Importance of Continuous Sequential Chemotherapy and Multimodal Treatment for Advanced Testicular Cancer

A High-Volume Japanese Center Experience

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Abstract: Patients with “difficult-to-treat” advanced testicular cancer can require multiple therapies. We retrospectively assessed our patients with advanced germ cell tumors (GCTs) and characterized the clinical efficacy, outcomes, and factors affecting overall survival (OS).

Two hundred fifty-three patients with advanced GCTs were treated at Kyoto Prefectural University of Medicine, Kyoto, Japan, from June 1998 to September 2013. Of 253 patients, 142 patients had salvage chemotherapy.

As first-line therapy, bleomycin, etoposide, and cisplatin, and etoposide and cisplatin therapies were performed in 234 cases (92.5%). As second-line therapy, etoposide, ifosfamide, and cisplatin/vinblastine, ifosfamide, and cisplatin, and paclitaxel, ifosfamide, and cisplatin/paclitaxel, ifosfamide, and nedaplatin therapies were carried out in 44 and 59 cases, respectively. Furthermore, 111, 72, 44, and 28 cases had third, fourth, fifth, and sixth-or-later-line chemotherapy, respectively. Five-year OS rate stratified by chemotherapy line was 95.5% in the first line, 89.4% in the second line, 82.1% in the third line, 45.1% in the fourth line, and 58.9% in the fifth or after line. A statistical significant difference was found when comparing fourth-or-after-line versus first to third-line therapy. Additional procedures were performed, including retroperitoneal lymph node dissection (RPLND) (n = 168), extra-RPLND resection (n = 114), and extra beam radiotherapy/stereotactic radiotherapy (n = 78).

Multivariate analysis showed that factors predicting better outcomes were in serum tumor marker (STM) normalization, RPLND, and extra-RPLND resection.

Good outcomes were obtained in patients who completed chemotherapy up to third line. After fourth-line chemotherapy, approximately 50% of “difficult-to-treat” patients could be cured with normalization of STM levels and residual mass resection. Continuous or sequential chemotherapy with multimodality therapy is important for patients with “difficult-to-treat” advanced GCTs. Effective chemotherapy after third line should be developed.

INTRODUCTION

A
dvanced metastatic germ cell tumors (GCTs) can be cured in 80% of cases.1 Survival improvement in poor prognosis should be noted in the modern chemotherapy era. Population-based analysis by Swedish–Norwegian group showed overall survival (OS) was 67.4% in poor prognosis.2 However, 20% to 30% of cases of advanced GCTs require salvage chemotherapy, such as vinblastine, ifosfamide, and cisplatin (VeIP), etoposide, ifosfamide, and cisplatin (VIP), high-dose chemotherapy (HDCT), and paclitaxel, ifosfamide, and cisplatin (TIP).

Although VIP and VeIP therapy have been used as standard salvage therapy for 2 decades, no evidence of disease (NED) rate was approximately 30%.3,4 These results led investigators to develop other therapies. HDCT was made possible by the development of peripheral stem cell blood harvest and transfusion. Two randomized control trials (RCTs) of HDCT as first salvage therapy (second-line) failed to show that HDCT was superior to standard-dose salvage therapy.5,6 In addition, after failing HDCT therapy, it is very difficult to continue treatment.7,8

TIP therapy as first salvage chemotherapy, introduced by Motzer in 2000,8 results in a very good response rate (RR) in cases with specific prognostic features (eg, testis primary and first relapse after previous complete response [CR]). Other investigators tested TIP as second-line therapy for patients with bleomycin, etoposide, and cisplatin (BEP) failure and reported relatively good results with manageable adverse events.9 Therefore, TIP has been recognized as a standard first salvage therapy.
chemotherapy, especially for the patients with favorable prognostic features.

Other salvage chemotherapies have been developed for advanced GCTs. Some of them seem to be good candidates for second-line treatment or for use after salvage chemotherapy. Gemcitabine and irinotecan in combination with cisplatin or its derivatives resulted in relatively good cure rates. A regimen including gemcitabine or irinotecan has mainly been used as third-line therapy or after salvage chemotherapy.

Guidelines equally recommend VeIP/VIP, TIP, and HDCT as second-line therapy. With regard to third-line therapy, gemcitabine-containing regimens might be good candidates, but no specific regimen was recommended by the guidelines.

To our knowledge, there are no definitive data to guide the sequential treatment regimens for patients with “difficult-to-treat” advanced testicular cancer. In addition, there are no reports that studied the entire treatment sequence and survival from induction chemotherapy to completion of treatment. Thus, the goal of this retrospective study was to assess the response and OS of sequential chemotherapy and additional modalities for patients with advanced GCT at each step of treatment, regardless of the chemotherapy regimen.

**PATIENTS AND METHODS**

We retrospectively assessed 253 patients having GCT with metastasis treated in our institution from June 1998 to September 2013. Patient characteristics are summarized in Table 1. Of 253 patients, 111 patients had only first-line chemotherapy (induction group) and 142 patients had second-line-or-later chemotherapy (salvage group). The salvage group had worse initial clinical stage and International Germ Cell Cancer Collaborative Group risk criteria compared with induction group. This study was approved by the Institutional Review Board of Kyoto Prefectural University of Medicine, Kyoto, Japan, and written informed consent for each treatment was obtained from all patients.

**Treatment Strategy**

We treated advanced patients with GCT according to our treatment strategy, as follows:

1. Patients who achieved tumor marker normalization with residual mass had residual mass resection such as retroperitoneal lymph node dissection (RPLND), cervical lymph node dissection, and visceral metastatic site resection.

2. Patients without serum tumor markers (STMs) normalization after chemotherapy were treated with a subsequent chemotherapy. Our salvage chemotherapy strategy was as follows: second-line (TIP or paclitaxel, ifosfamide, and nedaplatin [TIN]), third-line (irinotecan and cisplatin [IrP] or irinotecan and nedaplatin [IrN]), fourth-line (paclitaxel, gemcitabine, and cisplatin [TPG] or paclitaxel, gemcitabine, and nedaplatin [TGN]), and fifth-line-or-after (clinical trial). For the patients who had already been treated at another institution, our first selection was a therapy that had not been used for that patient before.

3. If tumor marker level had been progressively decreasing, the current chemotherapy was continued. On the contrary, when tumor marker levels increased or if progressive disease (PD) was seen by radiographic studies, the patient was switched to a different chemotherapy.

4. Extrabeam radiotherapy and/or radiofrequency ablation as alternative focal therapy were performed, even for nonseminoma patients, in the curative or palliative setting according to the physician’s decision.

5. For brain metastasis, stereotactic radiotherapy, such as γ-knife or cyber-knife, was selected first. When dissemination or relapse occurred, whole brain irradiation was considered.

6. When viable cancer, not including teratoma, was found at residual mass resection, an additional 2 cycles of chemotherapy was typically performed.

**Response Assessment**

Response assessment was carried out following every other cycle according to the Response Evaluation Criteria in Solid Tumors Criteria ver1.1. CR was defined as the disappearance of all clinically detectable disease and as STM normalization. Partial response (PR) with STM normalization (PRm−) was defined as >30% reduction of the tumor size and normalization of previously elevated tumor markers. PR without STM normalization was considered marker-positive PR (PRm+). No change of visible disease (NC) was also classified as NCm− (NC with...
STM normalization) and NCm+ (NC without STM normalization). If significant STM elevation (>50%) and/or radiological progression (>25%) occurred after the beginning of treatment, the patient was classified as having PD.

RR was defined as CR + PR regardless of STM normalization. STM normalization (STMn) was defined as normal STM regardless of tumor shrinkage.

**Statistical Analysis**

Survival analysis was performed using the Kaplan–Meier method, and statistical difference was tested by the log-rank test. The primary endpoint was OS. Univariate and multivariate analysis were performed using JMP 10 software (SAS Institute, Inc, Cary, NC). Survival was confirmed by last visit to our institution or telephone.

**RESULTS**

**Sequential Chemotherapy**

Table 2 shows the treatment sequence at our department with other additional procedures. Briefly, BEP or etoposide and cisplatin (EP) therapy was chosen in 234 patients as induction chemotherapy. As second-line therapy, VIP or VeIP were selected in 44 patients, and TIP or TIN was done in 59 patients. With regard to third-line therapy, the most commonly selected therapy was TIP or TIN therapy in 53 patients, and IrP or IrN were the second most commonly selected therapy (18 patients). The most common trend of sequential chemotherapy for “difficult-to-treat” GCTs was BEP/EP-TIP/TIN-IrP/IrN-TGP/TGN. The second most common sequential chemotherapy was BEP/EP-VeIP/VIP-TIP/TIN-IrP/IrN.

With regard to additional procedures during or after chemotherapy, 150 surgeries and 14 radiation therapies were performed during or after first-line therapy. Out of 169 RPLND carried out, 156 were integrated with first, second, and third-line therapy.

**Response Rate**

The RRs (CR + PR) for the second, third, and fourth-line therapies are shown in Table 3. RR and STMn were obtained in 69.5% and 61.1%, respectively, in response to TIP/TIN therapy. VIP or VeIP also showed good STMn rate (50.0%). In third-line therapy, STMn occurred in 52.8% and 41.7% in response to TIP/TIN and VIP/VeIP, respectively. Even in the fourth-line setting, TIP/TIN resulted in a good STMn rate (44.0%).

**Overall Survival**

OS stratified by required chemotherapy line is shown in Figure 1A. In this analysis, second-line meant that the final chemotherapy was second-line therapy. Thus, the number of patients who completed therapy as first line, second line, third line, fourth line, fifth line, and sixth line or after was 111, 41, 28, 23, 18, and 32 cases, respectively. Figure 1B shows OS stratified by chemotherapy line. In this analysis, “third-line~” represented patients who had third-line-or-after chemotherapy (eg, fourth, fifth, and sixth-line-or-after therapy). In the patients with RPLND, residual viable cancer was found in 20.5% and teratoma was found in 23.7%. The 5 and 10-year OS rate was 91.5% and 87.9%, respectively.

In the search for the best sequence from second line to third line, we could not identify a sequence that was statistically significant superior to others in any combination. The sequence of second line and third line chemotherapy with VeIP/VIP and TIP/TIN had no significant difference, compared with other combinations, such as TIP/TIN and IrP/IrN (hazard ratio; 1.02, 95% confidence interval; 0.39–3.20, P = 0.97).

**Statistical Analysis**

Univariate and multivariate analysis are shown in Tables 4 and 5, respectively. Univariate analysis showed significant differences in each category of the International Germ Cell Consensus Classification, each clinical stage, doing RPLND or not, doing extra-RPLN resection or not, with or without radiation, and achieving STM normalization or not. Multivariate analysis showed significant differences in each clinical stage, doing RPLND or not, doing extra-RPLN resection or not, with or without radiation and achieving STM normalization or not.

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**TABLE 2. Chemotherapy Sequence in Our Department, n = 253**

| Chemotherapy Line (Median Cycles: Range) | First Line (n = 253) | Second Line (n = 142) | Third Line (n = 101) | Fourth Line (n = 73) | Fifth line (n = 50) |
|------------------------------------------|---------------------|----------------------|---------------------|---------------------|-------------------|
| BEP or EP                                | 234 (4:1–7)         | 16 (3:1–9)           | 3 (2:1–2)           | 1 (2)               | 1 (1)             |
| PBV                                      | 3 (5:2–5)           | 44 (3:1–6)           | 12 (3:1–4)          | 3 (3:3–4)          | 2 (2,2)           |
| HDCT                                     | 7 (1:1–3)           | 11 (2:1–3)           | 2 (12)              | 2 (1:1)            | –                 |
| TIP or TIN                               | –                   | 59 (4:1–14)          | 53 (4:1–18)         | 25 (3:1–11)        | 17 (4:1–7)        |
| IrP or IrN                               | –                   | 8 (4:3–7)            | 18 (3:2–9)          | 20 (3:1–6)         | 13 (2:1–9)        |
| TGP or TGN                               | –                   | 2 (2,2)              | 6 (3:10)            | 15 (2:1–7)         | 8 (2:1–11)        |
| Others                                   | 3 (3:1–3)           | 2 (3,7)              | 7 (4:1–6)           | 7 (2:1–2)          | 9 (2:1–11)        |
| Additional procedure RPLND: 168          | 106                 | 26                   | 23                  | 5                   | 5                 |
| ExRPLN resection: 114 (RFA: 25)          | 44 (2)              | 28 (5)               | 19 (5)              | 10 (2)             | 10 (5,5)          |
| EBRT/SRT                                 | 78                  | 14                   | 18                  | 17                  | 8                 |

BEP = bleomycin, etoposide, and cisplatin, EBRT = external beam radiotherapy, ExRPLN = extraretroperitoneal lymph node, HDCT = high-dose chemotherapy, IrN = irinotecan and nedaplatin, IrP = irinotecan and cisplatin, PBV = cisplatin, vinblastine, and bleomycin, RFA = radiofrequency ablation, RPLND = retroperitoneal lymph node dissection, SRT = stereotactic radiotherapy, TGP = paclitaxel, gemcitabine, and nedaplatin, TIP = paclitaxel, ifosfamide, and cisplatin, TIN = paclitaxel, ifosfamide, and cisplatin, VIP = etoposide, ifosfamide, and cisplatin. The number in the “fifth line~” column indicates the number of therapy that was performed as fifth-line therapy.
DISCUSSION

BEP therapy is widely used as first-line therapy for advanced testicular cancer. On the contrary, only 2 phase III trials of HDCT in the second-line setting have been performed, and there are no RCTs of conventional-dose salvage chemotherapy. Therefore, guidelines do not recommend salvage chemotherapy in a retrospective nature, definitive conclusion could not be obtained. Therefore, superiority of CDCT or HDCT should be reevaluated in a prospective RCT for patients with poor prognostic features, such as TIGER (Randomized Phase III Trial of Initial Salvage Chemotherapy for Patients with Germ Cell Tumors) study. 23

As shown in Table 6, after introducing ifosfamide, VIP or VeIP has been used as second-line therapy. Although its efficacy was relatively good, long NED could be achieved in about 30%, which is suboptimal. This led investigators to add sequential chemotherapy, even after fourth line, producing a good RR and a good OS rate. Recently, Necchi et al21 used modified VIP as second-line therapy in a large cohort. This report showed that 2-year progression-free survival (PFS) and 5-year OS was 34.3% and 42.1%, respectively. Another large retrospective study by Lorch et al22 showed better second-line outcomes with HDCT than with CDCT. PFS in all subgroups was better after HDCT than CDCT and OS was better than CDCT in all except 1 (low risk).

HDCT seemed to be superior to CDCT. However, since CDCT and HDCT regimen were varied and selection bias must exist in a retrospective nature, definitive conclusion could not be obtained. Therefore, superiority of CDCT or HDCT should be reevaluated in a prospective RCT for patients with poor prognostic features, such as TIGER (Randomized Phase III Trial of Initial Salvage Chemotherapy for Patients with Germ Cell Tumors) study. 23

Despite the absence of evidence from RCTs, TIP is effective first salvage chemotherapy. Furthermore, treatment options are more complicated in the third-line or later setting. Our sequential treatment strategy was comparable or better in all subgroups. This report showed that 2-year progression-free survival (PFS) and 5-year OS was 34.3% and 42.1%, respectively. Another large retrospective study by Lorch et al22 showed better second-line outcomes with HDCT than with CDCT. PFS in all subgroups was better after HDCT than CDCT and OS was better than CDCT in all except 1 (low risk).

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TABLE 3. RR and STM Normalization Rate at Each Line Stratified by Regimen

| Chemotherapy | First Line (253) | Second Line (142) | Third Line (101) | Fourth Line (73) | Fifth Line (50) |
|--------------|-----------------|------------------|-----------------|-----------------|----------------|
|              | RR | STMn | RR | STMn | RR | STMn | RR | STMn | RR | STMn |
| BEP/EP       | 206/234 | 162/234 | 3/16 | 4/16 | 2/3 | 0/3 | 1/1 | 1/1 | 1/1 | 0/1 |
|             | 88.0% | 69.2% | 18.8% | 25.0% | 66.7% | 9% | 100% | 100% | 100% | 0% |
| VeIP/VIP     | 5/6 | 2/6 | 33/44 | 22/44 | 6/12 | 5/12 | 3/3 | 1/3 | 1/2 | 1/2 |
|              | 83.3% | 33.3% | 75% | 50% | 50% | 41.7% | 100% | 33.3% | 50.0% | 50.0% |
| TIP/TIN      | — | — | 4/19 | 36/59 | 32/53 | 57/58 | 12/25 | 11/25 | 10/17 | 7/17 |
|              | 69.5% | 61.1% | 69.8% | 52.8% | 48.0% | 44.0% | 58.8% | 41.2% | — | — |
| HDCT         | 6/7 | 4/7 | 10/11 | 4/11 | 1/2 | 1/2 | 1/2 | 0/2 | — | — |
|              | 85.7% | 57.1% | 90.9% | 36.4% | 50% | 50.0% | 50.0% | 0% | — | — |
| IrP/IrN      | — | — | 7/8 | 2/8 | 9/18 | 6/18 | 5/20 | 1/20 | 4/13 | 2/13 |
| TGP/TGN      | — | — | 87.5% | 25.0% | 50.0% | 33.3% | 25.0% | 5.0% | 30.8% | 15.4% |
| Others       | 3/3 | 1/3 | 1/2 | 0/2 | 5/6 | 5/6 | 8/15 | 3/15 | 1/8 | 1/8 |
|              | 100% (PVB) | 33.3% (PVB) | 50.0% | 0% | 83.3% | 83.3% | 53.3% | 20.0% | 12.5% | 12.5% |
| Total        | 220/253 | 169/253 | 96/142 | 68/142 | 60/101 | 46/101 | 30/73 | 17/73 | 17/50 | 12/50 |
|              | 87.0% | 66.8% | 67.6% | 47.9% | 59.4% | 45.5% | 41.1% | 23.3% | 34.0% | 24.0% |

BEP = bleomycin, etoposide, and cisplatin, HDCT = high-dose chemotherapy, IrN = irinotecan and nedaplatin, IrP = irinotecan and cisplatin, PVB = cisplatin, vinblastine, and bleomycin, RFA = radiofrequency ablation, RPLND = retroperitoneal lymph node dissection, RR = response rate, SRT = stereotactic radiotherapy, STMn = serum tumor marker normalization, TGN = paclitaxel, gemcitabine, and nedaplatin, TGP = paclitaxel, gemcitabine, and cisplatin, TIN = paclitaxel, ifosfamide, and nedaplatin, TIP = paclitaxel, ifosfamide, and cisplatin, VeIP = vinblastine, ifosfamide, and cisplatin.

Better than the OS (20%) seen in previous studies. In addition, sequential chemotherapy, even after fourth line, produced a good RR and a good OS rate.

Recently, Necchi et al21 used modified VIP as second-line therapy in a large cohort. This report showed that 2-year progression-free survival (PFS) and 5-year OS was 34.3% and 42.1%, respectively. Another large retrospective study by Lorch et al22 showed better second-line outcomes with HDCT than with CDCT. PFS in all subgroups was better after HDCT than CDCT and OS was better than CDCT in all except 1 (low risk).
Sequential Chemotherapy for Advanced Testicular Cancer

Residual mass resection is an important and essential part of GCT treatment. The rate of persistent viable cancer and teratoma are 10% and 40%, respectively, in the modern chemotherapy era. Disease-specific survival rate is reported to be 75% in the literature. Our data involving patients with complicated background showed that viable cancer was found in 20.5% and that teratoma was found in 23.7%. The 5 and 10-year OS rate was 91.5% and 87.9%, respectively. These results are comparable to those from the previous reports.

The results of univariate and multivariate analysis suggest that it is very important to continue chemotherapy sequentially until STM normalization and resect residual mass, including RPLN and extra-RPLN, after finishing chemotherapy. Guidelines emphasize this point.

This study has several limitations. First, this was a retrospective study of unselected patients. Second, since multiple centers contributed and only a small number of patients started induction chemotherapy at our institution, the treatment strategy was inconsistent, and patient backgrounds were heterogeneous in each treatment. Third, prognostic factors were unadjusted when comparing RRs. This is the first report of sequential continuous treatment that described the response and survival in each treatment line in the real clinical world. We believe these data show the importance of sequential treatment for advanced GCTs, despite the various study limitations.

In conclusion, this is the first report of multimodal and chemotherapeutic sequences for patients with advanced GCT. Sequential treatment for advanced GCTs, especially “difficult-to-treat” GCTs, is very important to improve outcomes. Very high cure rates were achieved in patients who completed chemotherapy up to third-line therapies. In addition, even in heavily treated patients who had fifth or sixth-line therapy, continuous treatment might save their lives if accompanied by additional modalities. More systematic trials that include third-line or fourth-line treatment are needed.

**TABLE 4.** Univariate Analysis of Factors Related to Overall Survival

| Variables          | HR (95% CI) | P Value |
|--------------------|-------------|---------|
| IGCCC Good         | 1           | —       |
| IGCCC Intermediate | 1.86 (0.93–3.70) | 0.08 |
| IGCCC Poor         | 3.01 (1.61–5.72) | <0.001 |
| Seminoma vs nonseminoma | 0.79 (0.34–1.59) | 0.33 |
| RPLND Yes/no       | 0.19 (0.10–0.34) | <0.01 |
| ExRPLNR Yes/no     | 0.57 (0.40–0.97) | 0.05 |
| Radiation Yes/no   | 1.99 (1.16–3.38) | 0.01 |
| STM normalization Yes/no | 0.05 (0.02–0.08) | <0.001 |

CI = confidence interval, ExRPLNR = extraretroperitoneal lymph node resection, HR = hazard ratio, IGCCC = International Germ Cell Consensus Classification, RPLND = retroperitoneal lymph node dissection, STM = serum tumor marker.

**TABLE 5.** Multivariate Analysis of Factors Related to Overall Survival

| Variables          | HR (95% CI) | P Value |
|--------------------|-------------|---------|
| RPLND Yes/no       | 0.32 (0.15–0.62) | <0.001 |
| ExRPLNR Yes/no     | 0.40 (0.19–0.81) | 0.01 |
| STM normalization Yes/no | 0.04 (0.02–0.08) | <0.001 |

CI = confidence interval, ExRPLNR = extraretroperitoneal lymph node resection, HR = hazard ratio, RPLND = retroperitoneal lymph node dissection, STM = serum tumor marker.
| Introduced Drug | Regimen | Type of Study | No. of Patients | Treatment Setting | Response Rate, % | CR, % | NED, % |
|-----------------|---------|--------------|----------------|-------------------|-----------------|------|-------|
| Ifosfamide      | Farhat et al, 1996<sup>3</sup> | VIP/VeIP Phase II | 54 | Second line | 19 | 44 | 30 |
|                 | Loehrer et al, 1998<sup>4</sup> | VeIP Phase II | 135 | Second line | — | 49.6 | 24 |
|                 | Necchi et al, 2013<sup>21</sup> | VIP Retrospective | 189 | Second line | 53.9 | 18.5 | 5-year OS: 42.1 |
| Dose intensification | Pico et al, 2005<sup>7</sup> | HDCT RCT | CDCT: 128; HDCT: 135 | Second line | CDCT: 67; HDCT: 75 | 49.6 | 24 |
|                 | Lorch et al, 2007<sup>6</sup> | HDCT RCT | HDCTx1: 108; HDCTx3: 103 | Second line: 86% | HDCTx1: 48; HDCTx3: 46 | 5-year OS: HDCTx1: 48%; HDCTx3: 46% |
| Paclitaxel      | Motzer et al, 2000<sup>3</sup> | TIP<sup>7</sup> Phase II | 30 | Second line | 80 | 77 | 73 |
|                 | Mead et al, 2005<sup>9</sup> | TIP Phase II | 43 | Second line | 60 | 19 | 2-year OS: 65 |
|                 | Nonomura et al, 2007<sup>13</sup> | TIN Retrospective | 8 | Third line | 75 | 25 | 75 |
| Gemcitabine     | Nicolai et al, 2009<sup>11</sup> | TGP Phase II | 22 | Third line or later | 36.4 | 0 | 18.2 |
|                 | Shirasaki et al, 2009<sup>16</sup> | TGN Phase II | 15 | Third line or later | 47 | 0 | — |
|                 | Oechsle et al, 2011<sup>17</sup> | GO/GOP Phase II | 35/49 | Second line or later | — | — | GO: 3; GOP: 17 |
|                 | Necchi et al, 2013<sup>18</sup> | TGP Retrospective | 75 | Third or fourth line | 49 | 10.7 | 2-year OS: 29.5 |
| Irinotecan      | Miki et al, 2002<sup>20</sup> | IrN/IrP Phase II | 18 | Second line or later | 50 | 11 | 5-year OS: 53 |
|                 | Pectasides et al, 2004<sup>19</sup> | IrO Phase II | 18 | Third line | 40 | 17 | 17 |
|                 | Shamash et al, 2007<sup>20</sup> | IPO Phase II | 28 | Third line | 71 | 18 | 29 |

CDCT = conventional dose chemotherapy, CR = complete response, EFS = event-free survival, GO = gemcitabine and oxaliplatin, GOP = gemcitabine, oxaliplatin, and paclitaxel, HDCT = high-dose chemotherapy, IPO = irinotecan, paclitaxel, and oxaliplatin, IrN = irinotecan, nedaplatin, IrO = irinotecan and oxaliplatin, IrP = irinotecan, cisplatin, NED = no evidence of disease, OS = overall survival, TGN = paclitaxel, gemcitabine, and nedaplatin, TGP = paclitaxel, gemcitabine, cisplatin, TIN = paclitaxel, ifosfamide, and nedaplatin, TIP = paclitaxel, ifosfamide, and cisplatin, VeIP = vincristine, ifosfamide, and cisplatin, VIP = etoposide, ifosfamide, and cisplatin.
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