



Effects of Neoadjuvant Laparoscopic Hyperthermic Intraperitoneal Chemotherapy and Neoadjuvant Intraperitoneal/Systemic Chemotherapy on Peritoneal Mesothelioma

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Abstract

Purpose: The purpose of the manuscript is to verify the effects of Neoadjuvant Laparoscopic Hyperthermic Intraperitoneal Chemotherapy (NLHIPEC) and Neoadjuvant Intraperitoneal/Systemic Chemotherapy (NIPS) on PCI and postoperative survivals of patients with Peritoneal Mesothelioma (PM).

Patients and Methods: From 2007 to 2021, 92 PM patients were treated. The population was divided into three groups: No Neoadjuvant Chemotherapy (no NAC), Neoadjuvant Systemic Chemotherapy (NASC) and Neoadjuvant Intraperitoneal/Systemic Chemotherapy (NIPS) and Neoadjuvant Laparoscopic HIPEC (NLHIPEC).

Results: Among 92 patients, NASC, and NLHIPEC plus or minus (\pm) NIPS and no NAC were performed in 34, 33, and 25 patients, respectively.

Ten patients underwent one cycle of NLHIPEC. PCIs in 2nd laparoscopy one month after NLHIPEC alone were 14.1 ± 11.1 , and those in the 1st laparoscopy were 19.3 ± 9.4 . PCIs of 17 patients received both NLHIPEC plus NIPS reduced from 25.0 ± 10.7 to 17.3 ± 7.6 ($P=0.039$). Operations were performed in 67 (72.8%), and were done in 12 (48%), 27 (82.5%), and 28 (82.1%) of no NAC, NLHIPEC \pm NIPS and NASC group, respectively. Rates of CCR-0 in each group were 19.3%, 37.5%, and 20.6%, respectively. CCR-0 rate of NLHIPEC \pm NIPS group was significantly higher than that of no NAC group ($P=0.0065$, $X^2=7.85$).

Post-treatment survival of patients treated with NLHIPEC \pm NIPS was superior to those of other treatment groups ($P=0.016$, $X^2=5.799$). Median survival time of NLHIPEC \pm NIPS, NASC, and non NAC groups were 47.4, 15.5 and 6.0 months, respectively.

Conclusion: This retrospective study suggests that NLHIPEC \pm NIPS may increase CCR-0 resection rate by reducing PCI scores and may improve post operative survival.

Keywords: Peritoneal mesothelioma; Mesothelioma; Intraperitoneal chemotherapy; HIPEC; Peritonectomy

Introduction

Peritoneal Mesothelioma (PM) is a rare peritoneal malignancy characterized by diffuse involvement of the peritoneal surface.

About 33% to 50% of patients diagnosed with PM report known prior exposure to asbestos [1-3]. After a reduction of this rate to a low level by the ban of asbestos usage globally, it was expected that the number of PM deaths would decrease [4]. However, it is estimated that approximately 15,000 new cases of PM will be diagnosed between 2005 and 2050 in the USA [4].

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In the past, PM has been regarded as a rapidly lethal disease, because it is highly invasive and metastatic to lymph node [5].

Before the late 1990s, PM was not a surgical disease, because of diffusely distribution along the peritoneal surface at the time of diagnosis. Accordingly, systemic chemotherapy had been considered only way to treat PM. However, systemic chemotherapy has little effects on the long-term survival of patients with PM [6-9]. Recently, comprehensive treatment consisting of Cytoreductive Surgery (CRS) and Hyperthermic Intraoperative Intraperitoneal Chemoperfusion (HIPEC) has emerged as a hopeful treatment to improve survivals and cure rates in patients with PM [10-12]. The mean survival time of patients who received the comprehensive treatment ranged from 29 to 92 months, and was significantly longer than that of patients who received systemic chemotherapy alone [6-9]. When the patients received complete resection, survival rates ranged from 29% to 52% at 5 years, and 12% to 45% at 10 years [10-15]. However, complete cytoreduction was performed only in 30% to 69% of patients who underwent CRS due to high Peritoneal Cancer Index (PCI), especially patients with the diffuse involvement of mesentery and serosal surface of the small bowel [4,11-15]. A prognosis was significantly poorer in patients who received incomplete cytoreduction than in those who received complete cytoreduction. Additionally, one fourth (452/1740) of PM patients underwent surgery due to diffuse invasion of peritoneal surface [16]. If PCI levels could be reduced by neoadjuvant chemotherapy, the rate of complete cytoreduction may be increased, resulting in the improvement of survival after comprehensive treatment.

The purpose of the manuscript is to verify the effects of Neoadjuvant Laparoscopic Hyperthermic Intraperitoneal Chemotherapy (NLHIPEC) and Neoadjuvant Intraperitoneal/Systemic Chemotherapy (NIPS) on PCI and postoperative survivals in patients with PM including Diffuse Malignant Peritoneal Mesothelioma (DMPM) and Well Differentiated Papillary Peritoneal Mesothelioma (WDPPM).

Patients and Methods

All patients were treated according to a protocol approved by the Institutional Ethics Committee (The title: A study of comprehensive treatment for peritoneal metastasis. The protocol code of H19-2, accepted on June 15th, 2007).

Patients

The study has 92 patients with histologically proved DMPM or WDPPM by our Pathology Department. As shown in Table 1, 45 patients were male, and mean age was 56.6 years old (range: 23 to 86). Four histologic types were included epithelioid type in 75 (81.6 %), biphasic type in 8 (8.7%), sarcomatoid type in 5 (5.4%) and WDPPM in 4 (4.3%). According to Kusamura's classification, PM consists of DMPM, WDPPM and Multicystic Peritoneal Mesothelioma (MCPM); MCPM was excluded, because of its indolent biological behavior with favorable prognosis, as compared with DMPM and WDPPM [10].

Treatment and operations

Neoadjuvant Chemotherapy (NAC) was performed in 66 (71.7%) patients. Among them, 32 patients were treated with Neoadjuvant Systemic Chemotherapy (NASC), including pemetrexed + cisplatin in 21, gemcitabine + cisplatin in 4, docetaxel + cisplatin in 2, oral S1 in 2 and others in 3 (CPT-11 + cisplatin, S1 + taxol, and doxorubicin + cisplatin one each). NLHIPEC was performed in 13 patients, and

NLHIPEC plus NIPS was performed in 21 patients.

NLHIPEC

NLHIPEC was performed as described previously [17]. The patients were put under general anesthesia and 3 trocars were introduced through an incision above the umbilicus, on the right upper quadrant, and on the left lower quadrant. Lesion size scores of 13 peritoneal sectors were observed and PCI was counted. Then, HIPEC was performed at 43°C to 43.5°C for 60 min by administering 3 liter of isotonic saline containing docetaxel (30 mg/m²) and cisplatin (50 mg/m²). Second session of LHIPEC was done one month after the first session of LHIPEC in 10 cases. Peritoneal cytology and PCI were reevaluated and compared between sessions.

NIPS

An Intraperitoneal (IP) port system (Bird Co., Ltd, USA) was inserted in the lower abdominal wall, and the tip was introduced into the peritoneal cavity. Oral S1 (60 mg/m²) was started on day 1 and continued until day 14, which was followed by a rest for 7 days, and docetaxel (30 mg/m²) and cisplatin (30 mg/m²) in 500 ml of saline were intraperitoneally introduced through IP port system on day 1 and day 14 [18]. More than 3 cycles of NIPS were performed.

Operations

Surgery could not be performed in 25 patients due to diffuse involvement on the peritoneal surface. Three patients with WDPPM were treated with two cycles of LHIPEC alone. CRS was performed in 67 patients, and achieved complete cytoreduction (CCR-0) in 24 (31%) patients.

Peritonectomy was performed at the sites of disease involvement with the intent of removing all the metastasis on the peritoneal surface [19].

The reasons for incomplete cytoreduction (CCR-1) were high PCI and diffuse involvement of the small bowel and its mesentery in 21 patients, and diaphragmatic, hepatic and peripancreatic metastasis in 4 patients.

Intraoperative HIPEC with open abdomen perfusion was conducted at an intraperitoneal temperature of 43°C to 43.5°C with vigorous stirring of saline with the hands to achieve an even intraperitoneal distribution. The thermal dose was calculated according to the equation by Sapareto et al. [20], and HIPEC was continued until the thermal dose reached 40 min.

Statistical analysis

All patients were followed and no patients were lost to follow-up. Outcome data were obtained from medical records and patients' interview. All statistical analyses were performed using SPSS software statistical computer package version 17 (SPSS Inc., Chicago, USA). The clinical variables were analyzed by X² tests and student T-test. Statistical significance was defined as a p-value ≤ 0.05. Survival times were estimated using Kaplan-Meier method, and survivals between groups were evaluated by univariate analysis.

Results

Among 92 patients, 34 patients were treated with NASC, and 32 patients were treated with NLHIPEC ± NIPS. The other 25 patients were not treated with neoadjuvant chemotherapy. An operation was not planned in 25 patients due to high PCI scores or diffuses involvement of the small bowel or its mesentery. Cytoreduction in the 67 patients who received an operation was complete (CCR-0) in

Table 1: Patients characteristics.

Clinicopathologic Parameters	Values, No of Cases
Age (mean, range)	5.6 ± 13.9 (23-86 years old)
Gender	
Male	45
Female	47
Histologic type	
Epithelioid	75
Biphasic	8
Sarcomatoid	5
WDPPM	4
Neoadjuvant chemotherapy	
No NAC	26
NLHIPEC or/and NIPS	34
Systemic chemotherapy	32
PCI	2 4.6 ± 12.2 (2-39)
≥ 26	48
≤ 25	44
Operation	
Non	25
CCR-0	24
CCR-1	43

Table 2: PCI changes after NLHIPEC and NLHIPEC plus NIPS.

	N	Before Treatment	After Treatment	P
One cycle of NLHIPEC	10	19.3 ± 9.4 (2-39)	14.1 ± 11.1 (0-37)	NS
NLHIPEC plus NIPS	17	25.0 ± 10.7 (6-39)	17.3 ± 7.6 (5-27)	0.039

24 (31.2%) patients and incomplete (CCR-1 in 43 (46.7%)) patients (Table 1). Regarding PCI scores determined by imaging diagnostic modalities, laparoscopy or surgery, PCI was determined to be ≥ 26, in 48 patients and ≤ 25 were in 44 patients.

Ten patients underwent one cycle of NLHIPEC and 2nd laparoscopy one month after NLHIPEC to evaluate PCI changes.

Table 3: Lesion size scores of 13 peritoneal sectors before and one month after NLHIPEC.

	Peritoneal Sector												
	0	1	2	3	4	5	6	7	8	9	10	11	12
1 st LAP	2.28 ± 1.11	2.28 ± 1.11	1.75 ± 1.28	1.37 ± 1.19	0.63 ± 1.06	2.25 ± 1.04	2.15 ± 1.36	2.38 ± 1.06	1.25 ± 1.48	0.88 ± 1.13	0.86 ± 1.07	1.13 ± 0.99	1.13 ± 0.99
2 nd LAP	1.57 ± 1.13	1.50 ± 1.31	0.75 ± 1.16	0.75 ± 1.04	0.88 ± 0.99	1.16 ± 1.35	1.25 ± 1.39	0.75 ± 1.16	1.25 ± 1.39	0.88 ± 1.13	1.00 ± 1.15	1.25 ± 1.28	1.38 ± 1.30
P	NS	NS	0.024	NS	NS	0.03	NS	0.02	NS	NS	NS	NS	NS

Table 4: Small bowel PCI before and one month after treatment with one cycle of NLHIPEC and NLHIPEC plus NIPS.

	N	Before Treatment	After Treatment	P
One month after NLHIPEC	10	4.13 ± 4.08 (2-12)	4.508 ± 4.54(0-12)	NS
NLHIPEC plus NIPS	17	7.09 ± 3.88 (2-12)	5.18 ± 3.18(0-12)	0.027

Table 5: Lesion size scores of 13 peritoneal sectors before and one month after NLHIPEC plus NIPS.

NLHIPEC+NIPS	Peritoneal Sector												
	0	1	2	3	4	5	6	7	8	9	10	11	12
1 st	2.38 ± 0.74	2.25 ± 0.89	2.28 ± 0.95	2.00 ± 1.07	1.88 ± 0.99	2.38 ± 0.74	2.50 ± 0.76	2.38 ± 0.92	2.38 ± 0.74	1.80 ± 1.14	1.70 ± 1.25	1.80 ± 1.03	2.10 ± 0.88
2 nd	2.38 ± 0.52	1.88 ± 0.35	1.00 ± 0.82	1.50 ± 1.07	1.50 ± 0.76	1.75 ± 0.46	1.88 ± 0.35	1.75 ± 0.46	1.38 ± 0.92	1.20 ± 0.92	1.30 ± 0.82	1.40 ± 0.84	1.40 ± 0.84
P	NS	NS	0.012	NS	NS	NS	0.049	NS	0.033	NS	NS	NS	0.44

PCI was 14.1 ± 11.1 (rang: 0 to 37) after NLHIPEC alone at the 2nd laparoscopy and, and 19.3 ± 9.4 (range: 2 to 39) at the 1st laparoscopy (Table 2). There was no significant change in PCI scores between 1st and 2nd laparoscopies.

Regarding the Lesion Size Scores (LSSs) of 13 peritoneal sectors (Table 3), the LSS of sector 2 and 7 were significantly lower at the 2nd laparoscopy one month after LHIPEC than those at the 1st laparoscopy, i.e., they had decreased from 1.75 ± 1.28 to 0.75 ± 1.16, and from 2.38 ± 1.06 to 0.75 ± 1.16 (P=0.02), respectively.

Seventeen patients received both NLHIPEC plus NIPS, and PCI change was assessed at CRS or 2nd laparoscopy. The mean cycle of NIPS was 4.9 ± 2.7 (ranging from 1-12).

In patients who received both NLHIPEC and NIPS, and CRS or 2nd laparoscopy was performed 3 to 4 weeks after the last cycle of NIPS. The PCIs before and after NLHIPEC plus NIPS were 25.0 ± 10.7 (range 6 to 39), and 17.3 ± 7.6 (range 5 to 27), respectively (P=0.039) (Table 2). Regarding LSSs of 13 peritoneal sectors, those of sector 2 and 7 were significantly reduced after NLHIPEC plus NIPS (Table 3).

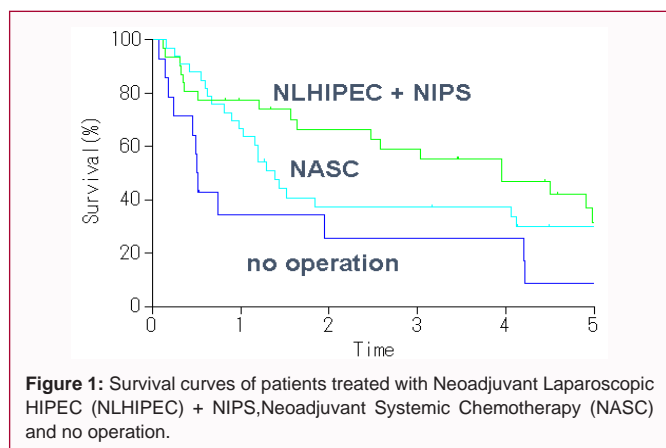
SB-PCIs before and after NLHIPEC plus NIPS were 7.09 ± 3.88 (range from 2 to 12) and 5.18 ± 3.18 (range 0 to 12), respectively (P=0.027, Table 4).

Operations were performed in 67(72.8%) patients, including 12 (48%), 27 (82.5%), and 28 (82.1%) patients in the no NAC, NIPS or NLHIPEC and NASC group, respectively. Rates of CCR-0 in the no NAC, NIPS or NLHIPEC and NASC groups were 19.3%, 37.5%, and 20.6%, respectively, and were significantly higher in the NLHIPEC ± NIPS group than no NAC group (P=0.0065, X²=7.85) (Table 5).

Figure 1 shows the survival curves of patients treated with NLHIPEC ± NIPS group, NASC and no NAC group. Post-treatment survival of patients treated with NLHIPEC ± NIPS was superior to those of other treatment groups (P=0.016, X²=5.799). The median survival time of NLHIPEC, NASC, and non-NAC groups were 47.4, 15.5 and 6.0 months, respectively.

Discussion

At present, patients with PM patients amenable to CRS are treated



with systemic chemotherapy. Studies of systemic chemotherapy including pemetrexed + CDDP, gemcitabine + CDDP, or nivolumab therapy showed a response rate of 11% to 24% [6-9,21]. Pemetrexed-based regimens are now considered as the standard chemotherapy in DMPM patients [6-10,21]. However, long-term survival after systemic chemotherapy is very poor, and no 5-year survivors have been reported [6-9].

The latest treatment for PM is CRS plus Perioperative Chemotherapy (POCs) including NASC, NIPS, NLHIPEC, intraoperative HIPEC, Early Postoperative Intraperitoneal Chemotherapy (EPIC), Non Hyperthermic Intraoperative Chemotherapy (NIPEC), and late postoperative systemic chemotherapy [10-12]. Among these treatments, CRS combined with POCs is proposed as the most powerful treatment to improve survival of patients with PM and with low PCI [10]. The cutoff PCI level for favorable prognoses is reported to be in the range of 12 to 30 [10,12,22]. However, there is no consensus on what perioperative chemotherapy should be combined with CRS. Additionally, there is no randomized phase III trials addressing the efficacy of POCs combined with CRS.

Neither surgery alone nor chemotherapy alone cures patients with Peritoneal Surface Malignancy (PSM). Patients with PSM treated with surgery alone will die due to the growth of residual micro-metastasis left on the peritoneal surface after complete resection of macroscopic metastasis [23]. After systemic chemotherapy, multi-drug resistant cancer cells always re-grow even in patients evaluated as responders.

To overcome the shortcomings of the treatment by surgical or chemotherapeutic treatment, the Peritoneal Surface Oncology Group International (PSOGI) proposed comprehensive treatment with the potential to cure patients with PSM. Comprehensive treatment is comprised of complete resection of macroscopic tumors by CRS and elimination of micrometastasis left over after CRS with POCs. In DMPM, seven treatment options have been used, including neoadjuvant chemotherapy (NASC, NIPS, NLHIPEC), CRS, intraoperative extensive intraperitoneal peritoneal lavage [24], intraoperative HIPEC, EPIC, and late postoperative systemic chemotherapy [10].

The residual cancer cell burden is lowest just after CRS, so intraoperative HIPEC has a crucial role in the cure of patients with PSM. Additionally, when NAC reduces the burden of micrometastasis to below the threshold level, micrometastasis can be completely eliminated by intraoperative HIPEC and postoperative

chemotherapy, and patients might be cured [24]. As described in previous articles, CCR-0 resection is the most powerful prognostic factor [11-15].

However, in about half of patients with DMPM, diffuse involvement is observed on the peritoneal surface. Accordingly, CCR-0 resection can be performed in less than 50% of patients who did not receive NAC.

NAC may play an important role in increasing the rate of CCR-0 resection. NIPS is a bidirectional chemotherapy, that attacks PM from both sides of the peritoneal metastasis i.e., infiltrate the intraperitoneal space and subperitoneal blood vessels, resulting in more effective treatment of wider areas as relative to the results of mono-directional chemotherapy. Le Roy et al. [23] reported that 55% (11/20) of DMPM not suitable for upfront surgery became resectable after bidirectional chemotherapy using a combination of intraperitoneal injection of pemetrexed and oxaliplatin plus intravenous cisplatin administration. The median PCI score changed from 27 (15 to 39) at staging laparoscopy to 18 (0 to 39) at reevaluation laparoscopy performed after a total of 118 intraperitoneal chemotherapy cycles. The clinical response rate was 60% after a median of 3 chemotherapy cycles.

In the present study, one cycle of NLHIPEC alone did not significantly reduce PCI level. However, median PCI score was significantly reduced from 25.6 to 17.3 after a combination of NLHIPEC plus NIPS. Additionally, NLHIPEC plus NIPS significantly reduce SB-PCI from 7.09 to 5.18.

Kepenekian et al. [24] reported that the rate of CCR-0/1 resection by pemetrexed-based NASC was 69%, and by no neoadjuvant chemotherapy group was 70.8%. The present study clearly demonstrated that the rate of CCR-0 resection by NIPS (36.4%) was significantly higher than those after NASC (20.6%) or no NAC group (20%). These results strongly suggest the superiority of NIPS and bidirectional chemotherapy over NASC.

Regarding the post treatment survival, Kepenekian et al. [24] showed a significant survival disadvantage in patients treated with CRS+HIPEC after NASC as compared with CRS+HIPEC alone, and CRS+HIPEC + perioperative chemotherapy. The 5-year survival rates were 40%, 67%, 62%, and 56% for NASC, adjuvant chemotherapy, perioperative chemotherapy, and no chemotherapy before or after CRS+HIPEC, respectively [24]. They assume that a lot of NASC patients have an intrinsically worse prognostic profile. Naffouje et al. [16] reported that systemic chemotherapy provides a short-term survival improvement at 1 year only, and does not have a survival benefit beyond the 1-year time point. In contrast, Deraco also studied the role of perioperative systemic chemotherapy using pemetrexed and CDDP in 116 DMPM patients with ECOG performance status of 0 and PCI<20. They reported no significant difference in survival between groups either preoperative chemotherapy, postoperative chemotherapy or no perioperative chemotherapy group [25]. Kusamura suggested that the benefit from neoadjuvant systemic chemotherapy after CRS+HIPEC is uncertain [10].

Conclusion

The present study demonstrated that the post-treatment survival of patients treated with NIPS or NLHIPEC was superior to that in other treatment groups ($P=0.016$, $X^2=5.799$). Median survival time of the NLHIPEC plus or minus NIPS, NASC, and no NAC groups was

47.4, 15.5 and 6.0 months, respectively. These results were derived from retrospective studies.

To verify the effect of NASC and bidirectional chemotherapy on postoperative survival after CRS+HIPEC, prospective randomized trials are mandatory.

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