Gynecologic Oncology 119 (2010) 531–537

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Health-related quality of life outcomes associated with four cisplatin-based doublet chemotherapy regimens for stage IVB recurrent or persistent cervical cancer: A Gynecologic Oncology Group study

David Cella [a,*], Helen Q. Huang [b], Bradley J. Monk [c], Lari Wenzel [c], Jo Benda [d], D. Scott McMeekin [e], David Cohn [f], Lois Ramondetta [g], Cecelia H. Boardman [h]

[a] Northwestern University Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA
[b] GOG Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY; Department of Biostatistics, University at Buffalo, Buffalo, NY, USA
[c] University of California Irvine, Chao Family Comprehensive Cancer Center, Orange, CA, USA
[d] University of Iowa, Iowa City, IA, USA
[e] University of Oklahoma, Oklahoma City, OK, USA
[f] The Ohio State University, Columbus, OH, USA
[g] MD Anderson Cancer Center, Houston, TX, USA
[h] Virginia Commonwealth University, Richmond, VA, USA

ARTICLE INFO

Article history:
Received 21 May 2010
Available online 15 September 2010

Keywords:
Health-related quality of life
Quality of life
Cervical cancer
Advanced
Recurrent
Clinical trial
Phase III
Chemotherapy

ABSTRACT

Purpose. To assess the differences in health-related quality of life (HRQL) of 4 cisplatin containing doublet chemotherapy combinations in women with advanced/recurrent cervical carcinoma.

Methods. Patients were randomized to three-week cycles of paclitaxel + cisplatin (PC); vinorelbine + C (VC); gemcitabine + C (GC); or topotecan + C (TC). We report HRQL results from data available on 434 eligible patients enrolled into this 513 patient trial. HRQL was assessed with the Functional Assessment of Cancer Therapy-Cervix (FACT-Cx) the FACT/Gynecologic Oncology Group (FACT/GOG) four-item neurotoxicity scale, and the 0–10 "worst pain" item from the Brief Pain Inventory, at baseline (pre-treatment), prior to beginning cycle 2, prior to beginning cycle 5, and at 9 months after enrollment. As reported by Monk et al. (2009) [13] VC, GC and TC were found not to be superior to PC with regard to progression-free survival or overall survival.

Results. The trial was terminated early due to planned interim futility analysis, reducing power for HRQL analysis from 85% to 55%. Patients receiving VC, GC and TC doublets did not report significantly different HRQL, neuropathy, or pain from those who received the PC (control) doublet. Patients receiving PC tended to report worse neuropathy during treatment than patients who received other doublets (especially GC and TC), but the differences were not statistically significant.

Conclusion. None of the 3 experimental doublets was different from PC in terms of HRQL during treatment. Long-term toxicity data are inconclusive. Except where patients may wish to reduce their risk of worsening pre-treatment neuropathy, PC remains the standard of care for this disease.

Introduction

Metastatic cervical cancer carries a poor survival prognosis, with small but meaningful extension of life afforded by the use of cisplatin (C) chemotherapy, either alone or in combination with agents such as topotecan [1–4]. Current treatment of advanced disease involves balancing considerations regarding toxicity with the possibility that it may palliate disease symptoms, lengthen progression-free survival (PFS) or improve overall survival (OS). The doublet regimen of paclitaxel and cisplatin (PC) has been commonly-used, based largely on its improvement of response rate (RR) and PFS compared to cisplatin alone [5]. However, in a Gynecologic Oncology Group (GOG) randomized trial comparing PC to C (GOG 169), median OS was not superior (9.7 versus 8.8 months, respectively) [5]. In a subsequent GOG comparison of topotecan/cisplatin (TC) versus C alone (GOG 179), the TC doublet was associated with significantly increased median OS (9.4 versus 6.5 months, $p = .017$) [2].

In both of these studies, the addition of a second agent to cisplatin was not associated with poorer health-related quality of life (HRQL), although in both cases the added agent contributed additional toxicity [3,5]. This suggested that the modest gains in RR, PFS and, in one case, OS, justified use of doublet chemotherapy in metastatic cervical

* Corresponding author. Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, 750 N. Lake Shore Drive — 9th floor, Chicago, IL, USA.
E-mail address: d-cella@northwestern.edu (D. Cella).

0090-8258/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2010.08.020

cancer, because the additional toxicities were not associated with worsened HRQL. Because the efficacy advantages in terms of OS or PFS have been modest, and the treatments have substantial toxicity, the study of HRQL while patients receive chemotherapy for this disease has been an enduring interest.

GOG 204 was initially designed as a 2-arm trial based on the results of GOG 169 and some interesting phase I/II data with vincristine and cisplatin [6–8], with PC as the standard arm. Once the results of GOG 179 were determined, it was recognized that TC needed to be compared directly to PC, due to the improvement in OS for women treated with TC. Concurrent with this, combined gemcitabine and cisplatin (GC) was showing promise in cervix cancer cell lines and phase II studies [9–12]. Therefore, the 2-arm trial was expanded to a 4-arm trial of doublet combinations (PC as reference arm; vinorelbine plus C (VC); TC and GC). OS was the primary endpoint, and RR, PFS, toxicity and HRQL were important secondary endpoints. In the primary efficacy analyses, VC, GC, and TC were not superior to PC in terms of OS. Median survival was 13 months for PC and approximately 10 months for the other 3 doublets. The trends in RR favored PC (29%) and VC (26% with more complete responses) over TC (23%) and GC (22%). Trends in PFS favored PC at 6 months compared to 4–5 months for the other doublets [13]. Therefore today, there is no clearly superior chemotherapy doublet for metastatic disease, although one could argue that the PC doublet has not been replaced. In such a case, the HRQL data available from the trial may help determine whether or when one or another regimen might be preferred. These HRQL results are reported here.

Patients and methods

Patient eligibility and treatment

Eligible patients were women with measurable advanced (stage IVB), recurrent, or persistent cervical cancer with squamous, adenosquamous or adenocarcinoma histology. Details of eligibility criteria are found elsewhere [13]. Patients were required to have a GOG performance status (PS) 0 or 1; recovered from the effects of recent surgery, or radiotherapy; and to be free of clinically significant infection. Participating institutional review boards approved the protocol and all patients provided written informed consent.

Chemotherapy treatment arms were as follows: PC = paclitaxel 135 mg/m^2 over 24 h plus cisplatin 50 mg/m^2 day 2 every 3 weeks; VC = vinorelbine 30 mg/m^2 days 1 and 8 plus cisplatin 50 mg/m^2 day 1 every 3 weeks; GC = gemcitabine 1000 mg/m^2 days 1 and 8 plus cisplatin 50 mg/m^2 day 1 every 3 weeks; and TC = topotecan 0.75 mg/m^2 days 1, 2 and 3 plus cisplatin 50 mg/m^2 day 1 every 3 weeks. All regimens were administered for a maximum of 6 cycles for non-responders. Patients who achieved a partial response with an acceptable level of toxicity were permitted to continue treatment with their assigned regimen beyond 6 cycles [13]. Granulocyte growth factors were permitted if febrile neutropenia occurred after dose modification for >grade 2 hematologic toxicity during the previous cycle of therapy. Response was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [14]. PFS was defined as the time from randomization until the date of last contact, documented disease progression, or death, whichever came first.

A total of 513 patients was enrolled from May 27, 2003 to Apr 30, 2007. Of the 513 patients enrolled to the trial from May, 2003 to April, 2007, 41 were entered prior to January, 2004 with either PC or VC, at which time the protocol was amended to include the GC and TC regimens. Of the 472 patients enrolled after January, 2004, 38 were found ineligible and were excluded from the analysis. This manuscript is based on 434 eligible patients, including 9 patients who never received protocol treatments (i.e., intent-to-treat analysis among eligible patients).

Health-related quality of life component

The HRQL objective in this trial was to determine if VC, GC, or TC improved HRQL when compared to the reference arm of PC. HRQL assessment was conducted at 4 times: Pre-cycle 1 (baseline); Pre-cycle 2; Pre-cycle 5; and 9 months Post cycle 1. The primary planned comparisons on HRQL, neurotoxicity, and pain were focused on assessments before the start of cycle 2 and before the start of cycle 5. It was recognized and documented in the original research protocol that the 9 month assessment would be exploratory in nature, due to the expected poor survival and follow-up by that time.

The HRQL instruments used in this trial were the Functional Assessment of Cancer Therapy-Cervix (FACT-Cx) Trial Outcome Index (TOI), for which a higher score indicates better HRQL; the FACT/GOG-Neurotoxicity 4-item Subscale (FACT/GOG-Ntx-4), for which a higher score indicates less neurotoxicity; and the Brief Pain Inventory (BPI) single item evaluating worst pain in the past 24 h, for which a higher score indicates more pain. All instruments have been widely-used in clinical research, have documented reliability and validity, and are available in English and Spanish [15–18]. Both English and Spanish language versions were used in this trial.

The Functional Assessment of Cancer Therapy-Cervix (FACT-Cx)

The FACT-Cx is the FACT-G plus a cervix cancer-specific subscale [15]. The FACT-G is a 27-item self-report quality of life (QOL) measure that includes 4 subscales (physical well-being, social well-being, functional well-being and emotional well-being) [16]. Each scale produces a score, and scores can be summed to produce a total QOL score. The FACT-Cx endpoint for this trial focuses on the aspects of HRQL that are most sensitive and responsive in clinical trials. This "Trial Outcome Index" of FACT-Cx (FACT-Cx TOI), is the summation of the Physical Well Being, Functional Well Being and Cervix Cancer Subscales. Based on guidelines from Yost and Eton [19], a clinically meaningful change for group comparisons is approximately 4–5 points.

FACT/GOG-Ntx 4-item scale

Four items from the 11-item FACT/GOG-Neurotoxicity (FACT/GOG-Ntx) subscale were included to evaluate this important side effect associated with many of the chemotherapy agents in this trial. This was the co-primary HRQL endpoint. Based on the data from a prior GOG study, these 4 questions on the 11-item scale correctly classified the vast majority of patients based on the physician reported CTC grade. These 4 questions also explain more than 50% of the variation in the total Ntx score [17]. Based on Huang et al. [17] and guidelines from Yost and Eton [19], a clinically meaningful change for group comparisons is approximately 1.5–2.0 points.

The Brief Pain Inventory (BPI)

The BPI is a 23-item, self-report instrument designed to assess pain in cancer and other diseases [18]. The BPI has demonstrated reliability and validity across cultures and languages and has been used to study the effectiveness of pain treatment [18]. To limit patient burden, we selected the most commonly-employed endpoint from the BPI which is the single item assessing "worst pain" in the past 24 h, on a 0–10 scale. The BPI single item was added to provide secondary confirmation of FACT-Cx TOI and FACT-Ntx results. A clinically meaningful change score for group comparisons is approximately 1.0–1.5 points [18].

Analysis plan

For each of the 3 endpoints mentioned earlier, each of the 3 experimental groups (VC, GC, and TC) was compared to the control arm (PC) using a linear mixed model, adjusting for baseline HRQL scores, GOG performance status at randomization and age. Since the correlation of reported HRQL scores between the 3 time points was unknown, the