European Journal of Cancer 65 (2016) 69–79

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Diffuse malignant peritoneal mesothelioma: Evaluation of systemic chemotherapy with comprehensive treatment through the RENAPE Database Multi-Institutional Retrospective Study☆

V. Kepenekian [a], D. Elias [b], G. Passot [a], E. Mery [c], D. Goere [b], D. Delroeux [d], F. Quenet [e], G. Ferron [f], D. Pezet [g], J.M. Guilloit [h], P. Meeus [i], M. Pocard [j], J.M. Bereder [k], K. Abboud [l], C. Arvieux [m], C. Brigand [n], F. Marchal [o], J.M. Classe [p], G. Lorimier [q], C. De Chaisemartin [r], F. Guyon [s], P. Mariani [t], P. Ortega-Deballon [u], S. Isaac [v], C. Maurice [w], F.N. Gilly [a], O. Glehen [a,*], on behalf of the French Network for Rare Peritoneal Malignancies (RENAPE)[l]

[a] *Department of Digestive Surgery, Lyon-Sud University Hospital, EMR 3738, Lyon 1 University, Lyon, France*
[b] *Department of Surgical Oncology, Gustave Roussy, Cancer Campus, Grand Paris, France*
[c] *Department of Pathology, IUCT, Toulouse, France*
[d] *Department of Digestive Surgery, Jean Minjoz University Hospital, Besançon, France*
[e] *Department of Surgical Oncology, Val d'Aurelle Montpellier Cancer Institute, Montpellier, France*
[f] *Department of Surgical Oncology, Claudius Regaud Institute – IUCT, Toulouse, France*
[g] *Department of Digestive Surgery, Estaing University Hospital, Clermont-Ferrand, France*
[h] *Department of Surgical Oncology, Francois Baclesse Comprehensive Cancer Center, Caen, France*
[i] *Department of Surgery, Léon Bérard Comprehensive Cancer Center, Lyon, France*
[j] *Surgical Oncologic & Digestive Unit, Lariboisière University Hospital, INSERM, U 965, Paris, France*
[k] *Department of General Surgery and Gastrointestinal Oncology, Archet 2 University Hospital, Nice, France*
[l] *Department of Digestive Surgery, University Hospital of Saint Etienne, Saint Etienne, France*
[m] *Department of Digestive Surgery, Michallon University Hospital, Grenoble, France*
[n] *Department of General Surgery, Hautepierre University Hospital, Strasbourg, France*
[o] *Department of Surgical Oncology, Lorraine Institute of Oncology, Vandoeuvre-les-Nancy, France*
[p] *Department of Surgical Oncology, René Gauducheau Integrated Center of Oncology, Nantes, France*
[q] *Department of Surgical Oncology, Paul Papin Integrated Center of Oncology, Angers, France*
[r] *Department of Surgical Oncology, Paoli-Calmettes Institute, Marseille, France*
[s] *Department of Surgical Oncology, Bergonie Institute, Bordeaux, France*
[t] *Department of Surgical Oncology, Curie Institute, Paris, France*
[u] *Department of Digestive Surgical Oncology, University Hospital of Dijon, Dijon, France*

☆ This study was presented at the iMig 2014 (International Mesothelioma Interest Group) meeting in Cape Town, South Africa, October 22, 2014.

* *Corresponding author:* Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Service de Chirurgie Digestive et Oncologique, Chemin du Grand Revoyet, 69495, Pierre-Bénite, France. Fax: +33 (0) 4 72 66 64 95.
E-mail address: olivier.glehen@chu-lyon.fr (O. Glehen).

http://dx.doi.org/10.1016/j.ejca.2016.06.002

[v] *Department of Pathology, Lyon-Sud University Hospital, Lyon, France*
[w] *Clinical Research Unit, Pôle IMER (Information Médicale Evaluation et Recherche), Hospices Civils de Lyon, Lyon, France*

Received 24 March 2016; received in revised form 26 May 2016; accepted 1 June 2016
Available online 26 July 2016

KEYWORDS
Peritoneal mesothelioma;
Cytoreductive surgery;
Hyperthermic intraperitoneal chemotherapy;
Systemic chemotherapy

Abstract ***Purpose:*** Diffuse malignant peritoneal mesothelioma (DMPM) is a severe disease with mainly locoregional evolution. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is the reported treatment with the longest survival. The aim of this study was to evaluate the impact of perioperative systemic chemotherapy strategies on survival and postoperative outcomes in patients with DMPM treated with curative intent with CRS-HIPEC, using a multi-institutional database: the French RENAPE network.
Patients and methods: From 1991 to 2014, 126 DMPM patients underwent CRS-HIPEC at 20 tertiary centres. The population was divided into four groups according to perioperative treatment: only neoadjuvant chemotherapy (NA), only adjuvant chemotherapy (ADJ), perioperative chemotherapy (PO) and no chemotherapy before or after CRS-HIPEC (NoC).
Results: All groups (NA: n = 42; ADJ: n = 16; PO: n = 16; NoC: n = 48) were comparable regarding clinicopathological data and main DMPM prognostic factors. After a median follow-up of 61 months, the 5-year overall survival (OS) was 40%, 67%, 62% and 56% in NA, ADJ, PO and NoC groups, respectively ($P = 0.049$). Major complications occurred for 41%, 45%, 35% and 41% of patients from NA, ADJ, PO and NoC groups, respectively ($P = 0.299$). In multivariate analysis, NA was independently associated with worse OS (hazard ratio, 2.30; 95% confidence interval, 1.07–4.94; $P = 0.033$).
Conclusion: This retrospective study suggests that adjuvant chemotherapy may delay recurrence and improve survival and that NA may impact negatively the survival for patients with DMPM who underwent CRS-HIPEC with curative intent. Upfront CRS and HIPEC should be considered when achievable, waiting for stronger level of scientific evidence.

[1] **French Network for Rare Peritoneal Malignancies (RENAPE):** G. Averous, Department of Pathology, Hautepierre University Hospital, Strasbourg, France; J. M. Bereder, Department of General Surgery and Gastrointestinal Oncology, Archet 2 University Hospital, Nice, France; F. Bibeau, Department of Pathology, Val d'Aurelle Montpellier Cancer Institute, Montpellier, France; D. Bouzard, Department of Surgery, Louis Mourier University Hospital, Colombes, France; A. Chevallier, Department of Pathology, Archet 2 University Hospital, Nice, France; S. Croce, Department of Pathology, Bergonie Institute, Bordeaux, France; P. Dartigues, Department of Pathology, Gustave Roussy Institute, Villejuif, France; S. Durand-Fontanier, Department of Visceral Surgery and Transplantation, Dupuytren University Hospital, Limoges, France; L. Gouthi, Department of Digestive Surgery, Purpan University Hospital, Toulouse, France; B. Heyd, Department of Digestive Surgery, Jean Minjoz University Hospital, Besançon, France; R. Kaci, Department of Pathology, Lariboisière University Hospital, Paris, France; R. Kianmanesh, Department of Digestive Surgery, Robert Debré University Hospital, Reims, France; M. H. Laverrière, Department of Pathology, Michallon University Hospital, Grenoble, France; E. Leblanc, Department of Gynaecological Surgery, Centre Oscar Lambret, Lille, France; B. Lelong, Department of Surgical Oncology, Paoli-Calmettes Institute, Marseille, France; A. Leroux, Department of Pathology, Lorraine Institute of Oncology, Vandoeuvre-les-Nancy, France; V. Loi, Department of Digestive Surgery, Tenon University Hospital, Paris, France; C. Mariette, Department of Digestive and Oncological Surgery, Claude-Huriez University Hospital, Lille, France; P. Meeus, Department of Surgery, Léon Bérard Comprehensive Cancer Center, Lyon, France; S. Msika, Department of Surgery, Louis Mourier University Hospital, Colombes, France; D. Pezet, Department of Digestive Surgery, Estaing University Hospital, Clermont-Ferrand, France; P. Peyrat, Department of Surgery, Léon Bérard Comprehensive Cancer Center, Lyon, France; N. Pirro, Department of Digestive Surgery, Timône University Hospital, Marseille, France; J. Paineau, Department of Surgical Oncology, René Gauducheau Integrated Center of Oncology, Nantes, France; F. Poizat, Department of Pathology, Paoli-Calmettes Institute, Marseille, France; J. Porcheron, Department of Digestive Surgery, University Hospital of Saint Etienne, Saint Etienne, France; F. Quenet, Department of Surgical Oncology Val d'Aurelle Montpellier Cancer Institute, Montpellier, France; P. Rat, Department of Digestive Surgical Oncology, University Hospital of Dijon, Dijon, France; J. M. Regimbeau, Department of Digestive Surgery, University Hospital of Amiens, Amiens, France; E. Thibaudeau, Department of Surgical Oncology, René Gauducheau Integrated Center of Oncology, Nantes, France; J. J. Tuech, Department of Digestive Surgery, Charles Nicolle University Hospital, Rouen, France; S. Valmary-Degano, Department of Pathology, Jean Minjoz University Hospital, Besançon, France; V. Verriele, Department of Pathology, Paul Papin Integrated Center of Oncology, Angers, France; P. Zerbib, Department of Digestive and Oncological Surgery, Claude-Huriez University Hospital, Lille, France; F. Zinzindohoue, Department of Digestive and General Surgery, G. Pompidou European Hospital, Paris, France.

1. Introduction

In 1908, Miller and Wynn [1] first described diffuse malignant peritoneal mesothelioma (DMPM). DMPM arises from the cell lining of the peritoneum and is characterised by thousands of tumour nodules that may coalesce to cover the entire peritoneal surface. Asbestos exposure may cause DMPM and the pleural forms of the disease [2]. Other risk factors are suspected, but evidence lack, thereby meaning that the pathogenesis remains largely unknown [3]. With fewer than two cases per million per year in industrialised countries, DMPM represents a quarter of all mesothelioma cases and is a highly aggressive disease [3–5]. Evolution of DMPM is almost exclusively locoregional and patients usually die from intestinal obstruction or terminal starvation [6]. Without dedicated treatment, death occurs within 6–12 months [7].

In contrast with pleural mesothelioma, systemic chemotherapy has not been shown to significantly improve patients' prognosis. Among the best regimens, the combination of the multitargeted antifolate pemetrexed and a platinum agent is associated with limited improvement in overall survival (OS) [8–10]. Locoregional therapies, as intraperitoneal chemotherapy (IPC) or radiation, had shown promising results [11,12]. With the development of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), survival increases up to 50 months, for selected patients [13,14]. Over the last decades, three major steps contributed to improve the management of DMPM. First, pathological diagnosis now includes a clear referential with well-defined histological types (epithelioid, sarcomatoid and biphasic), whereas a difficult differential diagnosis can be resolved at expert centres [15,16]. Multicystic and well-differentiated papillary mesotheliomas are considered border-line types characterised by far better prognoses despite high recurrence rates [17]. Secondarily, an international, retrospective, multicentric study defined pathological type, completeness of cytoreduction score (CC-score) and lymph node metastasis status as the main prognostic factors after CRS-HIPEC [13]. Finally, the DMPM TNM staging system definition strongly correlated with survival [18] is used as a rational basis for future comparable studies.

For treatment with curative intent, systemic chemotherapy is commonly used in association with CRS-HIPEC, either to downstage the disease or to consolidate the surgical result. However, there is no strong evidence whether systemic chemotherapy should be performed and when. Most of the reported data were extrapolated from studies performed in pleural mesotheliomas [5,10,19]. The few studies available in DMPM patients were done in non-operable patients without randomisation [8,9,20]. Only one study retrospectively assessed the role of perioperative chemotherapy (PO) and no significant survival differences were identified between groups [21]. Nevertheless systemic chemotherapy role as a part of a DMPM curative therapeutic strategy warrants further assessment.

The goal of this study was to evaluate the impact of systemic chemotherapy in combination with CRS-HIPEC on overall and progression-free survivals for DMPM patients treated with curative intent. As secondary end-point we assessed the association between postoperative results and chemotherapy protocol. The French national network database of rare peritoneal surface malignancies (RENAPE database) was used [22].

2. Patients and methods

2.1. Study population – RENAPE database

Data for the present analysis were collected from the RENAPE database, which is the French national network database, including 20 peritoneal surface malignancies (PSM) referral centres. A standard data form was created to retrieve relevant information on clinical, histological and treatment-related data. All included patients were treated according to protocols approved by the respective institutional ethics committees, in accordance with the precepts established by the Helsinki declaration.

All patients who underwent CRS, with or without IPC, for DMPM pathologically confirmed were included. Multicystic mesothelioma, well-differentiated papillary peritoneal mesothelioma, peritoneal spread from primary pleural mesothelioma and unknown histological types were excluded. Patients aged >80 years, or with Eastern Cooperative Oncology Group [23] performance status > 2, or presenting extraperitoneal metastases were excluded.

2.2. Systemic chemotherapy

Systemic chemotherapy strategy and regimen were determined in multidisciplinary team (MDT) meeting, expert in PSM, according to patient medical history, spread of disease, main DMPM prognostic factors and centre's treatment policy. All failure to complete the treatment strategy planned in MDT was recorded.

Neoadjuvant chemotherapy was defined as a systemic chemotherapy set before surgery with the last cure within 3 months before CRS. Adjuvant chemotherapy (ADJ) was defined as a systemic chemotherapy started within 3 months following CRS, and PO was defined as a systemic chemotherapy performed before and after CRS. We analysed type of drugs and number of cycles performed.

2.3. Operative treatment

The volume and extent of tumour deposits were recorded using the peritoneal cancer index (PCI) [24].

Peritonectomy was performed at the sites of disease involvement with the intent of removing nodules together with involved peritoneum. CRS was performed according to techniques described by Sugarbaker [25]. Residual disease after CRS was recorded using the completeness of using the completeness of cytoreduction score (CC-score) [24]. All centres shared two major concepts in PSM treatment strategies: CRS to remove macroscopic disease, and IPC delivered thereafter, usually heated (HIPEC), to eradicate residual microscopic disease.

HIPEC was conducted with either an open or closed abdomen technique, with a common intraabdominal target temperature of 42 °C–43 °C. The duration was 30, 60 or 90 min depending on the drug used intraperitoneally. The main chemotherapy regimens used intraperitoneally were: cisplatin (25 mg/m^2/l) with mitomycin C (3.3 mg/m^2/l) or doxorubicin (15.25 mg/l of perfusate); and oxaliplatin alone (460 mg/m^2) or combined with irinotecan (360 mg/m^2 for both). When early postoperative intraperitoneal chemotherapy (EPIC) was proposed, it was performed during the first five postoperative days, with either mitomycin C (10 mg/m^2) or paclitaxel (20 mg/m^2).

Postoperative complications were evaluated within 90 days after surgery and graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events. Major complications of grade III (severe adverse event), IV (life-threatening adverse event), and V (fatal adverse event) were analysed [26]. We also analysed whether preoperative chemotherapy impacts postoperative major complications.

The postoperative follow-up included: physical examination, thoracic/abdominal computed tomgraphy scan (CT-scan) and marker measurements every 3 months during the first 2 years, then every 6 months for 3 years and annually thereafter. Recurrent disease or progression was confirmed pathologically.

2.4. Statistical considerations

We assessed long-term and postoperative outcomes in patients receiving neoadjuvant, adjuvant, perioperative or no chemotherapy. We also tested whether patients receiving NA (versus those receiving only adjuvant or receiving no chemotherapy) had different oncological and postoperative outcomes.

The analysis was performed on intent-to-treat basis and postoperative deaths were included in the overall survival (OS) analysis. OS and progression-free survival (PFS), determined from the time of diagnosis to death or progression, respectively, were used as primary endpoints. Survival curves were created using the Kaplan–Meier method and were compared using the log-rank test. Univariate and multivariate Cox proportional hazards models were adjusted for centre. For multivariate analysis, a forward stepwise selection of covariates and entering and removing limits of $P < 0.20$ and $P > 0.05$ was used. All statistical analyses were performed with SAS (version 9.2, North Carolina). A significant difference was defined as $P < 0.05$.

3. Results

3.1. Patient characteristics

Among 1617 patients registered in RENAPE database between October 1991 and April 2014, 228 presented with DMPM, and 126 of them underwent CRS: 114 underwent CRS-HIPEC, 9 CRS alone, 2 CRS-EPIC and 1 CRS-HIPEC-EPIC (Fig. 1).

The population was divided into four groups according to perioperative treatment performed: NA only (NA; n = 42), adjuvant chemotherapy only (ADJ; n = 16), PO (PO; n = 20) and no perioperative systemic chemotherapy (NoC; n = 48). There were no significant differences regarding clinicopathological data between chemotherapy groups, notably in peritoneal treatment, types of HIPEC and main DMPM prognostic factors (Table 2).

3.2. Systemic chemotherapy

For patient who underwent systemic chemotherapy, pemetrexed-based regimens were used in 60%, 64% and 50% patients of the NA, ADJ and PO groups, respectively, whereas gemcitabine-based regimens were used for 12%, 13% and 25% of cases, respectively (Table 1).

In PO group, the median number of preoperative and postoperative cycles was 3.5 (range, 2–20) and 6 (range, 3–8), respectively. It was 6 (range, 1–17) and 6 (range, 3–9) in NA and ADJ groups, respectively. According to MDT report, 6 patients (16%) in NA group and 7 patients (15%) in NoC group did not have the postoperative chemotherapy planned in MDT meeting.

3.3. Survival

With a median follow-up of 61 months (range, 52–69 months), 5-year OS and PFS rates were, for the all patients, 53% and 28%, respectively, with a median OS and PFS of 61 and 17 months, respectively.

The 5-year OS was 40%, 67%, 62% and 56%, and the median OS was 37, 82, not reached, and 71 months for NA, ADJ, PO and NoC groups respectively ($P = 0.049$; Fig. 2A; Table 3). Univariate analysis identified four significant prognostic variables associated with improved OS: PCI $\leq$30 ($P = 0.007$), American Society of Anesthesiologists (ASA) score ≤ 2 ($P = 0.006$), CC-0/1 score ($P = 0.021$), and the absence of NA ($P = 0.021$; Table 4). The only factor independently associated with improved OS in multivariate analysis was the absence of NA (hazard ratio [HR], 2.297; 95% confidence interval [CI], 1.068–4.943; $P = 0.033$; Table 4).

The 5-year PFS rates were 41%, 67%, 65%, and 58%, and the median PFS were 11, 78, 27, 13 months, in NA, ADJ, PO and NoC groups, respectively (Fig. 2B; Table 3). Univariate analysis identified younger age ($P = 0.015$), PCI ≤ 30 ($P = 0.007$), CC-0/1 score ($P < 0.001$), treatment period after 2005 ($P = 0.030$) and administration of adjuvant chemotherapy ($P = 0.006$) as variables associated with improved PFS (Table 4). The assignment to a treatment group was also associated with PFS: favourably for PO group, unfavourably for NA and NoC groups. The only factor independently associated with improved PFS in multivariate analysis was CC-0/1 score (HR, 7.719; 95% CI, 3.539–16.835; $P < 0.0001$; Table 4).

3.4. Postoperative results

Within 90 d after CRS, 49 patients (39%) experienced major postoperative complications (grade III–IV) and four died (3%). Major complications occurred in 39%, 35%, 44% and 40% in NA, PO, ADJ and NoC groups, respectively ($P = .877$; Table 2). Grade III–IV complications occurred in 39% of patients with preoperative chemotherapy and 42% of those without preoperative chemotherapy ($P = 0.963$). Mortality rates were 5%, 0%, 0% and 4% in NA, PO, ADJ, and NoC groups, respectively ($P = 0.299$; Table 2).

4. Discussion

This large DMPM cohort analysis highlights some differences in survival regarding the type of perioperative treatment in combination with CRS-HIPEC. The NA group experienced the worse survival results and this result was not related to an increase of major postoperative complications. On the other hand, patients treated with postoperative chemotherapy showed a better survival with delayed recurrence, suggesting that systemic chemotherapy is more effective with a lower tumour burden in DMPM patients treated with curative intent.

The only factor independently associated with improved OS in multivariate analysis is absence of NA (HR, 2.297; 95% CI, 1.1–4.9). The NA group is heterogeneous in many points. First, prechemotherapy disease severity is not precisely evaluated because

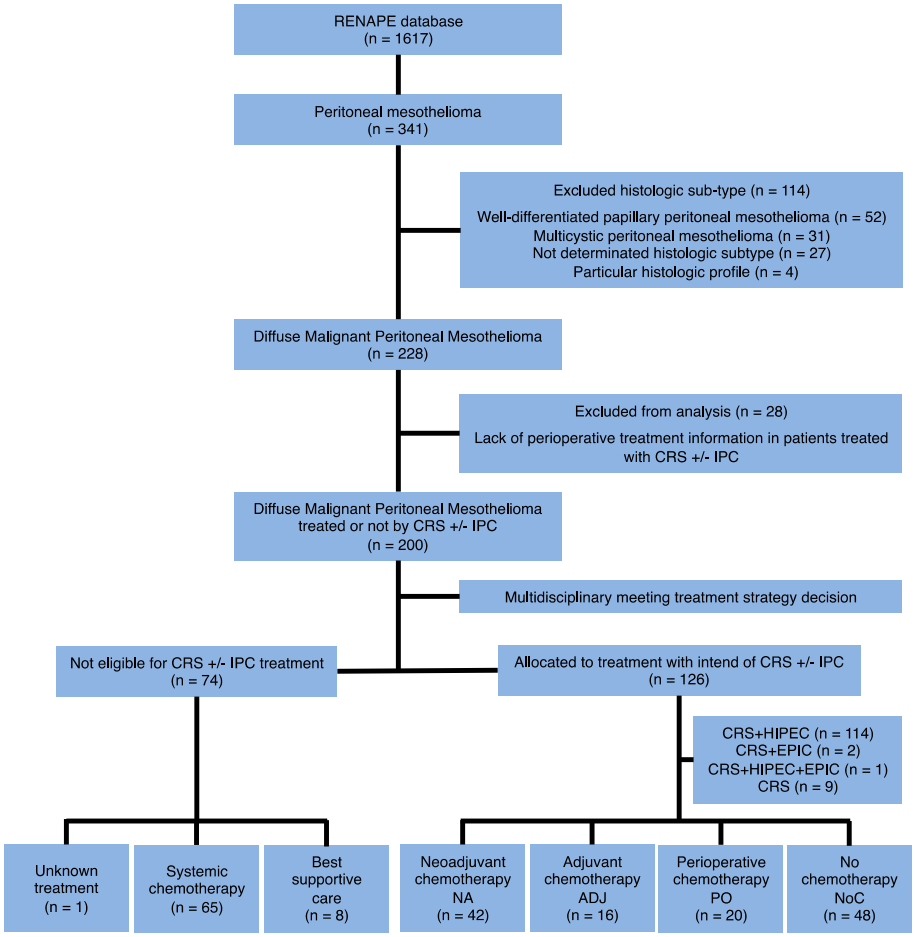

Fig. 1. Consort diagram. CRS, cytoreductive surgery; IPC, intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy.

Table 1
Systemic chemotherapy regimens for all patients treated by CRS-HIPEC for DMPM.

Chemotherapy data	Syst. Chem. (n = 78)		NA (n = 42)		ADJ (n = 16)		PO			
							PO-NA (n = 20)		PO-NA (n = 20)	
	n	%	n	%	n	%	n	%	n	%
No. of cycle										
Median			**6**		**6**		**3.5**		**6**	
Range			**1–17**		**3–9**		**2–20**		**3–8**	
First line										
Pemetrexed-based regimens	**48**	**62**	**27**	**60**	**9**	**64**	**10**	**50**	**10**	**50**
Cisplatin + pemetrexed			21		6		9		4	
Carboplatin + pemetrexed			4		3		1		3	
Oxaliplatin + pemetrexed			–		–		–		1	
Oxaliplatin + raltitrexed			2		2		–		1	
Pemetrexed			–		–		–		1	
Gemcitabine-based regimens	**12**	**15**	**5**	**12**	**2**	**13**	**2**	**25**	**5**	**25**
Gemcitabine + cisplatin			4		1		3		2	
Gemcitabine + oxaliplatin			1		–		2		1	
Gemcitabine			–		1		–		2	
Other regimens	**22**	**18**	**10**	**24**	**3**	**19**	**4**	**20**	**3**	**15**
Not determined	2	3	0	0	0	0	1	5	2	10
Second line and followings										
Patients concerned	**20**	**26**	**12**	**29**	**5**	**31**		**3**		**15**
No. of different regimens	**14**		**12**		**4**				**3**	
Pemetrexed-based regimens	7	43	5	42	1	20	–		1	33
Gemcitabine-based regimens	6	21	2	17	3	60	–		1	33
Other regimens	7	36	5	42	1	20	–		1	33

Other regimens first line: other cisplatin-based regimens, carboplatin + paclitaxel, fluorouracil + oxaliplatin + folinic acid. Other regimens second line and followings: other cisplatin-based regimens, doxorubicin, topotecan, oxaliplatin + topotecan, paclitaxel, carboplatin + paclitaxel, carboplatin + cyclophosphamide, fluorouracil + irinotecan + folinic acid, irinotecan + cetuximab.
Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; NA, neoadjuvant chemotherapy; ADJ, adjuvant chemotherapy; PO, perioperative chemotherapy.

peritoneal carcinomatosis is hardly evaluable by imaging and staging laparoscopy before chemotherapy is not performed in routine, then it is the best examination to explore the peritoneal carcinomatosis extent [27]. Second, NA has been indicated in different strategies: for patients of dubious resectability, as awaiting treatment in resectable patients before referring them to expert centres, or according to each centre's treatment policy regardless of illness presentation. Third, some of NA patients with good response to chemotherapy and early recovery after CRS had therefore adjuvant chemotherapy and were transferred to PO group.

So, we assume that a lot of NA patients are of intrinsic worse prognosis but looking to main DMPM prognostic factors and MDT conclusions balance this analysis. The rate of incomplete cytoreduction was higher in NA than in ADJ or PO groups, but lower than in NoC group. ASA score, mean PCI, and lymph node involvement were similar in NA and NoC groups. Drug regimens were homogeneously distributed between groups, and the slight differences are insufficient to explain the oncological outcomes, but the mean number of preoperative cycles was higher in the NA group than in the PO group, delaying CRS-HIPEC. Only 16% and 15% of patients from NA and NoC groups did not have the adjuvant chemotherapy they were supposed to receive according to MDT decision. This fact therefore might not impact the difference regarding survival between NA and NoC groups. As a consequence, the worse prognosis observed in the NA group may not be explained by more aggressive disease only. It may also be due to a worse sensitivity to chemotherapy of unresected patients and to the risk of disease progression during preoperative chemotherapy.

It is difficult to define the optimal role of PO in the management of DMPM because of the lack of scientific evidence. Many systemic chemotherapy regimens have been used for 70 years, but there are no randomised controlled studies in DMPM patients [28,19]. Many studies suggest that CRS-HIPEC provides the best long-term outcomes despite the absence of randomised trials [29–33,6,34,35]. The PO sequence was evaluated in only one retrospective study reported by Deraco *et al.* [21] The objectives and design were similar to the present study but the systemic chemotherapy indications were slightly different. Each patient was scheduled for chemotherapy, meaning that the patients without chemotherapy were judged unfit for this treatment. No patient had perioperative systemic chemotherapy. Two out of three patients received neoadjuvant treatment in order to downsize the disease, or because they were initially unfit for CRS-HIPEC. Preoperative treatment had no effect on morbidity, or on CC-score. There were no OS differences between groups. The only significant

Table 2
Patients and treatments characteristics in HIPEC group according to systemic chemotherapy regimens.

Characteristic	NA (n = 42)		ADJ (n = 16)		PO (n = 20)		NoC (n = 48)		*P*
	n	%	n	%	n	%	n	%	
Sex									0.715
Female	18	43	6	38	12	60	24	50	
Male	24	57	10	62	8	40	24	50	
Age, years									0.463
Median	56		58		59		59		
Range	18–76		17–73		13–66		27–79		
ASA score									0.554
Mean	1.9		2		1.9		1.8		
SD	0.6		0.5		0.4		0.7		
Unknown	8		2		4		7		
Extent of prior surgery[a]									0.543
Limited dissection or biopsy	33	79	10	63	14	70	35	74	
Previous surgical debulking	9	21	6	38	6	30	12	26	
Unknown	0		0		0		1		
Date of surgery									0.633
Before 2005	12	29	6	38	6	30	12	26	
After 2005	30	71	10	63	14	70	36	75	
PCI[a]									0.081
Mean	20		21		16		22		
SD	8		8			8	9		
0–10	3	13	1	20	2	14	4	11	0.659
11–20	10	43	1	20	11	79	11	31	
21–30	8	35	2	40	0	0	14	39	
31–39	2	9	1	20	1	7	7	19	
Unknown	19		11		6		12		
Completeness of cytoreduction									0.069
CCR-0/1	29	78	12	92	20	100	34	76	
CCR-2/3	8	22	1	8	0	0	11	24	
Unknown	5		3		0		3		
Histological type									0.263
Epithelial	38	91	13	81	19	95	44	92	
Biphasic/Sarcomatoid	4	10	3	19	1	5	4	8	
Lymph nodes[a]									0.904
Histologically pos	5	16	2	22	5	36	7	19	
Histologically neg	26	84	7	78	9	64	29	81	
Not sampled	11		7		6		12		
Extra-abdominal metastases[a]									0.889
Present	2	5	0	0	1	5	1	2	
Absent	36	95	13	100	19	95	45	98	
Unknown	4		3		0		2		
Peritoneal treatment									0.919
CRS + HIPEC	38	91	13	81	18	90	43	90	
CRS + HIPEC + EPIC	0	0	0	0	0	0	1	2	
CRS + EPIC	0	0	0	0	2	10	0	0	
CRS	4	10	3	19	0	0	4	8	
Duration of HIPEC, minutes[a]									0.200
30 or 60	23	70	5	42	17	94	14	35	
90	10	30	7	58	1	6	26	65	
Unknown	9		4		2		8		
Type of HIPEC									0.924
Closed	18	43	9	56	1	6	31	65	
Open	24	57	7	44	19	94	17	35	
Major morbidity (grade III–IV)[a]									0.877
Yes	16	39	7	44	7	35	19	40	
No	25	61	9	56	13	65	29	60	
Unknown	1		0		0		0		
90-d postoperative mortality[a]									0.299
Yes	2	5	0	0	0	0	2	4	
No	38	95	15	100	16	100	44	96	
Unknown	2		1		3		2		
Length of hospital stay, days									0.630
Mean	26		23		22		23		
SD	17		7		11		12		

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; NA, neoadjuvant chemotherapy; ADJ, adjuvant chemotherapy; PO, perioperative chemotherapy; NoC, no systemic chemotherapy.

[a] Percentages calculated on non-missing values.

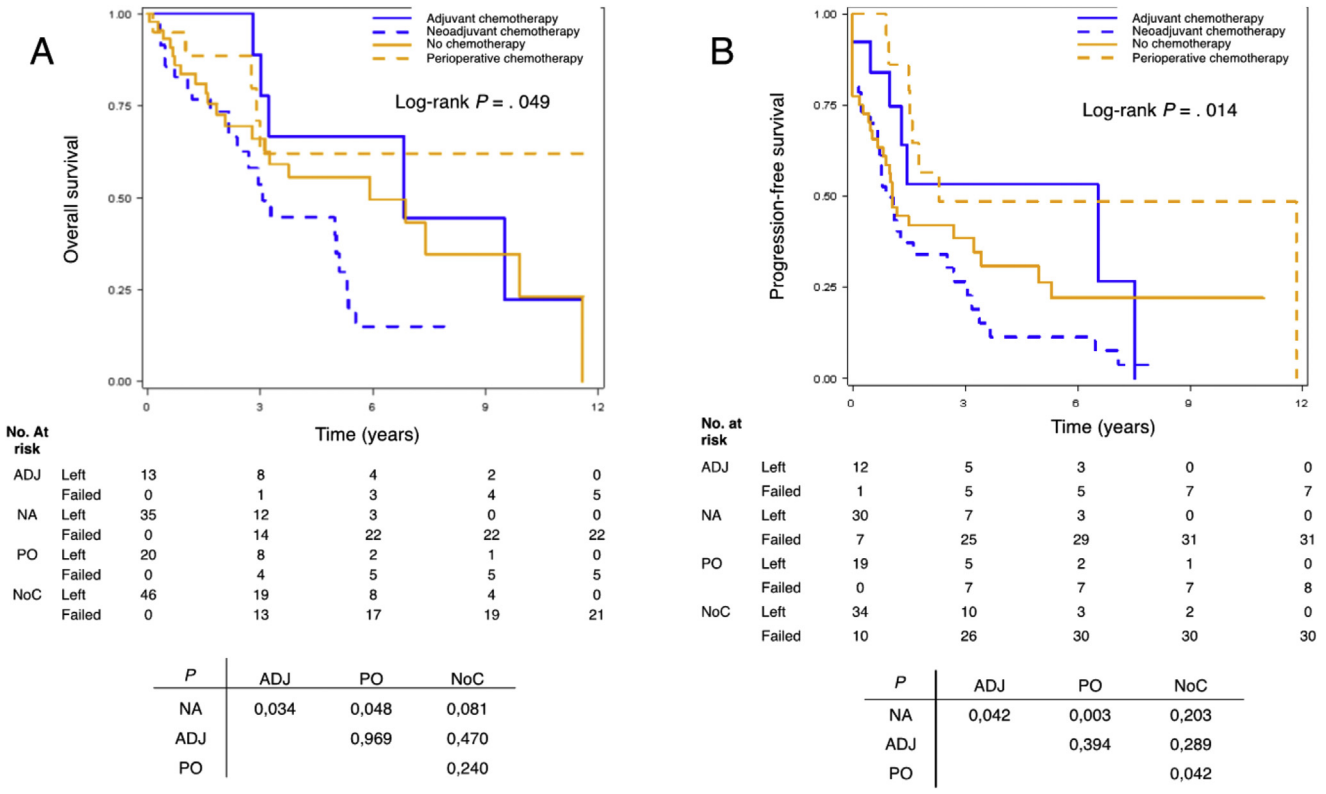

Fig. 2. Kaplan–Meier analysis of overall survival (A) and progression-free survival (B) by chemotherapy protocol. NA, neoadjuvant chemotherapy; ADJ, adjuvant chemotherapy; PO, perioperative chemotherapy; NoC, no chemotherapy.

Table 3
Survival outcomes according to treatment group.

Factor	All patients (n = 127)	NA (n = 42)	ADJ (n = 16)	PO (n = 20)	NoC (n = 48)	*P*
Overall survival						0.049
Median, months	61	37	82	nr	71	
Range, months	37.0–82.4	26.0–61.3	33.8 – nr	33.1 – nr	33.4–118.8	
Overall survival rates						0.049
1-year	87%	83%	100%	95%	84%	
5-year	53%	40%	67%	62%	56%	
7-year	35%	15%	44%	62%	43%	
10-year	21%	15%	22%	62%	23%	
Progression-free survival						0.014
Median, months	17	11	78	27	13	
Range, months	12.5–32.2	7.8–19.4	5.8–90.2	17.4–142.0	6.1–38.6	
Progression-free survival rates						0.014
1-year	60%	85%	100%	100%	88%	
5-year	28%	41%	67%	65%	58%	
7-year	21%	15%	44%	65%	45%	
10-year	14%	15%	22%	65%	24%	

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; NA, neoadjuvant chemotherapy; ADJ, adjuvant chemotherapy; PO, perioperative chemotherapy; NoC, no systemic chemotherapy; nr, not reached.

result was that patients who had not received NA had a better PFS than those who received neoadjuvant treatment (HR, 2.47; 95% CI, 1.42–4.29; *P* value < 0.01). This is consistent with our findings.

Then, Deraco *et al.* reported radiologic response rates after preoperative chemotherapy. Their results may be summarised as following: 55% of these patients have stable disease, one third may benefit from chemotherapy to downsize their tumours and 14–18% of patients treated with NA experience disease progression. As a result, it is possible that NA selects patients with favourable chemosensitive tumours, but may also contribute to missing the therapeutic window of resectability of an upfront surgical strategy.

Table 4
Univariate and multivariate analysis of factors influencing overall and progression-free survivals in HIPEC group.

Variable	Overall survival				Progression-free survival			
	Univ. *P* value	HR (95% CI)	Multiv. *P* value	HR (95% CI)	Univ. *P* value	HR (95% CI)	Multiv. *P* value	HR (95%CI)
Age	0.089	1.03 (1–1.06)			0.015	1.03 (1.01–1.05)	0.065	1.02 (1.00–1.05)
Sex (male vs female)	0.530	1.19 (0.62–2.29)			0.241	1.36 (0.81–2.26)		
PCI	0.007				0.007			
0–10		1.00				1.00		
11–20		1.36 (0.3–6.21)				0.9 (0.22–3.75)		
21–30		1.09 (0.21–5.6)				2.34 (0.58–9.41)		
31–39		9.14 (1.64–51.08)				6.78 (1.44–31.79)		
ASA (1–2 vs 3–5)	0.006	5.02 (1.57–16.03)			0.058	2.71 (0.97–7.59)		
Completeness of cytoreduction (CC-0/1 vs CC-2/3)	0.021	2.46 (1.07–5.68)	0.025	2.61 (1.13–6.04)	<0.001	9.52 (4.55–19.91)	<0.001	7.72 (3.54–16.84)
Histology (epithelial vs biphasic/sarcomatoid)	0.872	1.1 (0.35–3.47)			0.221	2.03 (0.65–6.29)		
Lymph nodes (histologically neg vs pos)	0.418	0.62 (0.22–1.8)			0.590	0.80 (0.35–1.83)		
Metastases (present vs absent)	0.963	1.04 (0.21–5.13)			0.404	0.53 (0.12–2.38)		
Treatment period (before 2005 vs after 2005)	0.308	0.72 (0.35–1.49)			0.030	0.53 (0.3–0.94)		
Type of HIPEC (open vs closed)	0.299	2.92 (0.34–24.88)			0.898	0.87 (0.1–7.57)		
HIPEC drug (oxaliplatin-based vs cisplatin-based)	0.293	0.46 (0.11–1.98)			0.513	0.57 (0.16–2.04)		
Major morbidity (grade III/IV)	0.700	1.17 (0.58–2.36)			0.608	1.16 (0.66–2.04)		
Hospital stay	0.517	0.99 (0.96–1.02)			0.569	0.99 (0.98–1.01)		
Neoadjuvant chemotherapy (no vs yes)	0.021	2.38 (1.14–4.97)	0.033	2.30 (1.07–4.94)	0.119	1.59 (0.89–2.86)	0.113	1.65 (0.89–3.08)
Adjuvant chemotherapy (no vs yes)	0.314	0.61 (0.2–1.59)			0.006	0.31 (0.14–0.71)	0.113	0.51 (0.22–1.17)
Treatment groups	0.143				0.020			
Neoadjuvant		3.25 (0.9–11.8)				3.63 (1.27–10.37)		
Adjuvant		1.00				1.00		
Perioperative		3.39 (0.56–20.64)				0.88 (0.24–3.23)		
No systemic chemotherapy		1.52 (0.41–5.66)				2.28 (0.79–6.59)		

Abbreviations: ASA, American Society of Anesthesiologists; PCI, Peritoneal carcinomatosis index; HIPEC, hyperthermic intraperitoneal chemotherapy; Multiv., multivariate; Univ., univariate; vs, versus.

The interest of adjuvant chemotherapy appears to be more important. Based on our results, the best outcomes were observed in PO and ADJ groups. Patients in those groups had the same median number of cycles postoperatively. One hypothesis could be that the adjuvant treatment is more efficient than preoperative chemotherapy because of the minimised postoperative tumour burden [36–38].

The 48 patients who did not receive any perioperative treatment had a median OS of 71 months. This result was obtained despite higher mean PCI and higher rates of incomplete cytoreduction, when compared to the characteristics of other groups. Similar results were observed in Deraco's series, suggesting that abstention from systemic chemotherapy could be an alternative for DMPM patients with resectable disease [21]. Decision criteria could be the association of the followings: patients evaluated in expert centres who are chemotherapy naïve, with PCI <20, an epithelioid subtype, negative lymph nodes after exhaustive assessment, no metastases, and CC-0/1 score.

To date, pemetrexed-based regimens are considered as the standard chemotherapy in DMPM patients since Vogelzang *et al.* [39] demonstrated that pemetrexed-cisplatin combination was associated with a better median OS in pleural mesothelioma. This result was extended to DMPM through an Expanded Access Program approved by the United States Food and Drug Administration and Eli Lilly Company, despite the absence of randomised clinical trial in DMPM [40]. Two studies evaluated pemetrexed through this non-randomised open study. Pemetrexed provided a 19% and 26% global response rate and it was 20% and 30% when combined with cisplatin [8,9]. A small phase II multicentre trial of pemetrexed combined with gemcitabine achieved a 15% response rate and median OS of 26.8 months, with a high incidence of severe adverse events and 5% treatment-related deaths [20]. Despite these poor data that could be a sufficient argument against NA, pemetrexed-based regimens are considered as the standard chemotherapy in DMPM patients. These regimens were the most commonly used in our study, and differences in drugs repartition were not correlated with survival outcomes. This analysis reinforces the need of controlled data related to the use of systemic chemotherapy in DMPM patients. Furthermore, despite a strong rational, biologic therapies

have been disappointing, to date, in malignant mesothelioma [41]. Recent encouraging results obtained with immunotherapy may suggest it should be evaluated in a so chemoresistant disease [42].

Our results are obtained over several decades but without major changes of chemotherapy protocols over this period. Indeed, period of treatment was not independently associated with survival. Because of the retrospective and non-randomised nature of our work, we acknowledge discrepancies in the indication for systemic chemotherapy, drugs regimens and HIPEC technique. Nevertheless, each participating centre was specialised in PSM and shared their experiences at a national level.

The combination of CRS and HIPEC is the cornerstone of a curative treatment strategy for DMPM. The present study raises issues on the optimal treatment sequence. Upfront surgery appears preferable to NA in patients amenable to complete CRS. Adjuvant systemic chemotherapy appears to delay recurrence and seems to offer survival benefit, although abstention of systemic treatment under certain condition may be an alternative. All patients with a diagnostic of DMPM should be evaluated prior any treatment in an expert PSM centre and a laparoscopically comprehensive exploration of the abdominal cavity should be advocate to define the initial resectability. International scientific collaboration should be able to evaluate this issue through an international randomised trial or a non-randomised study with propensity score analysis [43,44].

Acknowledgments of research support for the study

RENAPE is funded by the French National Cancer Institute (INCa).

RENAPE scientific committee accepts direct responsibility for this manuscript

F. Bibeau, D. Elias, O. Glehen, S. Isaac, M. Pocard, F. Quenet.

Role of the funding source

The funding source had no role in the study design, data collection, analysis, preparation of the manuscript, or decision to submit the manuscript for publication.

Conflict of interest statement

None declared.

Acknowledgements

The authors thank the French National Cancer Institute (INCa) and the French network for the treatment of rare peritoneal malignancies (RENAPE).

References

[1] Miller J, Wynn WH. A malignant tumour arising from the endothelium of the peritoneum, and producing a mucoid ascitic fluid. J Pathol 1908;12:267–78.
[2] Wagner JC. Asbestos cancers. J Natl Cancer Inst 1971;46:5–9.
[3] Boffetta P. Epidemiology of peritoneal mesothelioma: a review. Ann Oncol 2007;18:985–90.
[4] Antman K, Klegar K, Pomfret E, Osteen R, Amato D, Laron D, et al. Early peritoneal mesothelioma: a treatable malignancy. Lancet 1985;326:977–81.
[5] Robinson BWS, Lake RA. Advances in malignant mesothelioma. N Engl J Med 2005;353:1591–603.
[6] Manzini VDP, Recchia L, Cafferata M, Porta C, Siena S, Giannetta L, et al. Malignant peritoneal mesothelioma: a multicenter study on 81 cases. Ann Oncol 2010;21:348–53.
[7] Antman KH, Blum RH, Greenberger JS, Flowerdew G, Skarin AT, Canellos GP, et al. Multimodality therapy for malignant mesothelioma based on a study of natural history. Am J Med 1980;68:356–62.
[8] Carteni G, Manegold C, Garcia GM, Siena S, Zielinski CC, Amadori D, et al. Malignant peritoneal mesothelioma-results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. Lung Cancer 2009;64:211–8.
[9] Jänne PA, Wozniak AJ, Belani CP, Keohan ML, Ross HJ, Polikoff JA, et al. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. Clin Lung Cancer 2005;7:40–6.
[10] Garcia-Carbonero R, Paz-Ares L. Systemic chemotherapy in the management of malignant peritoneal mesothelioma. Eur J Surg Oncol 2006;32:676–81.
[11] Tattersall MHN, Fox RM, Newlands ES, Woods RL. Intracavitary doxorubicin in malignant effusions. Lancet 1979;1:390.
[12] Rogoff EE, Hilaris BS, Huvos AG. Long-term survival in patients with malignant peritoneal mesothelioma treated with irradiation. Cancer 1973;32:656–64.
[13] Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multiinstitutional experience. J Clin Oncol 2009;27:6237–42.
[14] Baratti D, Kusamura S, Cabras AD, Bertulli R, Hutanu I, Deraco M. Diffuse malignant peritoneal mesothelioma: long-term survival with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC). Eur J Cancer 2013;49:3140–8.
[15] Husain AN, Colby TV, Ordóñez NG, Krausz T, Borczuk A, Cagle PT, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2009;133:1317–31.
[16] Husain AN, Colby T, Ordonez N, Krausz T, Attanoos R, Beasley MB, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2013;137:647–67.
[17] Baratti D, Kusamura S, Nonaka D, Oliva GD, Laterza B, Deraco M. Multicystic and well-differentiated papillary peritoneal

mesothelioma treated by surgical cytoreduction and hyperthermic intra-peritoneal chemotherapy (HIPEC). Ann Surg Oncol 2007; 14:2790–7.
[18] Yan TD, Deraco M, Elias D, Glehen O, Levine EA, Moran BJ, et al. A novel tumor-node-metastasis (TNM) staging system of diffuse malignant peritoneal mesothelioma using outcome analysis of a multi-institutional database. Cancer 2010;117:1855–63.
[19] Mirarabshahii P, Pillai K, Chua TC, Pourgholami MH, Morris DL. Diffuse malignant peritoneal mesothelioma – an update on treatment. Cancer Treat Rev 2012;38:605–12.
[20] Simon GR, Verschraegen CF, Janne PA, Langer CJ, Dowlati A, Gadgeel SM, et al. Pemetrexed plus gemcitabine as first-line chemotherapy for patients with peritoneal mesothelioma: final report of a phase II trial. J Clin Oncol 2008;26:3567–72.
[21] Deraco M, Baratti D, Hutanu I, Bertuli R, Kusamura S. The role of perioperative systemic chemotherapy in diffuse malignant peritoneal mesothelioma patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2013;20:1093–100.
[22] Villeneuve L, Isaac S, Glehen O, Capovilla M, Chevallier A, Croce S, et al. The RENAPE network: towards a new healthcare organization for the treatment of rare tumors of the peritoneum. Description of the network and role of the pathologists. Ann Pathol 2014;34:4–8.
[23] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.
[24] Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res 1996;82:359–74.
[25] Sugarbaker PH. Peritonectomy procedures. Ann Surg 1995;221: 29–42.
[26] The National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0 update. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.
[27] Cotte E, Passot G, Gilly F-N, Glehen O. Selection of patients and staging of peritoneal surface malignancies. World J Gastrointest Oncol 2010;2:31–5.
[28] Berghmans T, Paesmans M, Lalami Y, Louviaux I, Luce S, Mascaux C, et al. Activity of chemotherapy and immunotherapy on malignant mesothelioma: a systematic review of the literature with meta-analysis. Lung Cancer 2002;38:111–21.
[29] Feldman AL, Libutti SK, Pingpank JF, Barlett DL, Beresnev TH, Mavroukakis SM, et al. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. J Clin Oncol 2003;21:4560–7.
[30] Sugarbaker PH, Yan TD, Stuart OA, Yoo D. Comprehensive management of diffuse malignant peritoneal mesothelioma. Eur J Surg Oncol 2006;32:686–91.
[31] Yan TD, Brun EA, Cerruto CA, Haveric N, Chang D, Sugarbaker PH. Prognostic indicators for patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma†. Ann Surg Oncol 2006;14:41–9.
[32] Baratti D, Kusamura S, Cabras AD, Dileo P, Laterza B, Deraco M. Diffuse malignant peritoneal mesothelioma: failure analysis following cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol 2008;16:463–72.
[33] Chua TC, Yan TD, Morris DL. Outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal mesothelioma: the Australian experience. J Surg Oncol 2009; 99:109–13.
[34] Ihemelandu C, Bijelic L, Sugarbaker PH. Iterative cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent or progressive diffuse malignant peritoneal mesothelioma: clinicopathologic characteristics and survival outcome. Ann Surg Oncol 2014;22:1680–5.
[35] Magge D, Zenati MS, Austin F, Mavanur A, Sathaiah M, Ramalingam L, et al. Malignant peritoneal mesothelioma: prognostic factors and oncologic outcome analysis. Ann Surg Oncol 2014;21:1159–65.
[36] Trump DL, Smith DC. Systemic therapies. In: Love RR, editor. Manual of clinical oncology. Berlin, Heidelberg: Springer Berlin Heidelberg; 1994. p. 202–23.
[37] Daydé D, Ternant D, Ohresser M, Lerondel S, Pesnel S, Watier H, et al. Tumor burden influences exposure and response to rituximab: pharmacokinetic-pharmacodynamic modeling using a syngeneic bioluminescent murine model expressing human CD20. Blood 2009;113:3765–72.
[38] Lin Y-Y, Kao H-W, Li J-J, Hwang JJ, Tseng YL, Lin WJ, et al. Tumor burden talks in cancer treatment with PEGylated liposomal drugs. PLoS One 2013;8:e63078.
[39] Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636–44.
[40] Guidance for Industry Expanded Access to Investigational Drugs for Treatment Use – Qs & As. Food and drug administration website. 2014. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf.
[41] Kelly RJ, Sharon E, Hassan R. Chemotherapy and targeted therapies for unresectable malignant mesothelioma. Lung Cancer 2011;73:256–63.
[42] Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455–65.
[43] Ioannidis JP, Haidich AB, Pappa M, Pantazis N, Kokori SI, Tektonidou MG, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. JAMA 2001;286: 821–30.
[44] Lonjon G, Boutron I, Trinquart L, Ahmad N, Aim F, Nizard R, et al. Comparison of treatment effect estimates from prospective nonrandomized studies with propensity score analysis and randomized controlled trials of surgical procedures. Ann Surg 2014; 259:18–25.