Update on topotecan for the treatment of advanced cervical cancer

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Summary

• Single agent cisplatin is the current standard treatment for recurrent cervical cancer, resulting in response rates (RR) of 20 to 30% and overall survival (OS) of about 7 months. Numerous combination regimens have been tested in an attempt to improve outcomes.

• Topotecan has been assessed in the Gynecologic Oncology Group (GOG) 0179 phase III trial (n= 356), the first prospective trial to identify a chemotherapy regimen yielding a statistically significant survival advantage in patients with advanced or recurrent disease. Cisplatin 50mg/m2 every 3 weeks (CPT, n=146) was compared with cisplatin 50mg/m2 day 1 plus topotecan 0.75mg/m2 days 1 to 3 every 3 weeks (CT, n= 147), and methotrexate 30mg/m2 days 1, 15 and 22, vinblastine 3mg/m2 days 2, 15 and 22, doxorubicin 30mg/m2 day 2 and cisplatin 70mg/m2 day 2 every 4 weeks (MVAC, n= 63). The treatments were administered for a maximum of 6 cycles or until disease progression or unacceptable toxicity. Survival was the primary endpoint of the study. The MVAC arm was closed after 4 treatment related deaths. According to the intention to treat (ITT) analysis, median survival was 6.5 months for CPT and 9.4 months for CT (unadjusted relative risk [RR] = 0.76; 95% CI, 0.593 – 0.979; p = 0.017). The RR was similar when adjusted for performance status, age and baseline disease status. Post hoc analyses suggest that patients who have received prior treatment with cisplatin may not respond as well and the added value of topotecan was also smaller for this group. Haematological toxicity occurred more frequently and was more severe in the CT arm: grade 3 and 4 neutropenia was reported in 70% receiving CT and 1.4% receiving CPT, febrile neutropenia in 17.7% on CT vs. 7.5% on CPT, grade 3 or 4 thrombocytopenia in 31.3% on CT vs. 3.4% on CPT. More infections were noted in the CT group because of the increased incidence of grade 3 or 4 adverse events. More cardiovascular adverse events were reported in patients on CT; grade 2 events in 12 on CT and 4 on CPT. There was no statistical evidence to indicate that quality of life and adverse effect scores in GOG 0179 changed differently over time across regimens, during the treatment period or up to 9 months after randomisation.

• The GOG 0204 study (unpublished) comparing doublet therapy [cisplatin with either paclitaxel (PC, reference arm), vinorelbine or topotecan] in patients with stage IVB, recurrent or persistent disease, was closed before reaching accrual maturity on the basis that none of the treatment arms was predicted to provide significant advantage over PC by the end of the study.

• Topotecan in combination with cisplatin is licensed for use in patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination, therefore the license excludes patients with persistent disease, and this is a somewhat narrower population of patients than that which made up the ITT population of GOG 0179.

• The cost of 6 cycles of CT (CPT 50mg/m2 day 1 and topotecan 0.75mg/m2 days 1- 3) is approximately £2000 vs. £290 for CPT in patient with average BSA 1.73m2.

• The SMC and the AWMSG have accepted for restricted use topotecan in combination with cisplatin-naive patients with either recurrent carcinoma of the cervix after radiotherapy or stage IVB disease.

• According to preliminary recommendations from NICE in its Appraisal Consultation Document, topotecan in combination with cisplatin, within its licensed indication, is not recommended for the treatment of women with recurrent or stage IVB cervical cancer, as it did not represent a good use of NHS resources (only data from GOG-0179 was included in its clinical effectiveness review).
Cervical cancer is one of the most common malignancies in women; the prognosis for advanced stage disease is poor and reported to be between 6 months to 2-years. In addition, women may experience substantial morbidity from both local recurrence and metastatic disease. Treatment options following failure of first line treatment include salvage surgery, chemotherapy and palliative treatment (including best supportive care). There have been no RCTs comparing chemotherapy to best supportive care in advanced disease and single agent cisplatin is the current standard chemotherapeutic agent for recurrent disease, despite low response rates (RR) ranging from 20% to 30% and overall survival (OS) of about 7 months. Numerous combination regimens have been tested in an attempt to improve outcomes. However, improved increased response rates (RR) have come at the expense of increased toxicity, whilst response durations have been short and survival rates have remained similar.

Topotecan in combination with cisplatin is licensed for use in patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. In those with prior exposure to cisplatin, a sustained treatment free interval is required to justify treatment with the combination, though the length of this interval has not been defined in the SPC.

Both the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) have accepted topotecan for restricted use in combination with cisplatin for cisplatin-naive patients with either recurrent carcinoma of the cervix after radiotherapy or stage IVB disease. The regimen was considered cost effective compared to cisplatin alone in cisplatin-naive patients, but not for those who have previous exposure to cisplatin. According to preliminary recommendations from NICE in its Appraisal Consultation Document (June 2009), topotecan in combination with cisplatin, within its licensed indication, is not recommended for the treatment of women with recurrent or stage IVB cervical cancer. In the submission, the manufacturer had submitted data from the GOG-0179 study and alluded to the GOG submission, the manufacturer had submitted data with recurrent or stage IVB cervical cancer. In the submission, is not recommended for the treatment of women with recurrent carcinoma of the cervix after radiotherapy and for patients with stage IVB disease. The regimen was considered cost effective compared to cisplatin alone in cisplatin-naive patients, but not for those who have previous exposure to cisplatin.

Epidemiology

In the UK in 2004, the age-standardised (European) annual incidence rate of cervical cancer was 8 per 100,000 females. At that time, 2726 new cases were diagnosed, making it the twelfth most common cancer in women and accounting for around 2% of all female cancers.

Efficacy

Topotecan has been assessed in the Gynecologic Oncology Group (GOG) 0179 phase III trial which involved 356 patients with advanced cervical cancer. Women in the study had stage IVb recurrent or persistent disease, were unsuitable for curative treatment with surgery and/or radiotherapy, and had a GOG performance status (PS) of 0 to 2. Nearly 60% of women had received prior (radiosensitising) treatment. This is a somewhat broader population of patients than that for which topotecan is licensed, as it included patients with persistent disease and those without a reasonable platinum free period. All patients were required to have an absolute neutrophil count > 1.5 x 10^9/L and platelet count > 100 x 10^9/L on the day of re-treatment and at that time, chemotherapy doses were adjusted based on nadir blood counts and toxicity. Filgrastim was allowed during subsequent cycles of treatment if febrile neutropenia occurred after dose modification for haematological toxicity during the previous cycle of therapy. The study compared the following regimens:

- Cisplatin 50mg/m^2 every 3 weeks (CPT, n=146)
- Cisplatin 50mg/m^2 day 1 plus topotecan 0.75mg/m^2 days 1 to 3 every 3 weeks (CT, n=147)
- Methotrexate 30mg/m^2 days 1, 15 and 22, vinblastine 3mg/m^2 days 2, 15 and 22, doxorubicin 30mg/m^2 day 2 and cisplatin 70mg/m^2 day 2 every 4 weeks (MVAC, n=63)

The treatments were administered for a maximum of 6 cycles for non-responders, or until disease progression or unacceptable toxicity. Those who achieved a partial response (PR) with an acceptable level of toxicity were allowed to continue treatment beyond 6 cycles after discussion with the chief investigator. The primary endpoint of the study was survival and secondary endpoints were response rate and progression free survival (PFS). Quality of life was also assessed.

The MVAC arm was closed after 4 treatment related deaths were observed and was not included in the data analysis, leaving the trial to continue as a two arm study. Seven patients on CPT and 12 on CT were not assessable for response.

According to the intention to treat analysis, CT was associated with a small but statistically significant survival benefit compared with CPT: median survival was 6.5 months in the CPT and 9.4 months in the CT group (unadjusted relative risk [RR] = 0.76; 95% CI, 0.593 to 0.979; p = 0.017), and when adjusted (aRR) for PS, age and baseline disease status, it was 0.77 (0.6 to 0.992, p = 0.021). Median PFS was 2.9 months for CPT and 4.6 months for CT; the unadjusted and adjusted RR estimates were 0.76 (0.597 to 0.969, p = 0.014) and 0.738 (0.578 to 0.942, p = 0.0075), respectively. The overall response rate was 13% to CPT (4 complete responses [CRs]) and 27%
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Overall 145 patients in each arm were included in the final analysis. The compliance rate for valid questionnaires decreased over time so that by the fourth time point, it was 56% and 62% for the CPT and CT arms, respectively. There was no statistical difference between arms in baseline QOL. After adjustment for baseline scores and age at entry, there was no statistical evidence that QOL and adverse effect scores changed differently over time across regimens, during the treatment period or up to 9 months after randomisation. Despite increased toxicity, CT did not significantly reduce patient QOL when compared with CPT alone.10

CT was also assessed in the GOG 0204 trial, which was designed to identify suitable cisplatin based doublet regimens for treating patients with stage IVB, recurrent or persistent cancer not amenable to cure.11,12 In the study, they were randomised to:

1. Paclitaxel 135 mg/m2 over 24 hrs + cisplatin (CIS) 50 mg/m2 day 2 every 3 wks (PC, reference arm)
2. Vinorelbine 30 mg/m2 day 1 and 8 + CIS 50 mg/m2 day 1 every 3 wks (VC)
3. Gemcitabine 1000mg/m2 day 1 and 8 + CIS 50 mg/m2 day 1 every 3 wks (GC)
4. Topotecan 0.75 mg/m2 days 1, 2, and 3 + CIS 50 mg/m2 day 1, every 3 wks (TC).

Between May, 2003 and April, 2007, 513 patients were enrolled and initially randomised to PC versus VC, but upon availability of results from the GOG 179, the trial was expanded and patients were randomised to receive PC, VC, GC, or TC. The median age in all four arms was approximately 50 years and performance status was 0 in the majority of cases in all arms. The proportion of patients with grade 2 versus grade 3 disease was approximately 1:1 in all arms. In April 2007, a planned interim futility analysis was performed, and recommended early closure of this study on the basis that none of the four arms was predicted to provide significant advantage over PC by the end of the study. Results were as follows:

- No significant overall survival difference was demonstrated across the four treatment arms: median survival with PC was 12.9 months, versus 10 to 10.3 months in the other three study arms: hazard ratios for death were 1.15, 1.32, and 1.26 with VC, GC, and TC when compared to PC (p = NS).
- Median progression-free survival was less than 6 months in all treatment arms and there were no significant difference between groups: hazard ratios for disease progression were 1.35, 1.39, and 1.27 with VC, GC, and TC, respectively, when compared to PC (p = NS).
- Tumour response rates were not significantly different across the four arms: rates of complete response were 29.1%, 25.9%, 22.3%, and 23.4% for PC, VC, GC, and TC, respectively.

The authors of the study note that they could not rule out the possibility that the survival advantage seen with the combination regimen was mainly due to topotecan, given that over half of the study population had received prior platinum therapy and thus may have been platinum resistant.9

Quality of life assessment was conducted at four time points using: Functional Assessment of Cancer Therapy- General (FACT-G), Cervix subscale (Cx subscale), FACT/GOG-Neurotoxicity subscale (NTX subscale), Brief Pain Inventory (BPI) and uniscale (UNI).6

<table>
<thead>
<tr>
<th>OS (months)</th>
<th>PFS (months)</th>
<th>RR (% no CRs)</th>
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<tr>
<td>Intention to treat</td>
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<tr>
<td>CT</td>
<td>CPT</td>
<td>aRR</td>
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<td>9.4</td>
<td>6.5</td>
<td>0.77, 95% CI 0.6 to 0.992</td>
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<td>Cisplatin naive subgroup</td>
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<td>14.5</td>
<td>8.5</td>
<td>0.587, 0.389 to 0.884</td>
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<td>SCFI subgroup</td>
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<tr>
<td>9.9</td>
<td>6.3</td>
<td>0.75, 0.492 to 1.155</td>
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The CT arm of the cisplatin naïve population (n = 44) had a median OS of 14.5 months compared to 8.5 months for the CPT (n=46) group (HR 0.587, 95% CI: 0.389 to 0.884). The CT arm in the SCFI population had a median OS of 9.9 months (vs. 6.3 months for CPT, HR 0.75, 95% CI: 0.492 to 1.155), this difference was not statistically significant. These findings suggest that compared to cisplatin naïve patients, those who have received prior treatment with cisplatin may not respond as well to CT and this is reflected in the licence which requires a treatment-free interval for those patients with prior cisplatin use. As these were post hoc analyses, the power of the study to detect true differences in effect between the treatment regimens in the sub groups is reduced.6

| Summary of results |
|-------------------|-----------------|-----------------|
| OS (months) | PFS (months) | RR (% no CRs) |
|                |                |                |
| CT | CPT | aRR | CT | CPT | aRR | CT | CPT |
| 9.4 | 6.5 | 0.77, 95% CI 0.6 to 0.992 | 4.8 | 2.9 | 0.73, 95% CI 0.578 to 0.942 | 27% (14) | 13% (4) |
| Cisplatin naive subgroup |               |               |               |
| 14.5 | 8.5 | 0.587, 0.389 to 0.884 |               |               |               |
| SCFI subgroup |               |               |               |
| 9.9 | 6.3 | 0.75, 0.492 to 1.155 |               |               |               |

to CT (14 CRs).9 Thirty-six months after the start of the trial, 129 (88%) patients in the CPT group and 118 (80%) patients on CT had died.6

In the submission to the AWMSG, additional subgroup analyses were undertaken as the licence for topotecan plus cisplatin does not include all patients in the GOG-0179 trial. The “licensed population” excludes patients with persistent disease (n=32 [11%] of the ITT population) and those patients without a sustained cisplatin-free interval (SCFI) [n=39, 13% of the ITT population]. For the purposes of this submission, the SCFI was assumed as 180 days which related to the period between the last cisplatin dose and disease recurrence. The company also analysed the two sub groups within the “licensed population” i.e. cisplatin-naïve population (both advanced and recurrent disease patients) and SCFI population.6

The CT arm of the cisplatin naïve population (n = 44) had a median OS of 14.5 months compared to 8.5 months for the CPT (n=46) group (HR 0.587, 95% CI: 0.389 to 0.884). The CT arm in the SCFI population had a median OS of 9.9 months (vs. 6.3 months for CPT, HR 0.75, 95% CI: 0.492 to 1.155), this difference was not statistically significant. These findings suggest that compared to cisplatin naïve patients, those who have received prior treatment with cisplatin may not respond as well to CT and this is reflected in the licence which requires a treatment-free interval for those patients with prior cisplatin use. As these were post hoc analyses, the power of the study to detect true differences in effect between the treatment regimens in the sub groups is reduced.6

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| OS (months) | PFS (months) | RR (% no CRs) |
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| CT | CPT | aRR | CT | CPT | aRR | CT | CPT |
| 9.4 | 6.5 | 0.77, 95% CI 0.6 to 0.992 | 4.8 | 2.9 | 0.73, 95% CI 0.578 to 0.942 | 27% (14) | 13% (4) |
| Cisplatin naive subgroup |               |               |               |
| 14.5 | 8.5 | 0.587, 0.389 to 0.884 |               |               |               |
| SCFI subgroup |               |               |               |
| 9.9 | 6.3 | 0.75, 0.492 to 1.155 |               |               |               |

The authors of the study note that they could not rule out the possibility that the survival advantage seen with the combination regimen was mainly due to topotecan, given that over half of the study population had received prior platinum therapy and thus may have been platinum resistant.9

Quality of life assessment was conducted at four time points using: Functional Assessment of Cancer Therapy- General (FACT-G), Cervix subscale (Cx subscale), FACT/GOG-Neurotoxicity subscale (NTX subscale), Brief Pain Inventory (BPI) and uniscale (UNI).6

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- Toxicities did not vary significantly across the four arms; the lowest incidence of myelosuppression was in the PC arm, although this difference was not statistically significant.

QOL was assessed prior to randomisation, prior to cycles 2 and 5, and 9 months post study entry. QOL measures included the Functional Assessment of Cancer Therapy - Cervix Trial Outcome Index (FACT-Cx TOI), the FACT/GOG-Neurotoxicity 4-item scale, and the Brief Pain Inventory 0-10 pain intensity item. The study was closed in April 2007 when 81.8% of target accrual was enrolled (n = 491). From pre-cycle 2 through the 9-month follow-up, there were no clinically or statistically significant differences across any of the groups in pain or QOL. Women on the CG and CT regimens reported less neuropathy at the last two assessments, although the difference was not statistically significant.13

The authors note that with median progression-free survival of less than 6 months in all arms evaluated in this study, and median overall survival ranging from 10 months to one year, treatment options for advanced and recurrent cervical cancer remain dismal. They suggest that as non-statistically significant differences in overall survival, tumour response, and quality of life were found between PC and the other doublets examined in the study, and actually non-statistically significant benefits seen in the reference arm, PC should remain the doublet of choice. They add that all systemic chemotherapeutic options should be viewed as palliative in this setting and impact on quality of life should be considered during choice of any palliative regimen (versus best supportive care) although no significant difference in QOL was observed across the arms investigated in this study.11,12

Safety

The GOG 0179 study noted that haematological toxicity occurred more frequently and was more severe in the CT arm: grade 3 and 4 neutropenia occurred in 70% on CT and 1.4% on CPT. Febrile neutropenia occurred in 17.7% on CT vs. 7.5% on CPT. Grade 3 or 4 thrombocytopenia occurred in 31.3% on CT vs. 3.4% on CPT. Infection was also greater in the CT group because of the increased incidence of grade 3 or 4 adverse events. More cardiovascular adverse events were reported amongst patients on CT (grade 2 events in 12 on CT and 4 on CPT).5 Five patients in the CPT arm (3.4%) required G-CSF support compared with 37 patients (26.4%) in the CT arm [Personal communication GSK]. In addition, more patients in the CT group received treatment with platelets, RBC and erythropoietin compared with the CPT group.5 According to the SMC assessment, “the European Medicine Agency noted that although the haematotoxicity of the combination regimen is rather profound for a treatment administered with palliative intent, toxicity was manageable and the adverse event profile for topotecan when given in combination with cisplatin is consistent with that seen with topotecan monotherapy.”25

Cost Implications for NHS

The cost of 6 cycles of CT (CPT 50mg/m2 day 1 and topotecan 0.75mg/m2 days 1-3) in patient with average BSA 1.73m2 is approximately £2000 vs £260 for CPT (MIMS June 2009 and BNF March 2009).

Cost of 6 cycles of regimens used in GOG 0204:
- Paclitaxel + cisplatin (PC, reference arm) ~ £3700
- Vinorelbine and + CIS (VC) ~ £2000
- Gemcitabine + CIS (GC) ~ £3640

NICE’s Appraisal Committee noted that the ICER for topotecan plus cisplatin compared with cisplatin alone was £59,000 per QALY gained when minimum wastage was assumed, and the ICER for topotecan plus cisplatin compared with paclitaxel plus cisplatin was £117,000 per QALY gained when maximum wastage was assumed. The Committee was also aware that when the hazard ratio derived from the trial based comparison of different combination therapies was used, topotecan plus cisplatin was less effective and more costly than paclitaxel plus cisplatin. On this basis, topotecan in combination with cisplatin could not be recommended as treatment for the licensed population as an efficient use of NHS resources.7
Points for consideration

GOG 0179 was the first prospective trial to identify a chemotherapy regimen yielding a statistically significant survival advantage in patients with advanced or recurrent cervical cancer. However, its study population was heterogeneous and considered by some not to be fully representative of current clinical practice. Questions that remain to be addressed include:

- If the study population does not reflect current clinical practice, what is the place of CT in the treatment of cervical cancer?
- Is the small (2.9 months) survival advantage of CT over CPT worth the higher incidence of haematological toxicity and associated costs of treating these problems (though quality of life remained unaffected in this group)?
- Would topotecan monotherapy be as effective and better tolerated than CT?
- Would patients who had received prior chemosensitisation with cisplatin be considered cisplatin naïve?
- What is the length of a sustained cisplatin free interval?

It has been noted that the median survival in GOG 0179 was not appreciably different from that for the two previous GOG phase III studies involving cisplatin plus either ifosfamide or paclitaxel. This observation based on cross study comparisons was confirmed in the GOG 0204 study, which was closed before reaching accrual maturity on the basis that none of the treatment arms (including CT) was predicted to provide significant advantage over PC by the end of the study. Therefore, it becomes even more questionable if CT does have a place in therapy in patients with advanced or recurrent cervical cancer.

References

11. Monk BJ, Hill C., Oncolink at ASCO, June 1, 2008 http://www.oncolink.org/conferences/article.cfm?c=3&s=48&ss=269&id=1786
Acknowledgements

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