Paclitaxel

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.1. Cytotoxic medicines

ATC codes: L01CD01

Indication	Malignant neoplasms of cervix uteri ICD11 code: 2C77
INN	Paclitaxel
Medicine type	Chemical agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 6 mg per mL
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Tags	Cancer
Wikipedia	Paclitaxel
DrugBank	Paclitaxel

Expert Committee recommendation

The Expert Committee recommended extending the indications for cisplatin, carboplatin and paclitaxel on the complementary list of the EML to include treatment of invasive cervical cancer. The Committee considered that the evidence presented demonstrated these medicines to be associated with relevant survival benefits for patients. The Committee noted that regimens including these medicines are considered standard care in the curative and non-curative settings for cervical cancer. Cisplatin is currently listed for use in the curative setting as a radiosensitizer and its listing is recommended to be extended to include the non-curative setting. Carboplatin is recommended for listing both in the curative and non-curative settings, and paclitaxel is recommended for listing in the non-curative setting. The Expert Committee did not recommend extending the indications for fluorouracil to include treatment of cervical cancer in the curative setting. The Committee noted that when combined with radiotherapy, fluorouracil alone or in combination with cisplatin, was not associated with additional benefit compared to radiotherapy alone or cisplatin plus radiotherapy.

Background

The application requested listing for cisplatin, carboplatin, paclitaxel and fluorouracil for the additional indication of treatment of invasive cervical cancer. As part of the comprehensive review of cancer medicines on the EML undertaken in 2015, the Expert Committee recommended the addition of single-agent cisplatin to the complementary list of the EML for the treatment of early-stage cervical cancer for use concurrently with radiotherapy in women at high risk of recurrence following surgery (1). All of the medicines proposed in this

application for cervical cancer are included on the EML. However, carboplatin, paclitaxel and fluorouracil lack a specific endorsement for the indication of cervical cancer, and the listing for cisplatin is specific for use as a radiosensitizer.

Public health relevance

Cervical cancer is the fourth most common cancer among women globally, with an estimated 570 000 new cases and 311 000 deaths annually in 2018 (2). The burden of cervical cancer is estimated to increase by almost 50%, reaching 460 000 related deaths by 2040, of which the large majority will occur in low- and middle-income countries (LMICs). Currently, the majority of cases in LMICs are diagnosed at late stage, as a result of delayed clinical presentation and untimely referral of symptomatic patients to the appropriate pathway of care for diagnosis and treatment (3). In response to a rising public health problem, the United Nations Joint Global Programme on Cervical Cancer Prevention and Control was established in 2016, as an inter-Agency programme to engage partners and key stakeholders, providing technical expertise to orient an evidence-based policy for cervical cancer planning and provide pragmatic solutions (4). The elimination of cervical cancer is a priority in the Sustainable Development Goals (SDG) agenda, contributing to the reduction of premature mortality due to noncommunicable diseases by one-third by 2030 and the realization of universal health coverage, in terms of access to essential health care interventions and financial risk protection (5, 6). The final aim is to reduce drastically the incident cases of cervical cancer per year, through prevention (human papilloma virus vaccination) and early detection (cervical cancer early detection and screening, and treatment of pre-invasive cancer) along with treatment of more advanced forms through diagnosis, cancer surgery and radiotherapy, systemic therapy and palliative care services (7).

Benefits

Cisplatin Cisplatin is a critical cytotoxic agent for the treatment of cervical cancer for radiotherapy is appropriate (8–12). It is also a key agent (alone or in combination with other agents) for the management of advanced disease, that is not amenable to locoregional control alone (i.e. surgery, radiotherapy, chemoradiotherapy (13–15). Clinical trials of cisplatin 50 mg/m2 every three weeks as monotherapy for cervical cancer provided disappointing results for disease control (objective response rate (ORR, 20%; progression-free survival (PFS), approximately three months) and poor survival (overall survival (OS), approximately eight months) (16, 17). When combined with other cytotoxic agents, improved outcomes have been reported. A Phase III clinical trial tested the combination of cisplatin and paclitaxel against cisplatin monotherapy, for FIGO IV B (metastatic), recurrent (after locoregional treatments) or persistent (not responding to locoregional treatments) cervical cancer (n=280) (18). The addition of paclitaxel increased the ORR (19% to 36%) and the median PFS (2.8 to 4.8 months), with no relevant difference in overall survival. However, 92% of patients had prior exposure to cisplatin, the majority pre-treated with a cisplatin-paclitaxel combination regimen. Different cisplatin combinations have been compared with cisplatin monotherapy in another trial enrolling patients with stage IV B recurrent or persistent cervix uteri carcinoma (19). Patients in the experimental arm received either cisplatin 50 mg/m2 plus topotecan (Cto) 0.75 mg/m2 every three weeks or MVAC (cisplatin, vinblastine, doxorubicin and cisplatin); the standard arm consisted of single-agent cisplatin 50 mg/m2 every three weeks (n=364). The escalated polychemotherapy (Cto or MVAC) showed a longer PFS (median PFS 2.9 vs 4.6 months; RR = 0.76, 95%CI 0.58 to 0.94) and OS (median OS 6.5 vs 9.4 months, RR=0.76, 95%CI 0.60 to 0.99) when compared to monotherapy. The greatest effect size on survival was observed in cisplatin-naive patients, where the gain of OS was 6.6 months vs 1.9 months in pre-exposed patients. The open-label, randomized, Phase III JCOG0505 trial compared cisplatin or carboplatin in combination with paclitaxel, in a non-inferiority (NI) design, with a NI-margin of 1.29 for hazard ratio (HR) of OS. The schedules used were: paclitaxel 135 mg/m2 plus cisplatin 50 mg/m2 every three weeks and paclitaxel 135 mg/m2 plus carboplatin 5 mg/mL/min (area-under-the-curve) each three weeks (n=253) (20). 98% of patients had a good performance status (WHO-ECOG scale 0-1), 83% presenting with squamous histology, 79% previously irradiated and 48% pre-exposed to cisplatin. The trial met the primary endpoint and confirmed carboplatin-based to be non-inferior to cisplatin-based chemotherapy, reporting HR= 0.99 (90% CI, 0.79 to 1.25), and median OS of 18.3 and 17.5 months, respectively. Median PFS was 6.9 and 6.2 months. An exploratory sub-group analysis showed

cisplatin to provide a greater effect size in platinum-naive patients, with a median OS of 23 months and 13 months for cisplatin and carboplatin, respectively. The sub-group analysis also favoured carboplatin and paclitaxel over cisplatin combination for platinum-resistant and platinum-intermediate sensitive disease (platinum-free interval inferior to 6 months or between 6–12 months), suggesting that carboplatin can still provide a benefit after cisplatin failure and, otherwise, that cisplatin provides the greatest effect in the naive and eligible patients (HR for platinum-resistant in cisplatin pre-treated patients: 0.57; HR for platinum-intermediate: 0.71). However, all platinum pre-treated patients were exposed to cisplatin and none to carboplatin, suggesting that the re-challenge with the same platinum compound would be less effective and an inter-class switch preferred, where possible. The 2009 GOG-204 Phase III clinical trial compared four different cisplatin-containing doublet combinations for stage IVB, recurrent or persistent cervical carcinoma patients (21). Patients were enrolled to receive vinorelbine, gemcitabine, topotecan or paclitaxel in combination as doublets with cisplatin 50 mg/m2 each three weeks (n=513). Patients presented predominantly with squamous cell (80–88%) persistent (74–80%) cervical cancer, mostly pre-treated with cisplatin and radiotherapy (70–81%). The trial was interrupted after 513 patients enrolled, as the futility analysis proved the different combinations to be non-superior to cisplatin plus paclitaxel. ORR ranged between 22% and 29%; median PFS between 4–5.8 months and OS 10–12.9 months. Nevertheless, paclitaxel–cisplatin showed the highest response rate (29%), median PFS (5.8 months) and median OS (12.8 months). The use of cisplatin requires the fulfilment of specific criteria for treatment initiation, particularly a conserved glomerular kidney function. Patients are considered to be cisplatin- unfit if presenting one of more of the following characteristics: Eastern Clinical Oncology Group (ECOG) performance status (PS) of 2 or more; creatinine clearance of less than 60 mL/minute; treatment-related hearing loss of Grade 2 or more according to the Common Terminology Criteria for Adverse Events (CTCAE) system and treatment-related neuropathy of Grade 2 or more (22). Carboplatin Guidelines include carboplatin in the treatment of advanced disease for cisplatin-unfit patients, as a category 1 treatment (according to National Comprehensive Cancer Network (NCCN) guidelines) (15). The role of carboplatin is highlighted in the present submission as an alternative in cisplatin-unfit patients, both as radiosensitizer and systemic agent for combination treatment in the locally advanced, refractory, relapsed and metastatic settings. The acknowledgment of carboplatin as an agent for cervical cancer is relevant for the specific anatomic topography and local invasiveness of the disease. Different series have described hydronephrosis in 20–35% of cervical cancer patients, with possible retrograde kidney parenchyma impairment, due to the close anatomical proximity of the ureter with genitourinary organs. A Nigerian analysis of the renal status of patients with cervical cancer prior to commencement of treatment, reported one-third of patients having a clinically significant urethral involvement or obstruction and nearly 10% having a kidney dysfunction for related parenchyma disease (23). Carboplatin has been shown in a sub-group analysis of the JCOG0505 trial to provide a greater benefit in cisplatin pre-treated patients compared to cisplatin (20). These findings were confirmed in a retrospective analysis of a cohort of Asian patients treated with paclitaxel combined either with cisplatin or carboplatin (n=116) (24). In the curative setting, the role of carboplatin must be restricted to the patients unfit for cisplatin but still eligible to receive a curative treatment, in the context of a concomitant chemoradiotherapy, as a radiosensitizer. Data on the efficacy of concurrent weekly carboplatin with radiotherapy in the treatment of cervical cancer have been evaluated in a recent meta-analysis, exploring whether differences between cisplatin and carboplatin exist when used as radiosensitizers (25). Twelve studies (1698 patients) were eligible for meta-analysis. Complete response (CR), PFS and OS were assessed. The use of carboplatin provided a lower rate of CR (OR: 0.53, 95%CI 0.34 to 0.82); lower PFS and OS were assessed at 3 years, with HR of 0.71 and 0.70, indicative of a potential difference. However, the authors concluded that carboplatin should still be a priority for cisplatin-ineligible patients, as it is the preferable alternative choice of treatment. Paclitaxel As previously described, paclitaxel represents the optimal partner of chemotherapy platinum- based doublets for the treatment of advanced disease. The doublet cisplatin plus paclitaxel (or carboplatin plus paclitaxel, in cisplatin-ineligible patients) is the recommended regimen for advanced cervical cancer, as reported by the principal guidelines (13–15). In a large randomized Phase III clinical trial (GOG-204), paclitaxel showed a greater effect size and a manageable safety profile, when compared with the combinations with topotecan, gemcitabine and vinorelbine (21). Fluorouracil Fluorouracil (5-FU) has a role as a radiosensitizer and is extensively used across different cancer indications. For cervical cancer, women with high-risk disease are eligible to receive concomitant adjuvant chemoradiotherapy. The features of high risk are defined as: positive pelvic lymph nodes, positive surgical

margins, and positive parametrium. The use of adjuvant chemotherapy in combination with radiotherapy has been tested in a clinical trial, enrolling 268 patients with clinical stage FIGO IA2 and IIA carcinoma of the cervix, treated with radical hysterectomy and pelvic lymph node dissection, and found to have lymph node involvement, invaded parametrium and positive margins (11). Patients received cisplatin as a bolus of 70 mg/m2 followed by 5-FU as continuous IV infusion over 96 hours at 1000 mg/m2 every three weeks, for four cycles concomitantly with radiotherapy for the first and second cycle. The pelvic radiotherapy consisted of 1.7 Gy per day on days 1 to 5 of each week, for a total of 29 fractions (49.3 Gy). Around one-third of patients presented with involvement of parametria, and 85% presented with metastatic pelvic lymph nodes after surgery. The addition of chemotherapy to radiotherapy showed a gain in overall survival, with 10% more patients alive at four years (OS 81% vs 71% at four years; HR=1.96, CI not reported, p=0.007). The projected progression-free survival at four years was 80% vs 63% (HR = 2.01, p=0.003), favouring the chemotherapy + radiotherapy arm. The role of 5-FU as a radiosensitizer agent has been investigated in three clinical trials for stage IB2 to IVA cervical cancer patients (8, 26, 27). The three trials reported similar results, supporting the use of cisplatin-based chemotherapy, including the combination of cisplatin and 5-FU, as radiosensitizer in as an adjunct to radiotherapy for locally advanced cervical cancer: HRs for OS ranged between 0.52 (stage IB2- IVA) and 0.72 (stage IIB-IVA).

Harms

Cisplatin and carboplatin In the JCOG0505 trial, cisplatin or carboplatin in combination with paclitaxel were associated with similar proportions of patients who terminated treatment because of intolerable adverse events, 9.5% in the carboplatin group and 11.8% in the cisplatin group (20). Most patients experience haematological toxicity from the medication combination including neutropenia, thrombocytopenia and anaemia, all of which are typically rapidly reversible upon discontinuation of agents (28, 29). Cisplatin is highly emetogenic, prophylactic antiemetics are necessary to reduce nausea and vomiting in all patients (30). Mild peripheral neuropathy is common. Patients should be followed carefully, and dose reduction or discontinuation may be required for moderate or severe symptoms. Ototoxicity is observed with cisplatin and is more common with increasing dose and number of cycles. Audiometry should be considered to monitor patients with toxicity; vestibular defects are less common. Serious renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Hypomagnesaemia, hypocalcaemia and hypokalaemia should be followed and deficits addressed. Intravenous hydration both before and after administering cisplatin is necessary to reduce the incidence of renal toxicity (31). Paclitaxel Paclitaxel is associated with infusion reactions in about 30% of patients; most reactions are mild and easily managed (32, 33). Paclitaxel frequently causes alopecia and peripheral neuropathy, which is often mild and reversible (32, 34). Fluorouracil The use of adjuvant chemotherapy (cisplatin followed by 5-FU), in combination with radiotherapy, is associated with an increase in Grade 4 adverse events, mostly haematological toxicity (Grade 4 adverse events: 17% vs 4%; Grade 3 and 4 granulocytopenia: 29% vs 2%) compared to radiotherapy alone (11).

Cost / cost effectiveness

An economic analysis of cisplatin alone versus cisplatin doublets in women with advanced or recurrent cervical cancer evaluated the impact of: (i) extending the use of cytotoxic agents to the advanced disease, with a highlight on systemic therapy; and (ii) the use of 5-FU and carboplatin as alternative radiosensitizers (35). The cost analysis showed that chemotherapy medicine costs for six cycles of cisplatin was US$ 89 while for cisplatin plus paclitaxel it was US$ 489. The highest chemotherapy cost was for gemcitabine plus cisplatin at US$ 18 306. According to the major effect size and manageable safety profile, the combination of cisplatin and paclitaxel was the most cost-effective option for the treatment of advanced cervical cancer, and, to a large extent, more cost-effective than cisplatin monotherapy. Sensitivity analyses confirmed that cisplatin plus paclitaxel would be the regimen of choice. For the same setting, another model showed that the incremental cost-effectiveness ratio for combination cisplatin plus paclitaxel compared to cisplatin alone was US $13 654 per quality-adjusted life-year (QALY) gained (36).

WHO guidelines

None available.

Availability

Originator and generic brands of the proposed medicines are available.

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