RENAPE
CENTRE NATIONAL DE RÉFÉRENCE DES TUMEURS RARES DU PÉRITOINE

Association pour la Recherche sur le Cancer

FONDATION DE L'AVENIR
Accélérateur de progrès médical

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Strategies to prevent peritoneal carcinomatosis formation

Marc Pocard

Lariboisière hospital Paris France

Surgical Unit / digestive and oncologic

INSERM 965 CART carcinomatosis angiogenesis and translational research – Network RENAPE

Inserm
Institut national de la santé et de la recherche médicale

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Lariboisière Hospital

RENAPE
CENTRE NATIONAL DE RÉFÉRENCE DES TUMEURS RARES DU PÉRITOINE

- An integrated structure for peritoneal disease
  - Diagnostic : new technology – expertise – Radiological examen
  - Treatment: surgery – HIPEC – phases I - PIPAC – Phases III
  - Learning: A national meeting – fellowship
  - Research: Inserm Unit – 5 national clinical research project

- National center for rare peritoneal cancer RENAPE since 2007
- National network for peritoneal cancer : BIG-RENAPE

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Natural history of peritoneal metastasis, in cases of

- Ovarian cancer
- Gastric cancer
- Colon cancer

Risk of secondary peritoneal metastasis

Ovarian : secondary peritoneal metastasis

- 60 % of recurrence after primary treatment
- 10 % of recurrence for stage I
- 30% of recurrence for stage II
- 55% of recurrence for stage III
- Serous type with CA 125 elevated (450 UI)

Australian and New Zealand Journal of Obstetrics and Gynaecology 2016; **56:** 639–647 DOI: 10.1111/ajo.12529

Original Article

Timing and patterns of recurrence in epithelial ovarian cancer patients with no gross residual disease after primary debulking surgery

E Sun PAIK, Yoo-Young LEE, Minhee SHIM, Hyun Jin CHOI, Tae-Joong KIM, Chel Hun CHOI, Jeong-Won LEE, Byoung-Gie KIM and Duk-Soo BAE

Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of M

Ovarian : secondary peritoneal metastasis

Table 2 Characteristics (stage, histology) of recurrent ovarian cancer

		Location of recurrence	
A: Stage	Total (%)	Locoregional (%)	Distant (%)
I-II	28 (100)	13 (46.4)	15 (53.6)
III-IV	60 (100)	10 (16.7)	50 (83.3)
Total (%)		23 (26.1)	65 (73.9)

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Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Se

Ann Surg Oncol (2014) 21:1991–1997
DOI 10.1245/s10434-014-3525-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Surgery-Induced Peritoneal Cancer Cells in Patients Who Have Undergone Curative Gastrectomy for Gastric Cancer

Katsushi Takebayashi, MD[1], Satoshi Murata, MD[1], Hiroshi Yamamoto, MD[1], Mitsuaki Ishida, PhD[2], Tsuyoshi Yamaguchi, MD[1], Masatsugu Kojima, MD[1], Tomoharu Shimizu, MD[1], Hisanori Shiomi, MD[1], Hiromichi Sonoda, MD[1], Shigeyuki Naka, MD[1], Eiji Mekata, MD[1,2], Hidetoshi Okabe, PhD[2], and Tohru Tani, MD[1]

[1]Department of Surgery, Shiga University of Medical Science, Otsu, Japan; [2]Division of Diagnostic Pathology, Shiga University of Medical Science, Otsu, Japan

Surgery-induced peritoneal cancer cells in patients who have undergone curative gastrectomy for gastric cancer. Takebayashi K, et al. Ann Surg Oncol. 2014;21:1991-7.

However, cells detection on peritoneal fluid did not implicated that all patient presented a carcinomatosis during the follow up.

To create a carcinomatosis , peritoneum barrier had to be altered and local condition to be favourable.

But on the study, the 24 patients with viable cancer cells in the peritoneal cavity after gastrectomy showed higher peritoneal recurrence rate than those without them (p=0.033), 45% (n=11/24) versus 9% (n=1/33).

Ann Surg Oncol (2013) 20:183–192
DOI 10.1245/s10434-012-2473-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – COLORECTAL CANCER

Definition of Patients Presenting a High Risk of Developing Peritoneal Carcinomatosis After Curative Surgery for Colorectal Cancer: A Systematic Review

Charles Honoré, MD, Diane Goéré, MD, Amine Souadka, MD, Frédéric Dumont, MD, and Dominique Elias, MD, PhD

TABLE 5 Influence of primary tumor perforation on recurrent PC after a curative resection

Study	Years	*n*	Recurrent PC incidence
Willett et al.[25]	1985	32	19 % (6/32)
Ogawa et al.[26]	2009	13	54 % (7/13)
Cheynel et al.[27]	2009	89	14 % (12/89)
Elias et al.[23]	2011	11	27 % (3/11)

PC peritoneal carcinomatosis

- Perforated tumor
- Isolated ovarian metastasis
- T4
- Mucinous right colon cancer T3

Rational

- Situation that increase the risk of peritoneal metastasis
- Prevention is better than cure
- Best time to treat is the most early
- Do something at the time of first surgery
- Actually proposed solution are based on **HIPEC** for gastric cancer and for colon cancer / including prospective randomized trials
- But HIPEC is a restricted solution in specific center

Rational

- Situation that increase the risk of peritoneal metastasis
- Prevention is better than cure
- Best time to treat is the most early
- Do something at the time of first surgery

- **Instillation in the abdominal cavity AFTER surgery of a solution able to decrease the risk AND safe**

Property of the best carrier Solution

- Extend the residence time of the drug in peritoneum
- Affect tumor cell survival

- No toxicity (nephro and hepato toxicities)
- Stable solution (can stay a long time in operative room)
- No pain induce in the postoperative course

- Risk of fistula or abscess controlled

Studied Carrier Solution

- Icodextrin
- Dextran
- Hydrogel
- Thermo sensible hydrogel
- Gelatine
- Gelatine with nanoparticles

- Decreasing cell adhesion it could decrease cancer cell survival and/or cancer cell migration

Icodextrin : in human / 20 years ago

British Journal of Cancer (1996) 74, 2032–2035

Prolonged intraperitoneal infusion of 5-fluorouracil using a novel carrier solution

DJ Kerr[1], AM Young[1], JP Neoptolemos[2], M Sherman[1], P Van-Geene[3], A Stanley[1], D Ferry[1], JW Dobbie[4], B Vincke[4], J Gilbert[4], D El Eini[4], N Dombros[5] and G Fountzilas[5]

[1]CRC Institute for Cancer Studies, Clinical Research Block, University of Birmingham, Birmingham B15 2TH; [2]Department of Surgery, Queen Elizabeth Hospital, Birmingham, B15 2TH; [3]Department of Obstetrics and Gynaecology, City Hospital NHS Trust, Dudley Road, Birmingham B18 7QH, UK; [4]Baxter R and D Europe, Nivelles, Belgium; [5]First Department of Internal Medicine, AHEPA University Hospital, Thessaloniki, Greece.

Br. J. Cancer (1994), **70**, 762–766

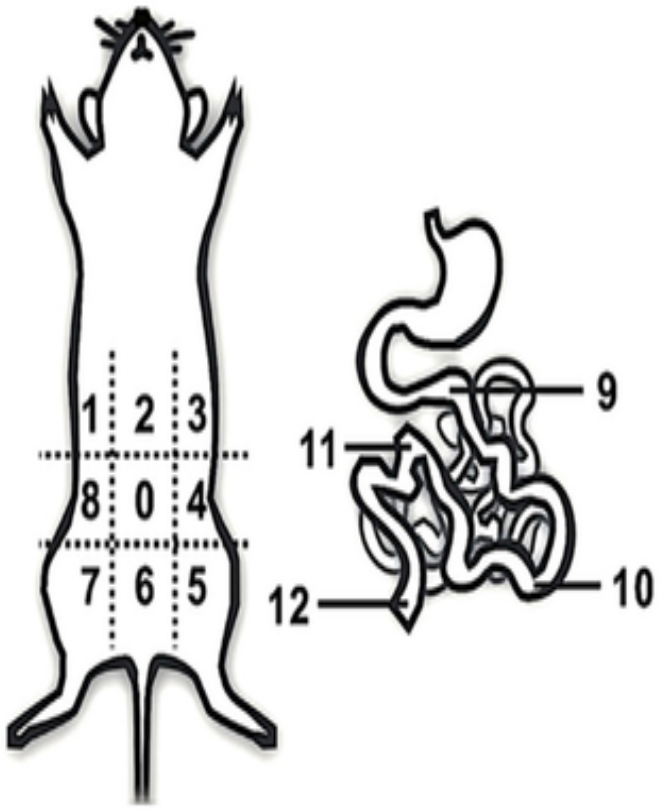
1994

Pharmacokinetic study of 5-fluorouracil in a novel dialysate solution: a long-term intraperitoneal treatment approach for advanced colorectal carcinoma

C.S. McArdle[1], D.J. Kerr[1], P. O'Gorman[1], H.A. Wotherspoon[1], H. Warren[1], D. Watson[2], B.J. Vinké[3], J.W. Dobbie[3] & D.I.D. El Eini[3]

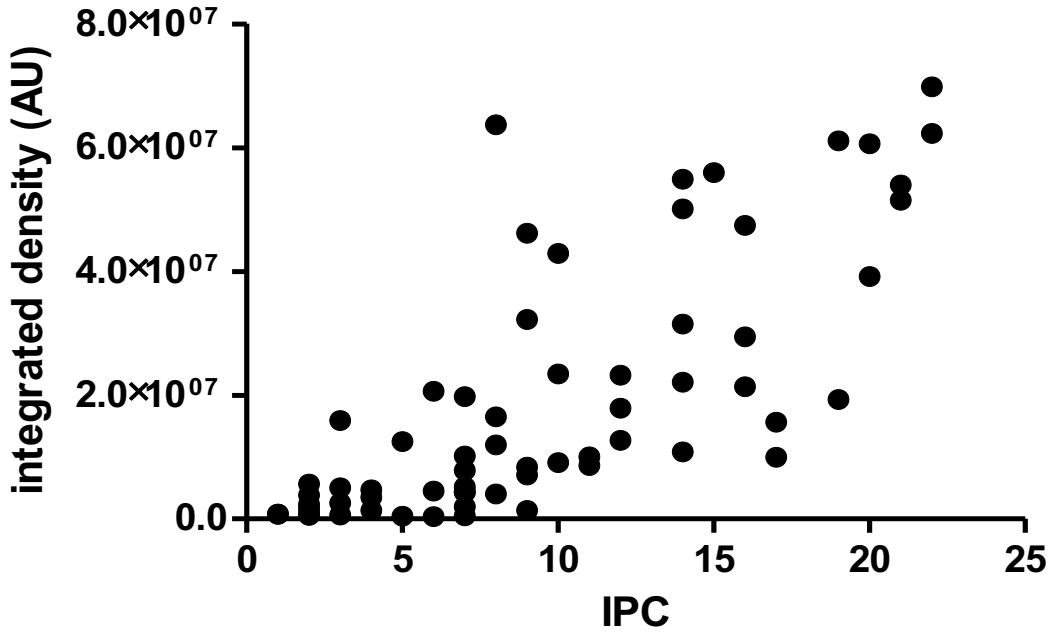
[1]University Department of Surgery, Glasgow Royal Infirmary, Glasgow, UK; [2]Department of Pharmacy, Strathclyde University, Glasgow, UK; [3]Baxter R&D Europe, Nivelles, Belgium.

Mimic the human PCI score index

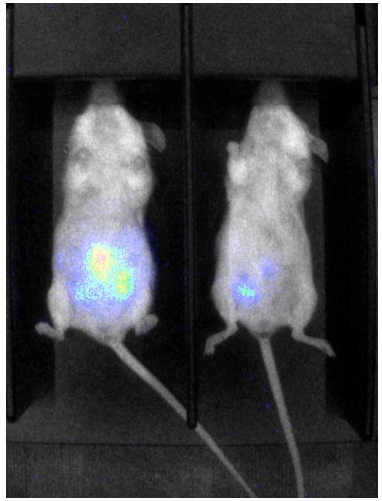


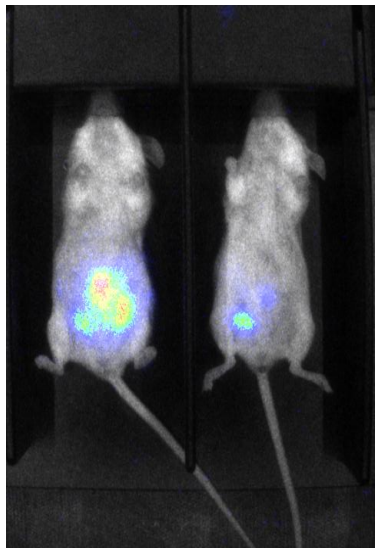
		Score	Tumor size
0	Central abdomen		
1	Right upper quadrant		
2	Epigastric region	0	no macroscopic lesion
3	Left upper quadrant		
4	Left middle quadrant	1	Lesion from 1 to 2 mm,
5	Left lower quadrant		1 to 2 sites
6	Pubic region		
7	Right lower quadrant	2	Lesion from 2 to 4 mm,
8	Right middle quadrant		1 to 2 sites
9	Proximal jejunum		
10	Distal jejunum	3	lesion over 4 mm
11	Proximal ileum		or more than 10 sites
12	Distal ileum		

Correlation regarding PCI and bioluminescence



Number of XY Pairs	64
Spearman r	0.7823
95% confidence interval	0.6601 to 0.8642
P value (two-tailed)	< 0.0001
P value summary	***
Exact or approximate P value?	Gaussian Approximation
Is the correlation significant? (alpha=0.05)	Yes





Reduction of carcinomatosis risk using icodextrin as a carrier solution of intraperitoneal oxaliplatin chemotherapy.

- Icodextrin 4% (ICDX), presently used to prevent postoperative abdominal adhesions, could inhibit the coactivation of the tumor cells and the microenvironment cells, associated with the development of Peritoneal Carcinomatosis

- The aim of this study was to inhibit the formation of the Peritoneal carcinomatosis in a murine model mimicking surgical situation using ICDX and intraperitoneal (IP) prophylactic chemotherapy.

Reduction of carcinomatosis risk using icodextrin as a carrier solution of intraperitoneal oxaliplatin chemotherapy.

- We created a model of growing Peritoneal carcinomatosis in mice using
- cells of murine colonic cancer CT26.
- Cells and treatments were injected simultaneously.
- Five groups were created: CT26 (control group), CT26 + ICDX (ICDX group), CT26 + chemotherapy (oxaliplatin and 5FU) (chemo group), CT26 + chemotherapy + ICDX (ICDX chemo group)
- At day 15, PC was evaluated with rodents PCI.

Reduction of carcinomatosis risk using icodextrin as a carrier solution of intraperitoneal oxaliplatin chemotherapy

I. Jouvin [a,b], H. Najah [a,b], C. Pimpie [b], C. Canet Jourdan [b], R. Kaci [c], M. Mirshahi [b], C. Eveno [a,b], M. Pocard [a,b,*]

[a] *Department of Oncologic & Digestive Surgery, Hospital Lariboisière – AP-HP, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France*

[b] *Université Paris Diderot, Sorbonne Paris Cité, CART, Carcinomatosis Angiogenesis Translational Research, INSERM U965, F-74575 Paris, France*

[c] *Department of Anatomopathology, Hôpital Lariboisière – AP-HP, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France*

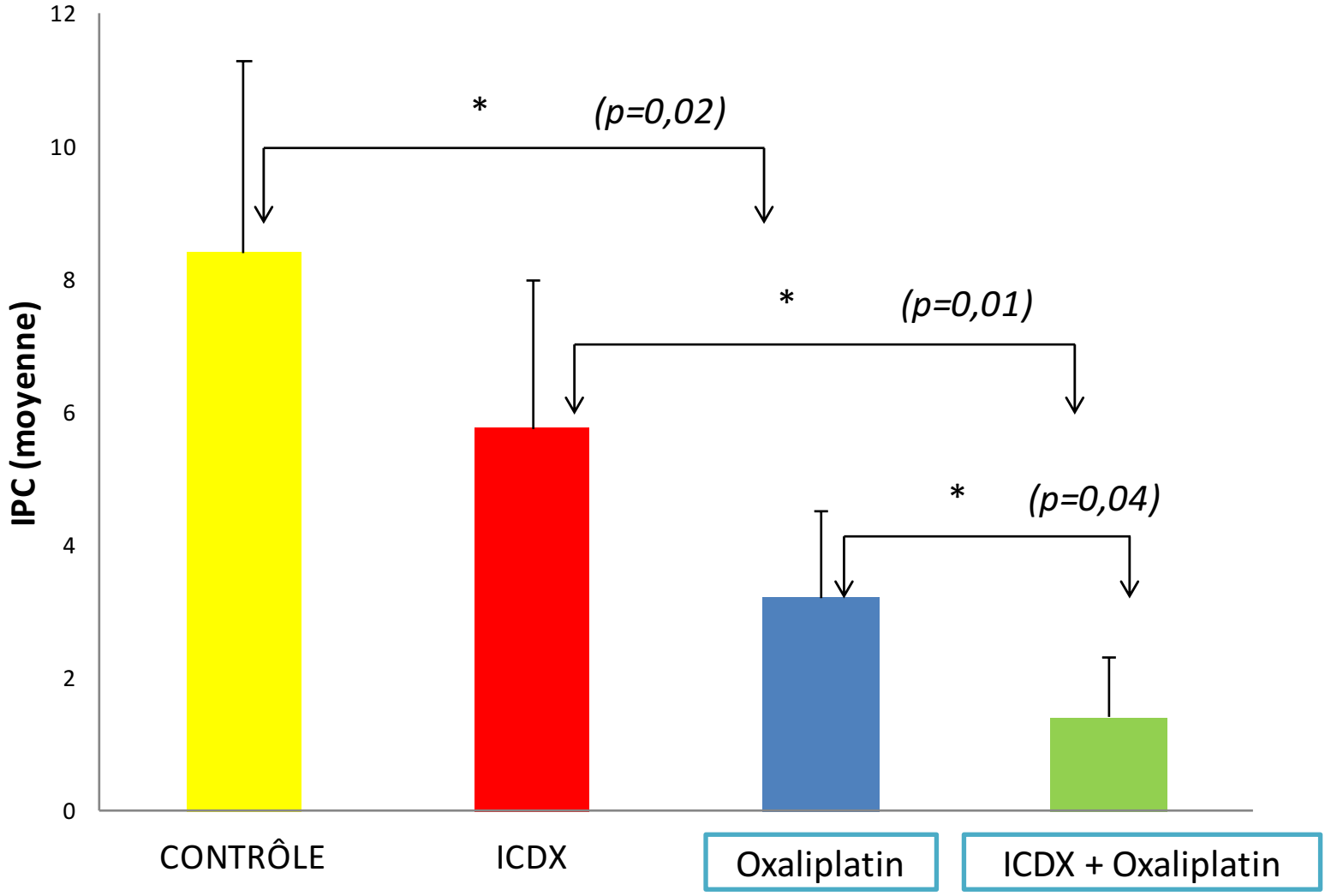
EJSO
the Journal of Cancer Surgery

Eur J Surg Oncol. 2017 Jan 9.
pii: S0748-7983(17)30036-7.

Reduction of carcinomatosis risk using icodextrin as a carrier solution of intraperitoneal oxaliplatin chemotherapy.

	Control group (n = 5)	ICDX group (n = 4)	Chemo group (n = 5)	ICDX Chemo group (n = 5)
Mouse 1	11	5	5	3
Mouse 2	7	9	4	1
Mouse 3	4	5	2	1
Mouse 4	10	4	3	1
Mouse 5	10	x	2	1
Mean PCI (SD)	8,4 (2,9)	5,75 (2,2)	3,2 (1,3)	1,4 (0,9)

PCI comparison at day 15 for the different groups, after CT26 cells induced carcinomatosis.



Cancer Chemother Pharmacol (2014) 73:1009–1020
DOI 10.1007/s00280-014-2436-6

ORIGINAL ARTICLE

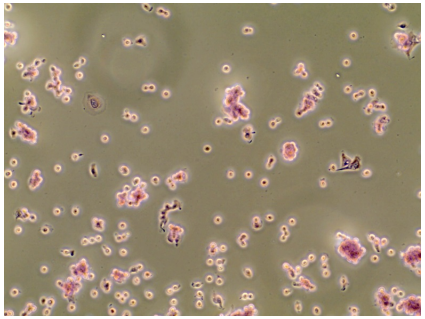
Rate and extent of oxaliplatin absorption after hyperthermic intraperitoneal administration in peritoneal carcinomatosis patients

Carlos Pérez-Ruixo · José E. Peris · Vanesa Escudero-Ortiz · Pedro Bretcha-Boix · José Farré-Alegre · Juan José Pérez-Ruixo · Belén Valenzuela

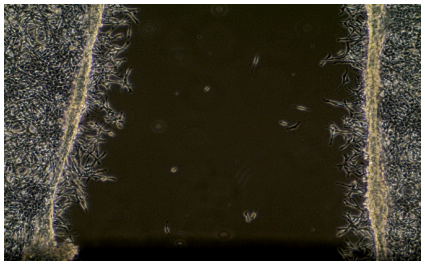
(NONMEM VII software). The effect of carrier solution (icodextrin 4 % vs. dextrose 5 %) and selected patient covariates on oxaliplatin pharmacokinetics was investigated. Model evaluation was performed using predictive

Icodextrin as other anti adherence solution

- Decrease the cell-cell adhesion
- Yes



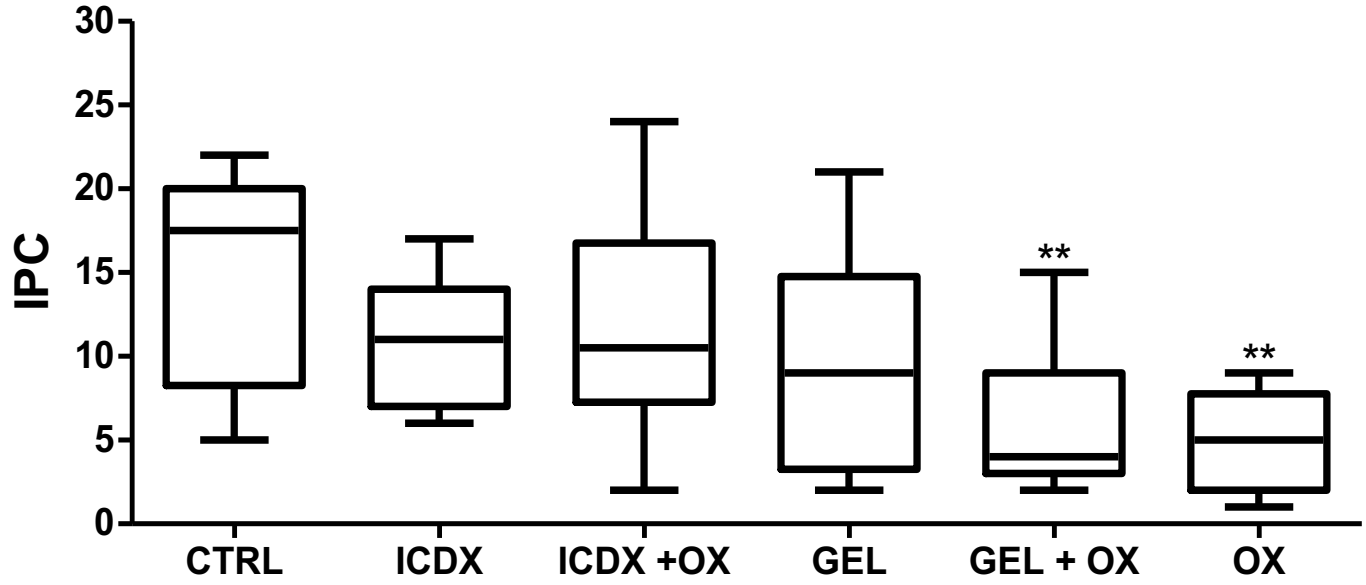
- Decrease the cell migration
- No



4% icodextrin solution reduces the inflammatory and mesenchymal infiltrate in the wounded area, thus improving the ratio of mesothel cells to mesenchymal infiltrate

(1) Klink et al., BMC surgery, 2013

Testing a new carrier solution : thermo gel



CT 26 murin colon cancer cell line

BUT
15% of death with mice ?

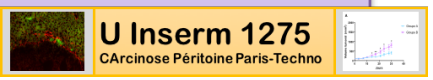
Property of the best chemotherapy

- Efficient for **every peritoneal carcinomatosis**

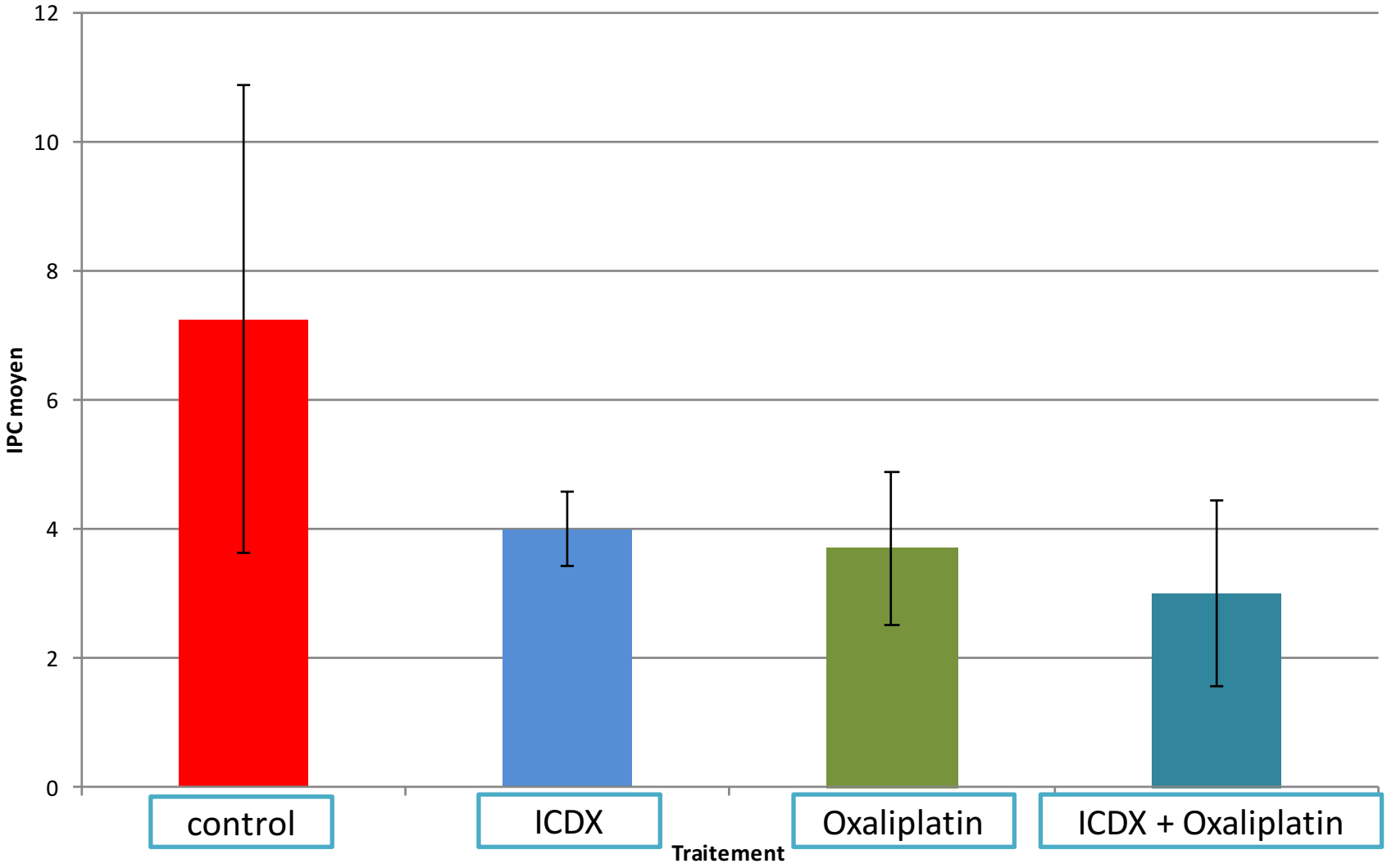
- No toxicity (nephro and hepato toxicicties)
- Stable solution (can stay in operative room)
- No pain induce in the postoperative course

- Risk of fistula or abscess controlled

Cisplatin Paclitaxel Doxorobicin
Taxol Mitomycin 5-FU



PCI comparison at day 15 for the different groups, after OVCAR cells induced carcinomatosis.



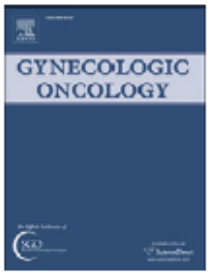
Another carrier solution

Gynecologic Oncology 122 (2011) 632–640

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



Intraperitoneal administration of novel doxorubicin loaded polymeric delivery systems against peritoneal carcinomatosis: Experimental study in a murine model of ovarian cancer

Pierre-Emmanuel Colombo [a,b,*], Mahfoud Boustta [b], Sylvain Poujol [c], Marta Jarlier [d], Françoise Bressolle [c,e], Isabelle Teulon [f], Maha-Zohra Ladjemi [f], Frederic Pinguet [c], Philippe Rouanet [a], Michel Vert [b]

Pleura and Peritoneum 2016; 1(4): 183–191

Review

Michael F. Flessner*

Pharmacokinetic problems in peritoneal drug administration: an update after 20 years

Area of contact

Penetration of intraperitoneally delivered agent

Review Article

Optimization of Drug Delivery Systems for Intraperitoneal Therapy to Extend the Residence Time of the Chemotherapeutic Agent

L. De Smet,[1] W. Ceelen,[2] J. P. Remon,[1] and C. Vervaet[1]

[1] *Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, 9000 Ghent, Belgium*
[2] *Laboratory of Experimental Surgery, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium*

Correspondence should be addressed to C. Vervaet; chris.vervaet@ugent.be

Table 1: Water solubility, the partition coefficient (log *P*), and peritoneal to plasma drug area under the curve (AUC) ratio of intraperitoneal chemotherapeutic agents.

Chemotherapeutic agent	Molecular weight	Water solubility	log *P*	Peritoneal to plasma AUC ratio
Cisplatin	300	Good	−2.19	12
Carboplatin	371	Good	1.06	10–18
Oxaliplatin	397	Good	1.73	16
Paclitaxel	854	Poor	3.54	1000
Docetaxel	862	Poor	2.92	181
5-Fluorouracil	130	Sparing	-0.89	367
Doxorubicin	544	Poor	1.27	474

Table 2: Advantages and disadvantages of the drug delivery systems investigated for IP therapy.

Drug delivery system	Advantages	Disadvantages
Microspheres	Prolonged retention time	Limited tumor penetration Risk of peritoneal adhesions
Nanoparticles	Small size passive targeting Avoiding MDR Lower incidence of peritoneal adhesions	Rapid clearance out of the abdominal cavity
Liposomes	Similar to nanoparticles Active targeting by varying parameters	Similar to nanoparticles
Micelles	Prolonged retention time	Increasing systemic toxicity
Injectable systems	Prolonged retention time Localized and sustained drug delivery Lower systemic toxicity Prevention against peritoneal adhesion	Viscosity issues
Implantable systems	Similar to injectable systems	Invasive Surgical expertise

Reduction of carcinomatosis risk using icodextrin as a carrier solution of intraperitoneal chemotherapy.

- This prophylactic treatment is easy to use and would be administrated at the end of a curative surgery for
- a colonic cancer. A gastric cancer = oxaliplatin
- An ovarian cancer / another chemotherapy ?
- Another carrier solution ?
- The chemotherapy drug concentration ?

- Your opinion interested **me**