Gynecologic Oncology Reports 10 (2014) 36–37

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

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

Cost effectiveness of concurrent gemcitabine and cisplatin and radiation followed by adjuvant gemcitabine and cisplatin in stages IIB–IVA cervical cancer

To the Editor,

We read with interest the two articles published in *Gynecologic Oncology* on the cost-effectiveness of gemcitabine with cisplatin chemoradiation in locally advanced cervical cancer (LACC) (Phippen et al., 2012; Smith et al., 2013). These two articles are useful additions, from a health economics perspective, to the evidence for the appropriate care of patients with LACC. The two articles reported cost-effectiveness analyses based on data from the same large, randomized, multinational Phase III study reported by Dueñas-González et al. (Duenas-Gonzalez et al., 2011), but came to different conclusions, raising the question of which conclusion is more appropriate. Our concern is that these different conclusions may confuse readers regarding the health economics associated with the improved outcomes of this regimen for LACC. The clinical data from the study are compelling in terms of statistically significant improvements in progression-free survival (PFS) and overall survival (OS) with acceptable toxicity. We hope that clarifying some of the major differences in the approaches taken in these two cost-effectiveness analyses will help readers make the appropriate access recommendation for their situation or critically evaluate a local access decision.

The Dueñas-González study compared concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin (arm A; n = 259) with concurrent cisplatin and radiation (arm B; n = 256) in patients with LACC (stages IIB to IVA) (Duenas-Gonzalez et al., 2011). In this study, PFS at 3 years (primary objective) was significantly improved in arm A vs arm B (74.4% vs 65.0%; p = 0.029), as were overall PFS (log-rank p = 0.0227; hazard ratio [HR], 0.68; 95% CI, 0.49–0.95) and OS (log-rank p = 0.0224; HR, 0.68; 95% CI, 0.49–0.95) (Duenas-Gonzalez et al., 2011). Grade 3 and 4 toxicities were more frequent in arm A vs arm B (86.5% vs 46.3%; p < 0.001).

Phippen et al. (2012) used a modified Markov model to compare the cost-effectiveness of the two regimens based on the study's published 5-year OS and treatment-related toxicity rates, and reported that the gemcitabine regimen was a cost-effective treatment for LACC compared with standard cisplatin chemoradiation. The mean cost was US$ 60,974 for the gemcitabine regimen and US$41,330 for cisplatin chemoradiation. The incremental cost-effectiveness ratio (ICER) for the gemcitabine regimen compared with cisplatin chemoradiation was US$33,080 per quality-adjusted life year. In contrast, Smith et al. (2013) used a hypothetical cohort of 10,000 patients based on the published study, and reported that the gemcitabine regimen was not cost effective, with the increased financial burden of this regimen and associated toxicities appearing to outweigh the benefits of increased PFS at 3 years. The cost of therapy and adverse events was US$259.8 million for the gemcitabine regimen and US $173.9 million for cisplatin chemoradiation, and the ICER for the gemcitabine regimen was US$97,799 per progression-free life-year saved (PF-LYS).

Smith (published after Phippen) discussed possible reasons for the different results between the two articles, including the different outcomes used in the analyses: the Smith model used the primary endpoint of PFS at 3 years, whereas the Phippen model used OS, last year of life cost, and quality of life utility scores (Smith et al., 2013). As patients survived longer than expected, the primary objective of the Dueñas-González study was changed from OS to PFS at 3 years (Duenas-Gonzalez et al., 2011). However, we suggest that it would be more appropriate to use OS (as used by Phippen), because this is universally recognized as a measure of clinical benefit, rather than PFS at 3 years (used by Smith). In a sensitivity analysis evaluating the effect of survival, Smith found that an increase in PFS at 3 years of 5% would decrease the ICER from US$97,799 to US$62,605 per PF-LYS, which demonstrates how the assumption of benefit can substantially affect the ICER. Smith also stated that if it is assumed that most patients with PFS at 3 years become long-term survivors, then the ICER becomes even more favorable (Smith et al., 2013). We believe that this is indeed the case, as this and previous studies of cervical cancer (Duenas-Gonzalez et al., 2011; Keys et al., 1999) have shown that the PFS Kaplan–Meier curves reach a plateau at approximately 3 years with cisplatin-based chemoradiation.

The different costs used in the two models should be noted, with Smith using lower costs for brachytherapy, but higher costs for transfusion and neutropenia intervention, than Phippen. Sensitivity analyses conducted by Smith indicated that drug cost had a substantial effect on the cost-effectiveness analysis. Chemotherapy costs were higher in the Smith than the Phippen model because of different body surface area (BSA) assumptions (2.0 m^2 vs 1.65 m^2), which substantially affected the amount of drug used in the calculations (mean BSA in the Dueñas-González study was 1.62 m^2, Mosteller formula, data on file). Using the mean female height (United States) of 1.622 m (McDowell et al., 2008), these BSA assumptions correspond to the weights of approximately 90 kg vs 60 kg (Mosteller formula); the average weight was therefore assumed to be 50% greater in the Smith than the Phippen model. Smith based their BSA assumption on the high prevalence of obesity in the United States; however, patients with LACC are generally not obese at presentation. Neither article provided evidence for the BSA assumption nor presented BSA sensitivity analyses.

In addition, the Smith model may have overestimated gemcitabine costs as it assumed that all patients completed the maximum number of cycles, with no dose reductions, to standardize treatment costs. However, the median number of concurrent radiation and gemcitabine/cisplatin chemotherapy cycles in the study was 5, with a range of 1–6 cycles (Duenas-Gonzalez et al., 2011), 54.6% of patients experienced at least one dose reduction in gemcitabine, and 90.4% omitted at least one dose of gemcitabine (data on file).

DOI of original article: http://dx.doi.org/10.1016/j.ygyno.2012.08.002, http://dx.doi.org/10.1016/j.ygyno.2013.05.024

http://dx.doi.org/10.1016/j.gore.2014.09.002

Using different models and assumptions, Smith and Phippen reached different conclusions on the cost-effectiveness of the gemcitabine with cisplatin chemoradiation in LACC. The results of economic evaluations are taken seriously by governments, healthcare decision makers, and clinicians; therefore, it is imperative that we attempt to accurately map the costs and clinical outcomes for competing therapeutic options. As a developing field of research, we need to continually evaluate the available evidence and ensure that economic evaluations are based on high-quality clinical research and methodology.

Acknowledgments

Funding support

Medical writing assistance was provided by Justine Southby, PhD, CMPP, and Julie Monk, PhD, CMPP, of ProScribe — part of the Envision Pharma Group, and was funded by Eli Lilly and Company. ProScribe's services complied with the international guidelines for Good Publication Practice (GPP2).

Role of the sponsor

Eli Lilly and Company was involved in the preparation of the manuscript.

Role of contributors

All authors participated in the drafting, critical revision, and approval of the final version of the manuscript.

Conflicts of interest

All authors are employees of Eli Lilly and Company. NR, TP, and MO own stock in Eli Lilly and Company.

References

Duenas-Gonzalez, A., Zarba, J.J., Patel, F., Alcedo, J.C., Beslija, S., Casanova, L., et al., 2011. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J. Clin. Oncol. 29, 1678–1685.

Keys, H.M., Bundy, B.N., Stehman, F.B., Muderspach, L.I., Chafe, W.E., Suggs 3rd, C.L., et al., 1999. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N. Engl. J. Med. 340, 1154–1161.

McDowell, M.A., Fryar, C.D., Ogden, C.L., Flegal, K.M., 2008. Anthropometric Reference Data for Children and Adults: United States, 2003–2006. National Health Statistics Reports, Number 10, 2008.

Phippen, N.T., Leath III, C.A., Chino, J.P., Jewell, E.L., Havrilesky, L.J., Barnett, J.C., 2012. Cost effectiveness of concurrent gemcitabine and cisplatin with radiation followed by adjuvant gemcitabine and cisplatin in patients with stages IIB to IVA carcinoma of the cervix. Gynecol. Oncol. 127, 267–272.

Smith, B., Cohn, D.E., Clements, A., Tierney, B.J., Straughn Jr., J.M., 2013. Is the progression free survival advantage of concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin in patients with advanced cervical cancer worth the additional cost? A cost-effectiveness analysis. Gynecol. Oncol. 130, 416–420.

Narayan Rajan
Helen Barraclough
Eli Lilly Australia, 112 Wharf Rd., West Ryde NSW 2114, Australia

Tarun Puri
Eli Lilly Interamerica Inc., Tronador 4890, Piso 12, Buenos Aires 1430, Argentina

Mauro Orlando
Eli Lilly Interamerica Inc., Tronador 4890, Piso 12, Buenos Aires 1430, Argentina
Corresponding author: Fax: +54 11 4546 4171.
E-mail address: orlando_mauro@lilly.com.