1), and the goal temperature was set up to 44°C. A flow rate of 300-500 ml/min was applied during the "patient filling phase" and increased to 700-1000 ml/min during

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Table 1. *Summary of relationship between flow rates and temperature parameters in HIPEC procedures.*

Parameters[1]	600ml/min	700ml/min	800ml/min	900ml/min	1000ml/min	p-value[2]
Inlet Temperature	43.6 (43.6-43.7)	43.3 (43.2-43.4)	42.8 (42.8-42.9)	42.8 (42.7-42.8)	41.8 (41.7-41.8)	< 0.001
Outlet Temperature	40.6 (40.5-40.7)	41.2 (41.1-41.3)	41.0 (40.9-41.0)	40.6 (40.5-40.6)	40.7 (40.6-40.7)	< 0.001
Mean Temperature[3]	42.1 (42.1-42.2)	42.2 (42.2-42.3)	41.9 (41.9-41.9)	41.7 (41.6-41.7)	41.2 (41.1-41.2)	< 0.001
Temperature Lost[4]	3.1 (2.9-3.2)	2.1 (2.0-2.3)	1.8 (1.8-2.0)	2.2 (2.2-2.3)	1.1 (1.0-1.2)	< 0.001

[1] Descriptive statistics summarized as median and IQR (interquartile range).
[2] According to Kruskal-Wallis test.
[3] Mean temperature: mean between inlet and outlet temperature probes.
[4] Temperature lost: difference between the inlet and outlet temperature probes.

the early "circulation phase". Thereafter, flow rate was adjusted between 600 to 1000 ml/min at intervals of 100ml/min, maintaining stable parameters into the peritoneal cavity just before the "drug circulation phase".

The device provided us with the main functional and patient parameters, and we recorded data from the "HIPEC phase" every minute. We permitted variations of ±10% in the flow rate values and rounded them accordingly. Flow rates were related to temperature parameters. We summarize descriptive statistics as median and interquartile range. We performed the statistical analysis and graph construction applying conventional methods in the STATISTICA Data Analysis Software System, Version 8.0 (Statsoft, Inc., Tulsa, OK, USA).

Data from the first five cases enrolled into our trial were analyzed involving 148 time-points of information, since two records were excluded because a variation higher than 10% in the flow rate. The mean of inlet temperature and losses from solution to peritoneal cavity was lower at 1000ml/min. Conversely, a lower rate resulted in higher inlet temperatures and temperature losses. Differences between inlet and outlet temperature probes were about 3°C at a flow rate of 600ml/min, and 1°C at 1000ml/min. The temperature lost to peritoneal cavity remained virtually stable by about 2°C at flow rates of 700, 800 and 900 ml/min. Table 1 summarizes these temperature parameters in regards to flow rates. Data on difference between inlet and outlet temperature probes is also presented in Figure 2.

DISCUSSION

HIPEC is now a preferred treatment of many peritoneal surface malignancies[1]. Unfortunately, no single technique has so far demonstrated its superiority, and several variations in techniques have produced heterogeneous and incomparable results. In this scenario, further efforts are needed to standardize the technical particularities of HIPEC, whereas temperature parameters and their dynamic relationship with other variables are important points to be scrutinized[2-5].

HIPEC involves the continuous heating and circulation of chemotherapy throughout the abdominal cavity in an attempt to enhance cytotoxicity[4]. Accordingly, flow rate is an important variable in achieving and maintaining goal temperatures during HIPEC, and a temperature threshold above 40°C is also critical to significantly enhance chemotherapy effects and improve survival outcomes[2-4]. By exploring the dynamic relationship between temperature parameters and flow rates in the first cases of our clinical trial, we noted that a higher flow rate may minimize the exchanging of heat from the system to the perfusate solution (i.e.: the mean inlet temperature was lower at 1000ml/min) and from the solution to the peritoneal cavity (i.e.: the mean of temperature losses was also lower at 1000ml/min). Conversely, a lower rate resulted in higher inlet temperatures and temperature losses. These findings confirm that heat exchanges are mitigated by higher flow rates, and that the peritoneal cavity may absorb

Figure 1. *Performer HT device in use during HIPEC procedure.*

more heat at lower flow rates. Herein, we found that the difference between inlet and outlet temperature probes were about 3°C at a flow rate of 600ml/min, and 1°C at 1000ml/min. Interestingly, the temperature lost to peritoneal cavity remained virtually stable at about 2°C at a flow rate of 700, 800 and 900 ml/min.

Despite increased flow rates are important to achieve and maintain uniform temperature distribution throughout the abdominal cavity during HIPEC, the assumption of added benefit for increased flow rates requires further considerations[2,4]. For example, even though there is a greater rise in overall esophageal temperature during perfusion at higher rates of flow, the average esophageal temperatures were lower as the flow rate was increased according to Furman *et al*.[2]. In their study, the average esophageal temperature rise during perfusion was 1.0°C at 2500ml/min, a similar temperature gradient that we found at a flow rate of 1000ml/min. Thus, we could suppose stable differences between inlet and outlet temperature (i.e.: heat lost to the peritoneal cavity and/or *viscera*) from 1000ml/min to 2500ml/min, as we found at a flow rate between 700ml/min and 900ml/min, and also, as these authors reported, at rates of 2000ml/min and 3000ml/min – about 0.8°C for both flow rates[2].

Another point of interest in this context is the dynamic relationship between hyperthermia and intra-abdominal pressures. Hyperthermia enhances diffusion in the visceral peritoneum, whereas increased pressure may enhance both visceral and parietal tissue concentrations of chemotherapy agents, without leading to increased systemic levels. The combination of the two achieves the highest tissue concentrations of chemotherapy, whereas a maximal distention of the abdomen by the perfusate is probably required to improve the synergism between such factors[4,5].

In conclusion, we present some dynamic relationships between flow rates and temperature parameters that may help in selecting better technical parameters during HIPEC procedures. These data resulted from our pioneering clinical trial in Brazil and also the very first to use the Performer HT device.

ACKNOWLEDGEMENTS

We would like to thank the medical student Victor A. Siqueira and our perfusionist, Gabriela M. N. Henriques, for helping us with data collection; the Rand Company (Medolla, Italy), for the excellent technical assistance; and Dr. Fernando Figueira and Nurse Adriana Pernambuco, for their logistic efforts.

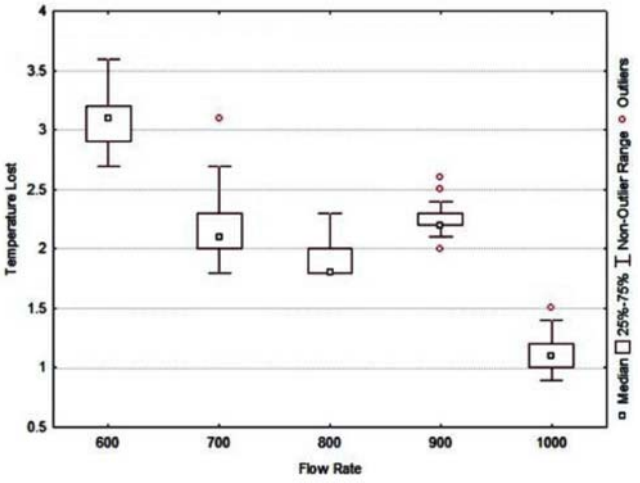

Figure 2. *Box Plot of temperature losses to peritoneal cavity (i.e.: differences between inlet and outlet temperature probes) according to flow rates.*

R E S U M O

Cirurgia citorredutora avançada e quimioterapia intraperitoneal hipertérmica (i.e.: *HIPEC*, sigla em inglês) têm se consagrado como promissora abordagem terapêutica multidisciplinar para neoplasias malignas peritoneais. Contudo, dados da literatura corrente são muito heterogêneos em torno de muitos de seus aspectos técnicos, o que demanda algum esforço na busca por padronizações do procedimento. Neste sentido, são apresentados dados de um ensaio clínico pioneiro no Brasil (*ClinicalTrials.gov Identifier*: NCT02249013), relacionando parâmetros dinâmicos de taxas de fluxo e temperaturas de perfusão nos primeiros casos do estudo, o que pode ajudar na seleção de melhores parâmetros técnicos para procedimentos de *HIPEC*.

Descritores: Injeções Intraperitoneais. Hipertermia Induzida. Quimioterapia. Neoplasias Peritoneais.

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Received in: 07/08/2016
Accepted for publication: 17/10/2016
Conflict of interest: none.
Source of funding: Decit/SCTIE/MS – CNPq/FACEPE/SES-PE (APQ:0187-4.01/13) and FAPE/IMIP.

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COMENTÁRIOS

4 COMENTÁRIOS

A utilização de quimioterapia por via intraperitoneal representa uma importante alternativa terapêutica multidisciplinar para o câncer de ovário, sobretudo pelo padrão de disseminação preferencialmente celômico desta neoplasia[1,56,65]. Habitualmente empregada por meio da aposição de cateteres intra-abdominais, esta abordagem tem propiciado taxas de sobrevivência livre de progressão mediana de cerca de 25 meses, segundo análise combinada de dois dos principais ensaios clínicos randomizados envolvendo o tema, na qual o tratamento adjuvante padrão endovenoso atingiu sobrevivência mediana de 20 meses[56]. A despeito deste inequívoco beneficio, a utilização de quimioterapia adjuvante intraperitoneal tem sido subutilizada na prática clinica[65], em muito devido à elevada morbidade relacionado ao cateter de administração[60] e prejuízo à qualidade de vida das pacientes, quando comparada ao tratamento convencional adjuvante por via endovenosa[62]. Num dos mais importantes ensaios clínicos de fase III envolvendo o tema[1], por exemplo, apenas 42% das pacientes completaram todo o esquema de tratamento intraperitoneal em avaliação, o que tem se correlacionado a sua utilização em menos de 50% das pacientes potencialmente candidatas a esta modalidade terapêutica no cenário da prática clínica atual[65].

Ao contrário das dificuldade encontradas para a incorporação da via intraperitoneal ao arsenal terapêutico adjuvante do câncer de ovário, a utilização de quimioterapia neoadjuvante por via endovenosa tem conquistado crescente espaço na prática clínica[43]. Sua utilização se baseia na menor morbidade relacionada a este opção de tratamento, isto sem prejuízo às taxas de sobrevivência, tanto no cenário de ensaios clínicos, [23,33,44,59] quanto no contexto da prática clinica[43,57]. Críticas a esta abordagem, contudo, têm se dirigido principalmente à possibilidade de aumento da resistência tumoral ao tratamento quimioterápico[15], e às reduzidas taxas de sobrevivência e baixa qualidade dos procedimentos

cirúrgicos observados nos dois principais estudos que a avaliaram[64]. Em ambos ensaios clínicos[33,59], por exemplo, a sobrevivência livre de progressão mediana foi de apenas 12 meses com a adoção do tratamento neoadjuvante, ao passo que o tempo cirúrgico mediano variou de apenas 120 a 180 minutos, o que contrasta com o tempo mediano de 240 a 451 minutos relatados preliminarmente nos estudos SCORPION[23] e JCOG0602[44]. Por outro lado, a despeito da citorredução cirúrgica ser considerada fundamental ao tratamento multidisciplinar do câncer de ovário[5,7,8,34], têm se demonstrado também que a sobrevivência destas pacientes parece mais relacionada à carga tumoral no momento de seu diagnóstico do que os resultados cirúrgicos propriamente ditos[31,40], o que favorece a adoção do tratamento neoadjuvante em pacientes com câncer de ovário avançado e grande carga tumoral[31]. Noutro extremo, a utilização do tratamento neoadjuvante limitada à quatro ciclos, como adotado neste estudo, também tem sido proposta a fim de se minimizar o risco de químio-resistência às platinas para as pacientes envolvidas neste estudo[13].

Visando a incrementar os resultados do tratamento do câncer de ovário, a utilização combinada de quimioterapia sistêmica neoadjuvante e intraperitoneal adjuvante foi avaliada no ensaio clinico randomizado de fase II denominado OV21/PETROC[38], o qual demonstrou taxas de progressão de doença aos nove meses de 38.6% versus 24.5%, em favor deste tratamento combinado. Outras associações de tratamento potencialmente promissoras, contudo, não alcançaram os resultados esperados; por exemplo, a combinação de quimioterapia intraperitoneal baseada em platinas com drogas-alvo como o *bevacizumab* não se mostraram superiores em termos de sobrevivência livre de progressão em comparação ao grupo controle tratado com quimioterapia convencional endovenosa e a mesma droga-alvo, segundo dados preliminares do esperado estudo ensaio clínico de fase III denominado GOG252[61]. Deste modo, o benefício da combinação de diferentes abordagens terapêuticas ainda permanece incerto, requerendo mais estudos para melhor elucidação.

No contexto de terapias combinadas, a *HIPEC* se apresenta como promissora oportunidade de oferecer quimioterapia intraperitoneal às pacientes com câncer de ovário avançado, cumulando as vantagens de se administrar o quimioterápico apenas no transoperatório com os benefícios sinérgicos da hipertermia[6], em especial seus efeitos imunomoduladores[48,49,53], implicados no fenômeno de "re-sensibilização" tumoral às platinas[2,49]. Ademais, a associação de quimioterapia neoadjuvante endovenosa poderia contribuir para reduzir a radicalidade[44] e morbimortalidade dos procedimentos cirúrgicos empregados[23,33,44,59], ao passo que a adoção de um protocolo simplificado de quimioterapia intraperitoneal aplicados apenas sob a forma de *HIPEC* transoperatório poderia ser considerada mais simples para a equipe cirúrgica, corpo de enfermagem e para os próprios pacientes, evitando-se a necessidade de cuidados específicos para manuseio dos cateteres peritoneais e a morbidade relacionada a estes dispositivos de infusão[41]. No estudo em tela, por exemplo, seus resultados preliminares apontam para premissa de factibilidade do regime de tratamento proposto, evidenciando-se baixa morbidade dos procedimentos, curto tempo de internamento e rápido retorno ao tratamento sistêmico quimioterápico adjuvante, isto sem ocorrência de óbitos ou maior impacto sobre a qualidade de vida referida pelas pacientes. Desta maneira, caso também se confirme seu benefício em termos de sobrevivência, o protocolo de tratamento em estudo poderá se apresentar como promissora opção terapêutica multidisciplinar para o câncer de ovário, sobretudo pelo somatório dos benefícios sinérgicos de medidas de recuperação pós-operatória acelerada (i.e.: fast-track recovery)[37], da quimioterapia sistêmica neoadjuvante[23,33,44,59], e da *HIPEC*[2,6,17-19,22,32,34,45,49].

Em linha com os pressupostos deste protocolo, resultados do recém-publicado ensaio clínico de fase III denominado OVI-HIPEC demonstraram ganhos medianos de sobrevivência de 3,5 meses livres de recorrência, o que se traduziu em benefício de 12 meses em termos de sobrevivência global[58]. Num desenho de estudo semelhante ao apresentado nesta tese, pacientes com neoplasia epitelial de ovário em estágio III de grande carga

tumoral foram randomizados para tratamento no braço experimental contemplando quimioterapia endovenosa neoadjuvante por três ciclos, seguido de cirurgia citorredutora e *HIPEC* (i.e.: cisplatina 100mg/m^2, 90 minutos, 40^{o}C) e, posteriormente, quimioterapia endovenosa adjuvante por mais três ciclos. O braço controle compreendeu o mesmo regime de tratamento, mas sem a adição de *HIPEC*, enquanto a ocorrência de eventos adversos diferiu significativamente entre os braços de tratamento. Apesar de todo entusiasmo com a publicação deste primeiro ensaio clínico randomizado explorando o uso de *HIPEC* em pacientes com câncer de ovário avançado[51], muitos questionamentos acerca do real valor da hipertermia para incremento dos resultados, do custo-efetividade deste tratamento abrangente e da seleção de melhores candidatos a esta abordagem têm sido apontados[50].

Outro aspecto de grande relevância relacionado ao estudo em discussão diz respeito ao tempo cirúrgico notadamente baixo (i.e.: 338 minutos, IQR: 299 – 426), sobretudo se descontados os 90 minutos de *HIPEC* e cerca de 120 minutos adicionais gastos com os procedimentos não-cirúrgicos[58]. Nos estudos SCORPION[23] e JCOG0602[44], por exemplo, o tempo cirúrgico mediano no braço de tratamento com quimioterapia sistêmica neoadjuvante foi de 275 e 302 minutos, respectivamente. Tomando como outro exemplo os resultados iniciais deste ensaio clínico, o tempo cirúrgico mediano atuarial após a inclusão de 10 casos é de 430 (IQR: 347,5 – 591,3) minutos, com um protocolo de *HIPEC* de apenas 30min e um tempo total mediano gasto com a perfusão de apenas 50,5 minutos. Desta sorte, muitos dos resultados apresentados no supracitado ensaio clinico randomizado se aproximam ao do importante estudo previamente conduzido por VERGOTE[50,59] et al. (2010) o qual também fora muito criticado pela baixa qualidade dos procedimentos cirúrgicos empregados[64]. Estes dados sugerem um “esforço cirúrgico” insuficiente e poderiam justificar as sobrevivências relativamente baixas observadas no estudo em tela (i.e.: sobrevivência livre de recorrência de 14,2 vs. 10.7 meses e sobrevivência global de 45,7 vs. 33,9 meses), apesar de se ter demonstrado muito bem o

benefício da *HIPEC* em comparação ao tratamento mais ortodoxo envolvendo apenas quimioterapia neoadjuvante[58]. Na casuística de pacientes tratados com esta abordagem no A.C.Camargo Cancer Center, por exemplo, a sobrevivência livre de progressão e global alcançadas foram de 17,6 e 41,4 meses, respectivamente; mesmo incluindo 23% de pacientes com citorredução sub-ótima (i.e.: doença residual >1cm) nesta coorte[15].

Em revisão muito recente sobre a utilização de *HIPEC* em portadoras de câncer de ovário avançado, KUSAMURA et al.[34] (2017) destacam o potencial valor terapêutico desta abordagem em associação à citorredução de intervalo, ao contrário dos resultados mais modestos observados quando associada a táticas de tratamento envolvendo citorredução primária. Outrossim, também apontam a necessidade de se manter a devida radicalidade cirúrgica em associação à *HIPEC*, a fim de se vencer os limites de ressecabilidade impostas pela agressiva biologia tumoral destas neoplasias, sobretudo se considerado que o componente cirúrgico do binômio "Cirurgia Citorredutora – *HIPEC"* figura como o mais importante para o incremento dos resultados terapêuticos desta abrangente opção de tratamento.

Proservação Inicial e Continuidade do Estudo

Não há registro de complicações tardias relacionada aos procedimentos de *HIPEC* realizados neste estudo. Até a presente revisão de dados, as complicações apresentadas foram autolimitadas e/ou de fácil resolução, enquanto um único caso (1/9 casos) requereu tratamento invasivo (i.e.: reoperação por sangramento intraperitoneal). Durante a proservação inicial das pacientes já recrutadas, todavia, observou-se a necessidade de excluir quatro casos ao tempo da análise *per-protocol* em decorrência de violação do protocolo do estudo, a saber: citorredução incompleta (CC-2) (n=1); metástases linfonodais em raiz do mesentério que não puderam ser confirmadas por biópsia de congelação ao tempo da abordagem cirúrgica (n=1); diagnóstico de *HIV* ao tempo do tratamento neoadjuvante (n=1); e tratamento neoadjuvante iniciado em regime diferente do que fora proposto

para o estudo, apesar de posteriormente ajustado (n=1). Os dados referentes a estes casos, contudo, serão mantidos na análise de intenção de tratar, tanto para avaliação da morbi-mortalidade do procedimento de *HIPEC,* quanto para mensuração das taxas de sobrevivência resultantes do tratamento experimental.

Ao tempo desta defesa de tese, um novo caso foi recrutado para estudo e submetido ao tratamento experimental em discussão. O procedimento foi indicado em paciente jovem com tumor seroso de baixo grau e grande volume de doença visceral; envolveu ressecções multiviscerais do tubo digestivo alto e baixo (i.e.: gastrectomia subtotal e exenteração pélvica posterior), além de ressecções peritoneais parietais e linfadenectomias. O procedimento teve duração de 865 minutos e resultou em citorredução completa (CC-0). A paciente recebeu alta da UTI na manhã seguinte ao procedimento e deixou o hospital após 5 dias de internamento. Evoluiu com neupraxia do plexo nervoso axilar esquerdo relacionada ao longo posicionamento com abdução deste membro, além de linfocele pélvica relacionada à linfadenectomia; ambas com remissão completa. Reiniciou tratamento sistêmico após 74 dias do procedimento cirúrgico e completou os seis ciclos de quimioterapia inicialmente planejados recentemente. Outros dois casos se encontram em acompanhamento com vistas à participação no estudo; um deles se encontra em tratamento neoadjuvante e outro aguarda confirmação histológica e mensuração do volume de doença abdominal (estadiamento cirúrgico).

Dificuldades Encontradas e Soluções Implementadas

O desenvolvimento inicial deste projeto foi atrasado em decorrência do retardo na liberação e parcelamento dos recursos governamentais destinados à aquisição/importação dos equipamentos de perfusão intraperitoneal hipertérmica em uso no estudo (i.e.: *Performer HT,* RanD, Mendolla-MO, Itália). Isto exigiu a intervenção dos pesquisadores para renegociação da forma de pagamento destes equipamentos e

consequentemente prejudicou seu processo de aquisição/montagem e o agendamento dos primeiros casos tratados no escopo deste estudo. Ainda, ao longo de sua execução, a taxa de recrutamento de pacientes para o estudo tem se mantida abaixo do esperado, o que em muito fora agravado pelas repercussões da crise financeira e política vivida pelo país sobre a assistência médica prestadas às pacientes no âmbito do SUS – Sistema Único de Saúde. Deste modo, recrutamento de pacientes deve continuar até meados de 2019, ao tempo em que outras instituições voltadas ao tratamento do câncer têm sido convidadas a participar do estudo a fim de se incrementar a inclusão de novas participantes e abreviar a duração do estudo.

Considerações Finais

O projeto em tela tem permitido o intercâmbio científico entre o HCP – Hospital de Câncer de Pernambuco, IMIP – Instituto de Medicina Integral Prof. Fernando Figueira e o A.C.Camargo Cancer Center, contemplando a possibilidade de agregar outras instituições dedicadas ao tratamento do câncer, o que tem servido para envolver os autores em diversos eventos e atividades científicas referentes ao tema (ver **Apêndice 1** – *PRODUÇÃO CIENTÍFICA RELACIONADA AO PROJETO*), além de contribuir para difusão do conhecimento neste ramo da medicina. Em que pese se tratar do primeiro ensaio clínico nacional sobre o tema *HIPEC*, seu desenvolvimento também facilitou o registro do disposto de circulação hipertérmica de fluídos *Performer HT* junto à ANVISA, contribuindo para aquisição de novas tecnologias para o país.

Noutro extremo, tendo em vista a recente publicação do ensaio clínico de fase III OVI-HIPEC favorecendo a utilização de *HIPEC* durante a citorredução de intervalo pacientes com grande carga tumoral inicialmente tratadas com quimioterapia sistêmica neoadjuvante[58], a importância de nosso estudo se volta à validação desta nova evidência de origem europeia em um cenário brasileiro com características completamente diversas.

Ademais, se confirmados em nosso estudo os benefícios desta abordagem em termos de sobrevivência, nosso protocolo de *HIPEC* de curta duração poderá se apresentar como alternativa mais simplista e menos mórbida ao proposto pelo estudo europeu, o que contribuiria principalmente para abreviar o tempo de internamento hospitalar e, consequentemente, reduzir os custos relacionados a este tratamento.

CONCLUSÃO

5 CONCLUSÃO

Este é o primeiro ensaio clínico brasileiro envolvendo o uso de *HIPEC*. Ademais, o protocolo em estudo se mostrou factível e os primeiros casos apresentaram baixa morbidade, curto período de internamento hospitalar e baixa repercussão sobre a qualidade de vida das pacientes envolvidas. O dispositivo de circulação hipertérmica de fluídos *Performer HT* se mostrou de fácil manipulação, sobretudo por sua interface de controle amigável e interativa.

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6 REFERÊNCIAS BIBLIOGRÁFICAS

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ANEXO

Anexo 1 – Carta de aprovação do Comitê de Ética em Pesquisa em Seres Humanos do Instituto de Medicina Integral Prof. Fernando Figueira-IMIP

Instituto de Medicina Integral
Prof. Fernando Figueira
Escola de Pós-graduação em Saúde Materno Infantil
Instituição Civil Filantrópica

IMIP

DECLARAÇÃO

Declaro que o projeto de pesquisa **nº 3668- 13** intitulado **"Cirurgia citorredutora e quimioterapia intraperitoneal hipertérmica no tratamento primário dos tumores epiteliais de ovário: projeto terapêutico piloto para o Instituto de Medicina Integral Prof. Fernando Figueira"** apresentado pelo pesquisador **Thales Paulo Batista** foi APROVADO pelo Comitê de Ética em Pesquisa em Seres Humanos do Instituto de Medicina Integral Prof. Fernando Figueira – IMIP, em reunião ordinária de 14 de agosto de 2013.

Recife, 16 de agosto de 2013

Dr. José Eulálio Cabral Filho
Coordenador do Comitê de Ética
em Pesquisa em Seres Humanos do
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APÊNDICE

Apêndice 1 - Produção Científica Relacionada ao Projeto

Apresentação de Resultados Parciais em Eventos Científicos

1. Siqueira VA; Batista TP; Carneiro VCG; Tancredi R; Badiglian-Filho L; Leão CS. Cirurgia citorredutora e quimioterapia intraperitoneal hipertérmica (HIPEC) para tratamento do câncer de ovário avançado: relato dos primeiros dois casos de um ensaio clínico pioneiro no Brasil. XXXI Congresso Brasileiro de Cirurgia, CBC – Colégio Brasileiro de Cirurgiões, 2015, (ExpoUnimed) Curitiba/PR.

Descrição: Apresentação como pôster eletrônico dos primeiros dois casos realizados dentro do protocolo de estudo. O primeiro autor, Siqueira VA, é um estudante de medicina bolsista do projeto.

2. Oliveira DNA; Batista TP; Carneiro VCG; Tancredi R; Badiglian-Filho L; Leão CS. *Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of advanced ovarian cancer: the first two cases of a pioneering clinical trial in Brazil*. XII Congresso da Sociedade Brasileira de Cirurgia Oncológica – SBCO e I Congresso Latino-Americano de Cirurgia Oncológica – LASSO, 2015, (Bahia Othon Palace Hotel) Salvador/BA.

Descrição: Apresentação como pôster eletrônico dos primeiros dois casos realizados dentro do protocolo de estudo. O primeiro autor, Oliveira DNA, é um dos residentes de cirurgia oncológica que tem participado dos procedimentos.

3. Dias-Filho FA; Siqueira VA; Moraes NVM; Batista TP; Badiglian-Filho L; Leão CS. Cirurgia citorredutora e quimioterapia intraperitoneal hipertérmica (HIPEC) para tratamento do câncer de ovário avançado: relato dos primeiros cinco casos de um ensaio clínico pioneiro no Brasil. II Congresso N/NE da Sociedade Brasileira de Cirurgia Oncológica, SBCO – Sociedade Brasileira de Cirurgia Oncológica, 2016, (Grand Mercure Summerville) Porto de Galinhas/PE.

Descrição: Apresentação como pôster eletrônico dos primeiros cinco casos realizados dentro do protocolo de estudo. O primeiro autor, Dias-Filho FA, é um dos residentes de cirurgia oncológica que tem participado dos procedimentos, e o segundo autor, Siqueira VA, é estudante de medicina bolsista do projeto.

4. Oliveira DNA; Santos AL; Henriques GMN; Batista TP; Badiglian-Filho L; Leão CS. *Improving the Flow Rate Seletion During HIPEC*. II Congresso N/NE da Sociedade Brasileira de Cirurgia Oncológica, SBCO – Sociedade Brasileira de Cirurgia Oncológica, 2016, (Grand Mercure Summerville) Porto de Galinhas/PE.

Descrição: Apresentação como pôster eletrônico de trabalho avaliando parâmetros técnicos de perfusão hipertérmica de procedimentos do projeto. Os primeiros dois autores, Oliveira DNA e Santos AL*, são residentes de cirurgia oncológica e cirurgia geral que têm participado dos procedimentos, e a terceira autora,* Henriques GMN*, é a enfermeira perfusionista envolvidas no projeto.* Este pôster eletrônico foi selecionado para apresentação oral e premiado como **segundo lugar** dentre os três melhores trabalhos do evento.

5. Batista TP; Carneiro VC; Tancredi R; Badiglian-Filho L; Leão CS. Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of advanced ovarian cancer: reporting the first cases of a pioneering clinical trial in Brazil. *10th International Congress on Peritoneal Surface Malignancies*, PSOGI – Peritoneal Surface Oncology Group International (PSOGI), 2016, (Omni Shoreham Hotel) Washington/DC, EUA.

Descrição: Apresentação como pôster eletrônico dos primeiros sete casos realizados dentro do protocolo de estudo, durante o principal evento internacional sobre o tema, que ocorrerá entre 17 e 19 de novembro deste ano, em Washington/DC, EUA.

6. Vasconcelos JLD; Batista TP; Leão CS; Carneiro VCG; Badiglian-Filho L; Santos DHC; Magalhães DT; CâmaraLHLD. Cirurgia citorredutora com quimioterapia intraperitoneal hipertérmica (*HIPEC*) de curta duração para tratamento de câncer de ovário – baixa morbidade nos primeiros casos

de um ensaio clínico pioneiro no Brasil. XXXII Congresso Brasileiro de Cirurgia, CBC – Colégio Brasileiro de Cirurgiões, 2017, (Sheraton WTC) São Paulo/SP.

Descrição: Apresentação como pôster dos resultados da análise interina de morbimortalidade do protocolo de estudo. Vasconcelos JLD, Santos DHC, Magalhães DT e Câmara LHLD s*ão residentes de cirurgia que têm participado dos procedimentos.*

Publicações em Anais de Eventos (Resultados Parciais)

1. Oliveira DNA; Batista TP; Carneiro VCG; Tancredi R; Badiglian-Filho L; Leão CS. Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of advanced ovarian cancer: the first two cases of a pioneering clinical trial in Brazil. Eur J Surg Oncol. 2015 Oct 15;41 Suppl 1: S199-S203, abstr 029049. DOI: http://dx.doi.org/10.1016/S0748-7983(15)30008-1

Descritivo: Publicação como anais de evento, em periódico de renome na área do estudo. Trata-se do abstract referente ao pôster eletrônico de mesma denominação listado acima.

2. Batista TP; Carneiro VCG; Tancredi R; Badiglian-Filho L; Leão CS. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for treatment of advanced ovarian cancer: reportingthe first cases of a pioneering clinical trial in Brazil. Journal of Peritoneum (and other serosal surfaces). 2016 Nov 17;1(1s):59-67, abstr P402. DOI: https://doi.org/10.4081/joper.2016.48

Descritivo: Publicação como anais de evento, em periódico dedicado a publicações relacionadas a tratamento de enfermidades peritoneais, no qual foi publicado o Abstract Book of the 10th International Congress on Peritoneal Surface Malignancies. Trata-se do abstract referente ao pôster eletrônico de mesma denominação listado acima.

Artigos Publicados (Resultados Parciais)

1. Batista TP, Badiglian Filho L, Leão CS. Exploring flow rate selection in HIPEC procedures. Rev Col Bras Cir. 2016 Dec;43(6):476-479. DOI: https://doi.org/10.1590/0100-69912016006014

Descritivo: Publicação apresentada no corpo da tese.

2. Batista TP, Carneiro VCG, Tancredi R, Teles ALB, Badiglian-Filho L, Leão CS. Neoadjuvant chemotherapy followed by fast-track cytoreductive surgery plus short-course hyperthermic intraperitoneal chemotherapy (HIPEC) in advanced ovarian cancer: preliminary results of a promising all-in-one approach. Cancer Manag Res. 2017 Dec 13;9:869-878. DOI: https://doi.org/10.2147/CMAR.S153327

Descritivo: Publicação apresentada no corpo da tese.

3. Batista TP, Badiglian-Filho L, Baiocchi G. How much "surgical effort" should be added to HIPEC?. Braz J Oncol. 2018;14(48)1-2. DOI: https://doi.org/ 10.26790/BJO20181448A218

Descritivo: Texto publicado após a confecção desta tese, contextualizando nossos resultados preliminares com os resultados do ensaio clínico de fase 3 denominado OVI-HIPEC (Van Driel, et al. N Engl J Med 2018; 378:230-40.).

Outros Artigos do Orientando sobre o Tema (Publicados durante o Curso)

1. Batista TP. Comment on: Surgery and HIPEC in Recurrent Epithelial Ovarian Cancer: A Prospective Randomized Phase III Study. Ann Surg Oncol. 2017 Dec;24(Suppl 3):630. DOI: https://doi.org/10.1245/s10434-017-6151-5

Descritivo: Publicação de carta ao editor, em periódico de renome na área do estudo. Trata-se de comentários e críticas metodológicas direcionados à publicação do primeiro ensaio clinico randomizado explorando o uso de HIPEC em pacientes com câncer de ovário recorrente.

2. Batista TP, Sarmento BJQ, Loureiro JF, Petruzziello A, Lopes A, Santos CC, Quadros CA, Akaishi EH, Cordeiro EZ, Coimbra FJF, Laporte GA, Castro LS, Batista RMSS, Aguiar S Júnior, Costa WL Júnior, Ferreira

FO; on behalf of the BSSO/SBCO Committee on Peritoneal Surface Malignancies and HIPEC. A proposal of Brazilian Society of Surgical Oncology (BSSO/SBCO) for standardizing cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) procedures in Brazil: pseudomixoma peritonei, appendiceal tumors and malignant peritoneal mesothelioma. Rev Col Bras Cir. 2017 Sep-Oct;44(5):530-544. Erratum in: Rev Col Bras Cir. 2017 Nov-Dec;44(6):665. DOI: http://dx.doi.org/10.1590/0100-69912017005016

Descritivo: Publicação de "artigo especial", em periódico de grade abrangência nacional. Trata-se de publicação encabeçada pelo orientando, apresentando a proposta do Comitê de Neoplasias Peritoneais e HIPEC da Sociedade Brasileira de Cirurgia Oncológica (SBCO) para a padronização técnica destes procedimentos no Brasil.

Conferências do Orientando sobre o Tema em Congressos e Simpósios

1. Batista TP. Proposta brasileira de padronização de CRS/HIPEC para tumores do apêndice cecal e mesotelioma peritoneal. XIII Congresso Brasileiro de Cirurgia Oncológica, SBCO – Sociedade Brasileira de Cirurgia Oncológica, 2017, (Hotel Windsor Barra) Rio de Janeiro/RJ.

Descrição: Conferência apresentando a proposta do Comitê de Neoplasias Peritoneais e HIPEC da Sociedade Brasileira de Cirurgia Oncológica (SBCO) para a padronização técnica de procedimentos de CRS/HIPEC para pacientes com neoplasias de apêndice cecal, Pseudomixoma peritonei *e mesotelioma peritoneal maligno.*

2. Batista TP. Estado atual das cirurgias citorredutoras e quimioterapia intraperitoneal hipertérmica (HIPEC). II Simpósio de Oncologia do Hospital de Câncer de Pernambuco, HCP – Hospital de Câncer de Pernambuco, 2016, (Courtyard by Marriott Recife Boa Viagem) Recife/PE.

Descrição: Conferência sobre o estado da arte em CRS/HIPEC.

3. Batista TP. Apresentação da diretriz brasileira de tratamento das metástases peritoneais. II Congresso Norte/Nordeste da Sociedade

Brasileira de Cirurgia Oncológica, SBCO – Sociedade Brasileira de Cirurgia Oncológica, 2016, (Grand Mercure Summerville) Porto de Galinhas/PE.
Descrição: Conferência apresentando a pesquisa realizada entre cirurgiões oncologistas brasileiros para desenvolvimento da proposta do Comitê de Neoplasias Peritoneais e HIPEC da Sociedade Brasileira de Cirurgia Oncológica (SBCO) para a padronização técnica de procedimentos de CRS/HIPEC.

4. Batista TP. HIPEC (quimioterapia intraperitoneal hipertérmica) para tratamento do câncer ovário. XXXI Congresso Brasileiro de Cirurgia, CBC – Colégio Brasileiro de Cirurgiões, 2015, (ExpoUnimed) Curitiba/PR.
Descrição: Conferência sobre o estado da arte de CRS/HIPEC para tratamento do câncer de ovário.