Table 6. Costs and QALYs per 1000 people of varied vaccine effect

Strategy	Minimum vaccine effect*		Baseline vaccine effect*		Maximum vaccine effect*	
	Cost (¥)	QALYs	Cost (¥)	QALYs	Cost (¥)	QALYs
Screening 20% + vaccination	69,561,000	25 933.88	66,114,000	25 942.64	62,628,000	25 950.77
Screening 50% + vaccination	70,300,000	25 937.33	67,334,000	25 945.54	64,300,000	25 953.22
Screening 80% + vaccination	72,129,000	25 940.81	69,219,000	25 945.76	66,277,000	25 953.07

*Minimum vaccine effect means relative risks of 0.48 for persistent HPV16 and 18 infection and 0.7 for persistent HPV high-risk type excluding 16, 18 infection. Baseline vaccine effect means relative risks of 0.12 for persistent HPV16 and 18 infection and 0.5 for persistent HPV high-risk type excluding 16, 18 infection. Maximum vaccine effect means relative risks of 0.03 for persistent HPV16 and 18 infection and 0.3 for persistent HPV high-risk type excluding 16, 18 infection.

Table 7. Sensitivity analysis on vaccine effect (ICER)*

Strategy	Minimum vaccine effect**	Baseline vaccine effect**	Maximum vaccine effect**
Screening 20%	Dominated	Dominated	Dominated
Screening 50%	658	658	658
Screening 80%	Extended dominance	571 015	571 015
Screening 20% + vaccination	Extended dominance	Extended dominance	Extended dominance
Screening 50% + vaccination	Extended dominance	2 920 636	1 874 867
Screening 80% + vaccination	3 745 442	8 568 182	Dominated

*Incremental cost effectiveness ratio (Yen/QALY).

**Minimum vaccine effect means relative risks of 0.48 for persistent HPV16 and 18 infection and 0.7 for persistent HPV high-risk type excluding 16, 18 infection. Baseline vaccine effect means relative risks of 0.12 for persistent HPV16 and 18 infection and 0.5 for persistent HPV high-risk type excluding HPV16, 18 infection. Maximum vaccine effect means relative risks of 0.03 for persistent HPV16 and 18 infection and 0.3 for persistent HPV high-risk type excluding 16, 18 infection.

minimum efficacy, a combined strategy of 80% screening and universal vaccination is most cost-effective. On the other hand, with the maximum and baseline vaccine efficacy, a combined strategy of 50% screening and universal vaccination remains most cost-effective.

Discussion

The introduction of HPV vaccine to the Japanese population has been controversial because the coverage of Pap smear screening is low and the prevalence of HPV types is different from that observed in Western countries.

To date there has been only one study that has assessed the impact of introducing HPV vaccine in Japan.[16] However, this study suffered from several major limitations. It did not distinguish health status related to HPV type 16 and 18 from other high-risk types. We modelled the natural history of each HPV type status; HPV16/18, other HR, and LR. We used different vaccine efficacies depending on the HPV types with a range that was derived from a meta-analysis of the available evidence. The previous study also did not include strategies of varied screening rates without vaccination. The authors analysed the effect of screening atthe currently observed levels ranging from 13.6 to 24.7%, and so the impact of increasing Pap smear coverage was not considered. Instead, the present study compared the strategies of varied screening rates ranging from 20 to 80%.

Our analysis suggests that increasing cervical cancer screening coverage to 50% would halve the incidence of cervical cancer and save programme costs and that the introduction of HPV vaccination would reduce the incidence by two-thirds but result in a four-fold increase in programme costs. Using the model's default values, a combined strategy to expand the coverage of cancer screening up to 50% and the introduction of universal vaccination would be most cost-effective. The results are robust with sensitivity analysis in which the optimum coverage level most likely lies somewhere between 50 and 80%. Our result confirms the need for expanding coverage for Pap smears in Japan as previously suggested,[39] to maximise the impact of the cervical cancer strategy regardless of whether a national vaccine programme is also implemented.

The detection rate of HPV16 and 18 among women with cervical cancer in Japan is reported to be lower than that in other countries.[14] We used the latest age-dependent prevalence data, which consistently show that the younger population has a higher detection rate of HPV16 and 18 than the older population.[20] The prevention of cervical cancer in a young person shows larger QALYs gained than that of an older person because of the longer remaining life expectancy. Hence the effect of vaccine on cancer incidence or QALYs is not as low as might otherwise be expected.

The present study has several limitations. First, we assumed life-long lasting immunity acquired by the vaccine. The vaccine has only been recently introduced, and the latest evidence shows 7.3 years of efficacy and immunogenicity of the vaccine, which was derived from the population of the initial placebo-controlled study.[40] If additional vaccination is required to maintain immunity in the future, then programme costs are slightly underestimated. Second, there is no population-based survival data of women with cervical cancer by stages of FIGO. These data are essential when building a model. However, we managed to adopt and validate data from an existing Japanese regional cancer registry. Third, we did not incorporate the preferences of girls and their parents and the subsequent uptake of vaccine as a result of their preferences. Both effects and costs may be overestimated in that sense. Finally, we did not include the cost for campaigns to increase the coverage of screening and/or vaccination in this analysis, which may underestimate the programme costs but such a bias is minimal given the fact that the majority of costs is incurred by screening, vaccination and treatment interventions.

Vaccination for HPV is attracting considerable policy attention now as a strategy for cervical cancer prevention in Japan. Our analysis showed that increasing the rate of the current screening strategy would halve cancer incidence with a similar cost to the current screening strategy, though vaccination strategies may also be cost effective. We suggest further efforts to expand the current screening programme regardless of what support is provided for vaccination.

Some of the reasons why Pap smear coverage is so low in Japan relate to a lack of knowledge and from the fact that the financial support of the screening programme from the Ministry of Health, Labour and Welfare was discontinued because it was included in the general ones in 1998. Most cities, towns and villages decided to reduce the cost for the screening programme.[41–43] Free tickets for the Pap smear were provided under supplemental budgets for 2009. Distributing free tickets to a target population of certain ages showed a significant increase in the coverage rate by 2.8 times.[44] We need to continue endeavours to increase coverage by effective interventions such as providing free tickets and undertaking awareness campaigns. The involvement of gynaecologists in school education will also support the enhancement of knowledge about cervical cancer prevention and help to increase the coverage rate of screening as has been seen in other countries.[45,46]

Our analysis showed that introducing the HPV vaccination for all 11-year-old girls would reduce cervical cancer incidence to 33.9% with a net cost of only 49,000 yen per person (taking into account the social burden of cancer). Vaccinating all 11-year-old girls would cost 33.7 billion yen. Our analysis showed the cost-effectiveness of vaccination and that it would save future costs. It is important to give priority to policy which is evidence based medically and economically. If the prevalence of HPV infection is reduced as a result of universal vaccination, as our model predicts, then it may be possible to extend the interval between routine screens or to increase the age at which screening is first offered, as suggested in other cost-effectiveness studies.[34,47] The use of the HPV-DNA test in the screening programme is one choice that should be evaluated in the future.

In conclusion, the introduction of HPV vaccine in Japan is cost-effective as in other countries. It is more cost-effective to increase the coverage of the Pap smear along with the universal administration of HPV vaccine. Only by doing so, can the scarce healthcare resources be efficiently and effectively used to reduce the burden from cervical cancer in Japan.

Disclosure of interests

None of the authors have any conflicts of interest to declare.

Contribution to authorship

NY contributed to the study design of the current paper, model construction, data acquisition, data analysis and interpretation, drafting and revising the manuscript. RM contributed to the study design of the current paper, model construction, results interpretation and revising the manuscript. PJ contributed to the model construction, results interpretation and the critical review of the manuscript. YO contributed to the study design of the current paper. KK contributed to the model construction, data acquisition and interpretation of the results. KS and YT contributed to the study design of the current paper and interpretation of the results. All authors approved the final version of the manuscript.

Funding

This work was funded by two grants; Health and Labour Sciences Research Grants from the Japanese Ministry of Health, Labour and Welfare and a Research accomplishment cooperation system grant for doctoral courses at University of Tokyo.

Acknowledgements

We would like to thank Mitsuhiro Sado and Makoto Kobayashi for their technical advice on model building, and Koji Matsumoto for providing data on type-specific HPV prevalence. ■

References

1 World Health Organization. The global burden of disease 2004 update. 2008. [www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf]. Last accessed 10 September 2010.
2 Center for Cancer Control and Information Services. *Statistics*. Tokyo, Japan: Center for cancer control and information services, 2010. (http://ganjoho.ncc.go.jp/professional/statistics/index.html). Last accessed 10 September 2010.
3 Sherman ME, Wang SS, Carreon J, Devesa SS. Mortality trends for cervical squamous and adenocarcinoma in the United States. *Cancer* 2005;103:1258–64.
4 Cancer Research UK. *Cervical Cancer — UK Mortality Statistics*. London, UK: Cancer Research UK, 2010. (http://info.cancerresearchuk.org/cancerstats/types/cervix/mortality/). Last accessed 25 December 2010.
5 Ministry of Health, Labour and Welfare. *Guideline for Health Education of Cancer Prevention and Implementation of Cancer Screening*. Tokyo, Japan: Ministry of Health, Labour and Welfare, 2008. (www.mhlw.go.jp/bunya/kenkou/dl/gan_kenshin02.pdf). Last accessed 10 September 2010.
6 Ministry of Health, Labour and Welfare. *Business Report of Regional Healthcare and Healthcare of the Aged, Overview*. Tokyo, Japan: Ministry of Health, Labour and Welfare, 2008. (www.mhlw.go.jp/toukei/saikin/hw/c-hoken/08/dl/date03.pdf). Last accessed 10 September 2010.
7 Castellsague X, de Sanjose S, Aguado T, Louie KS, Bruni L, Munoz J, et al. HPV and Cervical Cancer in the World: 2007 Report Countries. *Vaccine* 2007;25 (Suppl 3):C27–219.
8 Schlecht NF, Kulaga S, Robitaille J, Ferreira S, Santos M, Miyamura RA, et al. Persistent human papillomavirus infection as a predictor of cervical intraepithelial neoplasia. *JAMA* 2001;286:3106–14.
9 Matsumoto K, Yoshikawa H. HPV vaccination and screening for cervical cancer. *Clin Gynecol Obstet* 2009;63:1140–7.
10 Armstrong EP. Prophylaxis of cervical cancer and related cervical disease: a review of the cost-effectiveness of vaccination against oncogenic HPV types. *JMCP* 2010;16:217–30.
11 Dasbach E, Insinga R, Elbasha E. The epidemiological and economic impact of a quadrivalent human papillomavirus vaccine (6/11/16/18) in the UK. *BJOG* 2008;115:947–56.
12 La Torre G, de Waure C, Chiaradia G, Mannocci A, Capri S, Ricciardi W. The health technology assessment of bivalent HPV vaccine cervarix® in italy. *Vaccine* 2010;28:3379–84.
13 Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *Br J Cancer* 2003;88:63–73.
14 Miura S, Matsumoto K, Oki A, Satoh T, Tsunoda H, Yasugi T, et al. Do we need a different strategy for HPV screening and vaccination in east asia? *Int J Cancer* 2006;119:2713–5.
15 Kawana K. New strategies for cervical cancer prevention. *Public Health* 2009;73:886–93.
16 Konno R, Sasagawa T, Fukuda T, Van Kriekinge G, Demarteau N. Cost-effectiveness analysis of prophylactic cervical cancer vaccination in Japanese women. *Int J Gynecol Cancer* 2010;20:385–392.
17 Goldie SJ, Kim JJ, Kobus K, Goldhaber-Fiebert J, Salomon J, O'Shea M, et al. Cost-effectiveness of HPV 16, 18 vaccination in brazil. *Vaccine* 2007;25:6257–70.
18 Surveillance Epidemiology and End Results (SEER). *SEER Cancer Statistics Review, 1975–2007*. Bethesda, MD: National Cancer Institute. (http://seer.cancer.gov/csr/1975_2007/). Last accessed 10 December 2010.
19 Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J. *SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988–2001, Patient and Tumor Characteristics*. Bethesda, MD: NIH Publications, 2007.
20 Onuki M, Matsumoto K, Satoh T, Oki A, Okada S, Minaguchi T, et al. Human papillomavirus infections among Japanese women: age-related prevalence and type-specific risk for cervical cancer. *Cancer Sci* 2009;100:1312–6.
21 La Torre G, de Waure C, Chiaradia G, Mannocci A, Ricciardi W. HPV vaccine efficacy in preventing persistent cervical HPV infection: a systematic review and meta-analysis. *Vaccine* 2007;25:8352–8.
22 Rambout L, Hopkins L, Hutton B, Fergusson D. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. *Can Med Assoc J* 2007;177:469–79.
23 Schiffman M, Castle PE. Human papillomavirus: epidemiology and public health. *Arch Pathol Lab Med* 2003;127:930–4.
24 Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow S-N, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009;374:301–14.
25 Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* 2006;367:1247–55.
26 Yoshida Y, Sato S, Okamura C, Nishino Y, Yajima A. Evaluating the accuracy of uterine cancer screening with the regional cancer registration system. *Acta Cytol* 2001;45:157–62.
27 Ministry of Health, Labour and Welfare. *Vital statistics Japan 2008*. Tokyo, Japan: Ministry of Health, Labour and Welfare, 2009. (www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei08/dl/01.pdf). Last accessed 10 September 2010.
28 Matsuda T, Ajiki K, Marugame T, Ioka A, Tsukuma H, Sobue T, et al. Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study. *Jpn J Clin Oncol* 2011;41:40–51.
29 Insinga R, Dasbach E, Elbasha E. Epidemiologic natural history and clinical management of human papillomavirus (HPV) disease: a critical and systematic review of the literature in the development of an HPV dynamic transmission model. *BMC Infect Dis* 2009;9:119.
30 Goldhaber-Fiebert J, Stout N, Ortendahl J, Kuntz K, Goldie S, Salomon J. Modeling human papillomavirus and cervical cancer in the united states for analyses of screening and vaccination. *Popul Health Metr* 2007;5:11.
31 Igakutsushinsha. *Quick Reference Matrix for Medical Service Score*. Tokyo, Japan: Igakutsushinsha, 2009.
32 Ministry of Health, Labour and Welfare. *The Result of Wage Structure Key Statistical Survey for 2008, Overview*. Tokyo, Japan: Ministry of Health, Labour and Welfare, 2009. (www.mhlw.go.jp/toukei/itiran/roudou/chingin/kouzou/z2008/index.html). Last accessed 10 September 2010.
33 Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, et al. Projected clinical benefits and cost-effectiveness of a

human papillomavirus 16/18 vaccine. *J Natl Cancer Inst* 2004;96: 604–15.

34 Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA* 2003;290:781–9.

35 Mandelblatt JS, Lawrence WF, Womack SM, Jacobson D, Yi B, Hwang Y, et al. Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA* 2002;287:2372–81.

36 Ministry of Economy, Trade and Industry. *Economic Society Evaluation Guideline for Medical Equipment*. Tokyo, Japan: Ministry of Economy, Trade and Industry, 2007. (www.meti.go.jp/committee/summary/0001460/files/0712_02.pdf). Last accessed 10 September 2010.

37 Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*, 3rd edn. Oxford, UK: Oxford University Press, 2005.

38 Eichler H, Kong SX, Gerth WC, Mavros P, Jönsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? *Value Health* 2004;7:518–28.

39 Ministry of Health Labour and Welfare. *Readjustment of Examination of Breast Cancer and Uterine Cancer Based on Elderly Health Services*. Tokyo, Japan: Ministry of Health Labour and Welfare, 2004. (www.mhlw.go.jp/shingi/2004/04/s0426-3.html). Last accessed 10 September 2010.

40 De Carvalho N, Teixeira J, Roteli-Martins CM, Naud P, De Borba P, Zahaf T, et al. Sustained efficacy and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine up to 7.3 years in young adult women. *Vaccine* 2010;28:6247–55.

41 Matsuura Y, Kawagoe T, Toki N, Hachisuga T, Kashimura M. Uterine cervical cancer screening in Japan: today and future. *J UOEH* 2009; 31:181–93.

42 Research group to protect women from cervical cancer. *Report of Research on the Cervical Cancer Screening*. Japan: Research group to protect women from cervical cancer, 2008. (http://www.cczero pro.jp/kenshin/result_data.html). Last accessed 22 December 2010.

43 Kaku T, Hirata N, Shinkoda H, Noguchi Y, Kitahara E, Hirakawa T, et al. Influences on women health care after change and reduction of financial resources for cytological screening of cervical cancer in Fukuoka prefecture, Japan. *Mem Kyushu U Sch Health Sci* 2003;1: 23–8.

44 Expert committee on cervical cancer control. *Research on Usage Situation of Free Ticket for Cervical Cancer Screening by Municipality, Promotion of Cancer Detection of Women 2009*. Tokyo, Japan: Expert committee on cervical cancer control, 2010. (www.cczero pro.jp/dl/rp_20101020_coupn.pdf.) Last accessed 22 December 2010.

45 Australian Government, Department of Health and Ageing. *Immunize Australia Program, Human Papillomavirus (HPV)*. Canberra, Australia: Australian Government, Department of Health and Ageing, 2010. (www.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpvH). Last accessed 22 December 2010.

46 Department of Health (UK). *Immunisations at Secondary School: Your Questions Answered About the HPV and Td/IPV Vaccinations Given Between 12 and 18 years of Age*. London, UK: Department of Health, 2010. (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123098). Last accessed 22 December 2010.

47 Jit M, Choi YH, Edmunds WJ. Economic evaluation of human papillomavirus vaccination in the United Kingdom. *BMJ* 2008;337:a769.

Med Oncol
DOI 10.1007/s12032-011-9893-0

CASE REPORT

Interstitial pneumonitis induced by pegylated liposomal doxorubicin in a patient with recurrent ovarian cancer

Kanako Inaba · Takahide Arimoto · Mari Hoya · Kei Kawana · Shunsuke Nakagawa · Shiro Kozuma · Yuji Taketani

Received: 24 February 2011 / Accepted: 28 February 2011

Abstract Interstitial pneumonitis after treatment with pegylated liposomal doxorubicin (PLD) has been rarely reported. We describe herein a case of interstitial pneumonitis in a 49-year-old woman with relapsed ovarian carcinoma treated with PLD. Twenty-five days after the second administration of PLD, she presented with fever and dry cough, and chest CT scans revealed bilateral interstitial infiltrates and ground-glass opacities. She was diagnosed to have interstitial pneumonitis induced by PLD. Steroid therapy improved her symptoms.

Keywords Interstitial pneumonitis · Pegylated liposomal doxorubicin · Drug induced · Japanese · Ovarian cancer

Introduction

Pegylated liposomal doxorubicin (PLD) is an active drug in recurrent ovarian cancer as demonstrated in trials in the second-line chemotherapy [–]. It has been designed to enhance the efficacy and to reduce the toxicities of doxorubicin such as cardiotoxicity, hematologic toxicity, and alopecia by using a unique delivery system: a polyethylene glycol coat [,]. Whereas hand-foot syndrome and planter palmar erythema are widely recognized as adverse effects of PLD, few cases of interstitial pneumonitis after treatment with PLD have been reported. Here, we describe a case of interstitial pneumonitis induced by PLD.

K. Inaba · T. Arimoto (✉) · M. Hoya · K. Kawana · S. Nakagawa · S. Kozuma · Y. Taketani
Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: tarimoto-tky@umin.ac.jp

Case report

A 48-year-old woman (gravida 4, para 3) with recurrent ovarian cancer was started on third-line chemotherapy with PLD (50 mg/m^2/4 weeks). She was initially diagnosed in February 2009 and underwent complete debulking surgery for a stage IIIC serous ovarian adenocarcinoma. Postoperatively, she received adjuvant chemotherapy with six cycles of paclitaxel (175 mg/m^2) and carboplatin (AUC 6). Four months later, because of peritoneum dissemination and elevation of CA125, she was treated with weekly CPT-11 (95 mg/m^2/week) with progressive disease after four cycles. In April 2010, PLD was given under her excellent performance status.

Twenty-three days after the first administration of PLD, she developed a fever from which she recovered without any treatment. However, 25 days after the second administration of PLD, she presented to our hospital with fever, chill, dry cough, and dyspnea (grade 3 according to Common terminology criteria for adverse events, version 4.0). Physical examination was remarkable for bilateral fine crackles at the lung bases. A chest X-ray and chest CT scans revealed bilateral interstitial infiltrates and ground-glass opacities, though chest CT scans performed before PLD therapy showed clear lung field (Fig. a, b). Oxygen saturation by pulse oximetry was 89% on room air and arterial blood gas analysis showed hypoxia (FiO_2 0.32, PaO_2 90.5 mmHg, alveolar-arterial oxygen gradient 94.9 mmHg). Laboratory analysis revealed white blood cells of 2,500/μl with 78% neutrophils, lactate dehydrogenase of 347 IU/l, C-reactive protein of 14.32 mg/dl, and Krebs von den Lungen-6 (KL-6) of 227 U/ml.

Her clinical course and laboratory data indicated that she has interstitial pneumonitis probably induced by PLD. She had not received granulocyte colony-stimulating

Published online: 10 March 2011

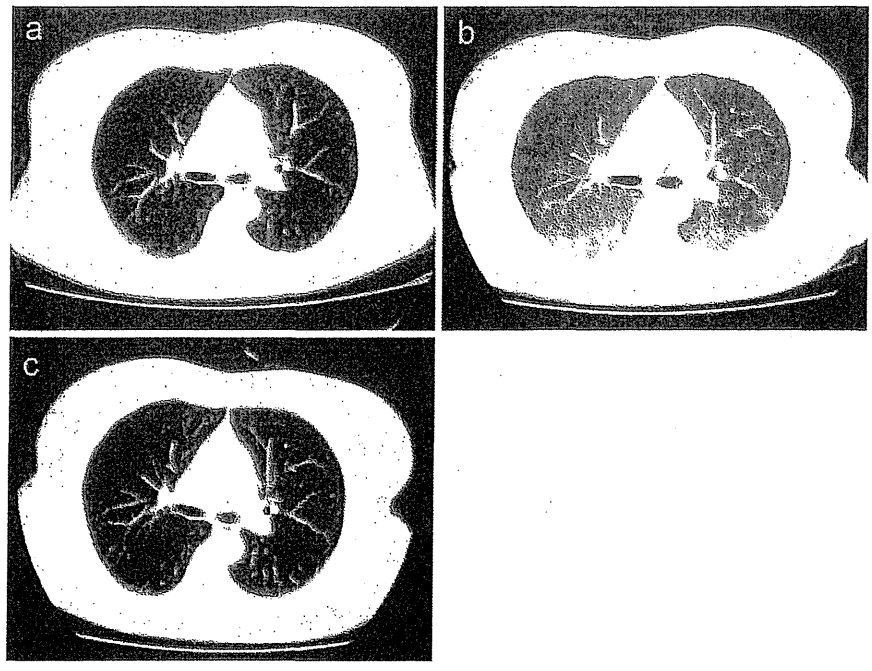

Fig. 1 **a** Chest computed tomography (CT) scan before PLD therapy showed clear lung field. **b** Twenty-six days after second administration of PLD, CT revealed bilateral interstitial infiltrates and ground-glass opacities. **c** Two months after steroid therapy, CT showed significant improvement

factor, which could induce interstitial pneumonitis. In addition to PLD, she received ascorbic acid, pyridoxal phosphate hydrate, rebamipide, and brotizolam. As they were all unlikely to induce interstitial pneumonitis, administration of these drugs except PLD was continued. The patient was treated with intravenous methylprednisolone 500 mg/day for 3 days. Azithromycin 1,000 mg per os and intravenous cefepime 4 g/day were administrated until all examinations of infection proved to be negative, including blood culture, β-D-glucan, influenza antigen detection, urinary pneumococcal antigen test, Chlamydia IgA/IgG, candida antibody assays, and galactomannan antigen of aspergillosis.

After the steroid pulse therapy, symptoms resolved promptly and lung function tests improved remarkably. Two months after the diagnosis of interstitial pneumonitis, a chest CT scan showed significant improvement (Fig. c). PLD was discontinued and her chemotherapy regimen was changed to docetaxel (70 mg/m^2). She has not shown any respiratory symptoms after cessation of PLD. Currently, she is alive with disease 24 months after the surgery and undergoing fifth-line chemotherapy.

Discussion

Pegylated liposomal doxorubicin is a reformulated version of doxorubicin, which takes the active agent doxorubicin and places it into a phospholipid bilayer called a liposome and another outer layer of methoxypolyethylene glycol. This coating allows PLD to evade detection and destruction by the immune system and to remain longer in the blood circulation.

PLD has a different toxicity profile compared with free doxorubicin. Though cumulative cardiac toxicities are unique to free doxorubicin, cardiac toxicities associated with PLD are rarely reported. Toxicities relatively unique to PLD are hand-foot syndrome or plantar palmar erythema (PPE), which are rarely reported with free doxorubicin.

It is reported that lung toxicity induced by doxorubicin is rare. Several cases of interstitial pneumonitis associated with doxorubicin or PLD have been described [,]. It was unclear whether the lung toxicities were directly attributable to doxorubicin in published case reports, because all patients were concurrently receiving other agents, mostly antineoplastic drugs, which were also implicated in causing lung toxicity.

In our case, though the symptoms were initially severe, discontinuation of PLD and steroid therapy immediately resolved them. Serum KL-6 levels have been reported to correlate with grade of interstitial lung disease [ ]. Normal serum KL-6 level in this case might associate with her excellent clinical course.

Two possible mechanisms of drug-induced interstitial pneumonitis have been described, one of which is the direct toxicity of the drug to the pulmonary organ and the other is immunological mechanism, although the etiology of PLD-induced interstitial pneumonitis is unclear.

Drug-induced pulmonary toxicity in Japan got a great deal of attention because of pulmonary toxicity induced by molecular-targeted chemotherapeutic drugs, gefitinib and an antirheumatic drug, leflunomide. It is reported that the

rates of interstitial lung disease associated with gefitinib and leflunomide are 2 and 1.1% in Japan and 0.3 and 0.02% in the United States, respectively. These data indicate that chemotherapeutic-drug-induced pulmonary toxicity is more frequent in Japan than in other nations [9, 10]. Fatal pneumonitis induced by gefitinib or leflunomide is less frequent in other Asian countries than in Japan. It may be that such drugs including PLD cause fatal pneumonitis predominantly in Japanese. The differences of genetic background or lifestyle between Japanese and non-Japanese might be involved in this event.

Drug-induced interstitial pneumonitis should be taken into consideration in the differential diagnosis of otherwise unexplained ground-glass lung lesions. Pulmonary toxicity induced by PLD is rare, but awareness of this toxicity is important, since it could be lethal. Additional investigation is required to elucidate how PLD induces interstitial pneumonitis or whether PLD-induced interstitial pneumonitis is more frequent in Japanese.

Conflict of interest No author has any conflict of interest.

References

1. Gordon AN, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol. 2001;19:3312–22.
2. Gordon AN, et al. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. Gynecol Oncol. 2004;95:1–8.
3. Ferrandina G, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol. 2008;26:890–6.
4. Uziely B, et al. Liposomal doxorubicin: antitumor activity and unique toxicity during two complementary phase I studies. J Clin Oncol. 1995;13:1777–85.
5. Thigpen JT, et al. Role of pegylated liposomal doxorubicin in ovarian cancer. Gynecol Oncol. 2005;96:10–8.
6. Huober J, Schoch O, Templeton A, Christian S, Thurlimann B. Interstitial pneumonitis after treatment with bevacizumab and pegylated liposomal doxorubicin in a patient with metastatic breast cancer. Chemotherapy. 2010;56:69–70.
7. Kim KM, et al. Rituximab-CHOP induced interstitial pneumonitis in patients with disseminated extranodal marginal zone B cell lymphoma. Yonsei Med J. 2008;49(1):155–8.
8. Satoh H, Kurishima K, Ishikawa H, Ohtsuka M. Increased levels of KL-6 and subsequent mortality in patients with interstitial lung diseases. J Intern Med. 2006;260:429–34.
9. Cohen MH, Williams GA, Sridhara R, Chan G, Pazdur R. FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets. Oncologist. 2003;8(4):303–6.
10. Takeishi M, et al. Leflunomide induced acute interstitial pneumonia. J Rheumatol. 2005;32(6):1160–3.

Int J Clin Oncol
DOI 10.1007/s10147-011-0280-9

ORIGINAL ARTICLE

Subsequent risks for cervical precancer and cancer in women with low-grade squamous intraepithelial lesions unconfirmed by colposcopy-directed biopsy: results from a multicenter, prospective, cohort study

Koji Matsumoto · Yasuo Hirai · Reiko Furuta · Naoyoshi Takatsuka · Akinori Oki · Toshiharu Yasugi · Hiroo Maeda · Akira Mitsuhashi · Takuma Fujii · Kei Kawana · Tsuyoshi Iwasaka · Nobuo Yaegashi · Yoh Watanabe · Yutaka Nagai · Tomoyuki Kitagawa · Hiroyuki Yoshikawa · For Japan HPV and Cervical Cancer (JHACC) Study Group

Received: 29 March 2011 / Accepted: 15 June 2011

Abstract
Objective To investigate the natural course of low-grade squamous intraepithelial lesions (LSILs) that cannot be histologically confirmed by colposcopy-directed biopsy.
Methods In a multicenter, prospective, cohort study of Japanese women with LSILs, we analyzed the follow-up data from 64 women who had a negative biopsy result at the initial colposcopy (biopsy-negative LSIL) in comparison with those from 479 women who had a histologic diagnosis of cervical intraepithelial neoplasia grade 1 (LSIL/CIN1). Patients were monitored by cytology and colposcopy every 4 months for a mean follow-up period of 39.0 months, with cytologic regression defined as two consecutive negative smears and normal colposcopy.
Results In women with biopsy-negative LSILs, there were no cases of CIN3 or worse (CIN3+) diagnosed within 2 years; the difference in the 2-year risk of CIN3+ between the two groups was marginally significant (0 vs. 5.5%; $P = 0.07$). The cumulative probability of cytologic regression within 12 months was much higher in the biopsy-

K. Matsumoto (✉) · A. Oki · H. Yoshikawa
Department of Obstetrics and Gynecology,
Graduate School of Comprehensive Human Science,
University of Tsukuba, Tsukuba 305-8575, Japan
e-mail: matsumok@mui.biglobe.ne.jp

Y. Hirai
Departments of Gynecology and Cytopathology,
Cancer Institute Hospital, Japanese Foundation
of Cancer Research, Tokyo 135-8550, Japan

R. Furuta · T. Kitagawa
Department of Pathology, Cancer Institute, Japanese Foundation
of Cancer Research, Tokyo 135-8550, Japan

N. Takatsuka
Department of Epidemiology and Preventive Medicine, Gifu
University Graduate School of Medicine, Gifu 501-1194, Japan

T. Yasugi · K. Kawana
Department of Obstetrics and Gynecology,
University of Tokyo, Tokyo 113-8655, Japan

H. Maeda
Department of Transfusion Medicine and Cell Therapy,
Saitama Medical Center, Saitama Medical University,
Saitama 350-8550, Japan

A. Mitsuhashi
Department of Reproductive Medicine,
Graduate School of Medicine, Chiba University,
Chiba 260-8670, Japan

T. Fujii
Department of Obstetrics and Gynecology,
Keio University School of Medicine, Tokyo 160-8582, Japan

T. Iwasaka
Department of Obstetrics and Gynecology, Faculty of Medicine,
Saga University, Saga 849-8501, Japan

N. Yaegashi
Department of Obstetrics and Gynecology, Tohoku University
School of Medicine, Sendai 980-8574, Japan

Y. Watanabe
Department of Obstetrics and Gynecology, Kinki University
School of Medicine, Osaka 589-8511, Japan

Y. Nagai
Department of Obstetrics and Gynecology, Faculty of Medicine,
University of the Ryukyus, Okinawa 903-0215, Japan

Published online: 13 July 2011

negative LSIL group (71.2 vs. 48.6%; $P = 0.0001$). The percentage of women positive for high-risk human papillomaviruses (hrHPVs) was significantly lower in the biopsy-negative LSIL group than in the LSIL/CIN1 group (62.1 vs. 78.4%; $P = 0.01$); however, the 12-month regression rate of biopsy-negative LSIL was similar between hrHPV-positive and -negative women (67.3 vs. 74.4%, $P = 0.73$).

Conclusion In women with biopsy-negative LSILs, the risk of CIN3+ diagnosed within 2 years was low; furthermore, approximately 70% underwent cytologic regression within 12 months, regardless of HPV testing results. Biopsy-negative LSILs may represent regressing lesions rather than lesions missed by colposcopy.

Keywords Low-grade squamous intraepithelial lesion · Colposcopy · Human papillomavirus · Cervical intraepithelial neoplasia

Introduction

In the Bethesda System for cytologic reporting, a low-grade squamous intraepithelial lesion (LSIL) represents mild cervical abnormalities, including cellular changes associated with human papillomavirus (HPV) infection and cervical intraepithelial lesion grade 1 (CIN1) [ ]. However, approximately 15–20% of women with a cytologic interpretation of LSIL have a grade 2 (CIN2) or grade 3 (CIN3) cervical intraepithelial lesion, which are immediately treated with cervical ablation, loop electrosurgical excision procedure (LEEP) or cone biopsy [,]. Therefore, women with LSILs usually undergo a colposcopy-directed biopsy for histologic evaluation of cervical abnormalities. Of the women with LSIL cytology, 40–60% are found to have a histologic diagnosis of CIN1 at the initial colposcopy, while 15–30% have a negative biopsy result [,]. According to the 2006 American Society for Colposcopy and Cervical Pathology consensus management guidelines [ ], the follow-up strategy for women with a negative biopsy result is identical to that of women with CIN1; that is, both groups are followed with either repeated cytology at 6 and 12 months or HPV testing at 12 months. However, the natural course of LSILs that cannot be histologically diagnosed by colposcopy-directed biopsy has not been well documented.

The Japan HPV and Cervical Cancer (JHACC) cohort study was designed to identify determinants of regression and progression of low-grade cervical abnormalities [,]. In the primary analysis, we used only the follow-up data from 570 women with cytologic LSIL and histologically confirmed CIN1 or CIN2 lesions, and demonstrated HPV type-specific risks of LSIL persistence and progression [ ]. In the present study, we analyzed the follow-up data of 64 women with biopsy-negative LSIL who were excluded from the main analysis cohort.

Methods

Study design

This study represents a secondary analysis of data from the prospective non-intervention cohort study conducted by the JHACC study group for identifying determinants of LSIL/CIN regression and progression. Details of the design, methods, and primary results have been provided in more detail elsewhere [,]. Briefly, 905 women with mildly abnormal cytology were recruited from nine hospitals that performed conventional Pap smears, colposcopy and cervical biopsies. The inclusion criteria of this secondary analysis were: evident LSIL cytology; histologic diagnosis of CIN1 or less at initial colposcopy and biopsy; age 18–54 years; first detection of cervical abnormality; and a sufficient number (two or more) of follow-up visits. Women entered the study voluntarily after giving their signed informed consent. Cervical smears were classified according to the Bethesda System [ ]. At the time of study entry, two (or more) small cervical specimens were taken by colposcopy-directed punch biopsy and stained with hematoxylin and eosin (H&E). A histologic diagnosis was determined based on the World Health Organization (WHO) classification system. Two cytopathologists (Y.H. and Masafumi Tsuzuku) and two pathologists (R.F. and T.K.) reviewed all cytologic and histologic specimens collected at the time of entry. Patients were tested for cervical HPV DNA, serum IgG antibodies to cytomegalovirus (CMV), *Chlamydia trachomatis*, and herpes simplex virus type 2 (HSV2) at the time of entry. The researchers who performed the assays were blinded to the clinical data collected from the study subjects. Information regarding smoking and sexual behavior was obtained from a self-administered questionnaire. Patients were routinely followed at 3- to 4-month intervals and received cytologic and colposcopic examinations at each visit. To avoid interference from the biopsy procedure on the natural course of the disease, a cervical biopsy was performed during the follow-up period only when Pap smears and colposcopic findings were suggestive of the presence of CIN3 or worse (CIN3+). A cytology result of HSIL triggered colposcopy-guided biopsy during follow-up examinations. The two cytopathologists and the two pathologists reviewed all cytologic and histologic specimens collected for the diagnosis of CIN3+. We chose an end-point of CIN3 or cancer rather than CIN2 or higher because CIN2 likely represents a heterogenous collection of cervical abnormalities [,], only some of which progress to CIN3 [,]. In this analysis, we defined regression as normal colposcopy results and at least two consecutive negative Pap smears. Persistent lesions were defined as lesions that did not regress or were diagnosed with CIN3+ during the follow-up period.

Overall, the study subjects consisted of 554 women who had a negative biopsy result (biopsy-negative LSIL; $n = 64$) or a histologic diagnosis of CIN1 (LSIL/CIN1; $n = 491$) at the initial colposcopy for LSIL cytology. Unfortunately, data from cervical samples, blood samples, or questionnaires were not available in all 554 study subjects. Cervical HPV data were not available in 21 women because of insufficient samples, while data on serum antibodies to sexually transmitted agents were lacking in 23 women. In addition, 54 women gave no responses to a self-administrated questionnaire. The study protocol was approved by the ethical and research review boards of the participating institutions.

HPV genotyping

We detected HPV DNA in cervical samples by polymerase chain reaction (PCR)-based methodology, as previously described [10]. In brief, exfoliated cells from the ectocervix and endocervix were collected in a tube containing 1 ml of phosphate-buffered saline (PBS) and stored at −30°C until DNA extraction. Total cellular DNA was extracted from cervical samples by a standard sodium dodecyl sulfate (SDS)–proteinase K procedure. HPV DNA was PCR amplified by using consensus primers (L1C1/L1C2 + L1C2M) for the HPV L1 region. A reaction mixture without template DNA was included in every set of PCR runs as a negative control. Primers for a fragment of the β-actin gene were also used as a control to rule out false-negative results for samples in which HPV DNA was not detected. HPV types were identified by an analysis of restriction fragment length polymorphism (RFLP), which has been shown to identify at least 26 types of genital HPVs [11].

IgG antibody against sexually transmitted agents

The level of IgG antibodies to *Chlamydia trachomatis* and HSV2 was determined by using commercially available enzyme-linked immunosorbent assay (ELISA) kits: *Chlamydia trachomatis* (HITAZYME; Hitachi Chemical, Tokyo, Japan) and HSV2 (HerpeSelect 2 ELISA IgG; Focus Diagnostics, Cypress, CA, USA). The serologic assay for *Chlamydia trachomatis* utilizes purified EB outer-membrane proteins of the *Chlamydia trachomatis* L2 strain as antigens and does not detect antibody to *Chlamydia pneumoniae* [12]. These serologic assays were performed at a clinical testing laboratory (SRL, Tokyo, Japan).

Statistical analysis

All time-to-event analyses were based on the actual date of the visits. For regression or progression, time to event was measured from the date of the index visit (i.e., the first instance of an abnormal cytology result) to the date of the visit at which cytologic transition to normal occurred or CIN3+ was first detected. Women whose lesions persisted or who dropped out of the study were censored at their last recorded return visit dates. Subjects who had only one negative colposcopy/cytology result before loss to follow-up were censored at the last date of positive Pap tests. Subjects who were biopsied were censored at the time of their biopsy, regardless of the biopsy results, to reduce the potential for interference by the biopsy procedure on estimates of time of regression. Cumulative probability of LSIL regression or progression was estimated by using the Kaplan–Meier method and compared with a log-rank test. All analyses were carried out using the JMP 7.0J (SAS Institute, Cary, NC, USA) statistics packages. Two-sided P values were calculated throughout and considered to be significant at less than 0.05.

Results

We analyzed the follow-up data from a total of 554 women with LSIL cytology who had a negative biopsy result (biopsy-negative LSIL; $n = 64$) or a histologic diagnosis of CIN1 (LSIL/CIN1; $n = 491$) at the initial colposcopy. Distributions of baseline characteristics between these two groups are presented in Table 1. The women with biopsy-negative LSILs were older than the women with LSIL/CIN1 (mean age ± SD 38.8 ± 9.2 vs. 36.2 ± 7.7 years); however, the difference in the age distribution between the two groups was only marginally significant ($P = 0.07$). Cervical HPV infections were found in 75.0% of women with biopsy-negative LSILs and in 84.6% of women with LSIL/CIN1 results and the difference was statistically significant ($P = 0.02$). The percentage of women positive for high-risk human papillomaviruses (hrHPVs) was also significantly lower in the biopsy-negative LSIL group than in the LSIL/CIN1 group (62.1 vs. 78.4%; $P = 0.01$). The percentage of women who had smoked was lower in the biopsy-negative LSIL group (32.6 vs. 48.7%), but the difference was only marginally significant ($P = 0.07$). The number of lifetime sexual partners was significantly greater among women with LSIL/CIN1 than among women with biopsy-negative LSILs ($P = 0.001$). The age at first sexual intercourse was also lower among women with LSIL/CIN1 compared to women with biopsy-negative LSILs, although the difference was only marginally significant ($P = 0.06$). Women with LSIL/CIN1 were likely to have a higher IgG antibody titer against *Chlamydia trachomatis* than women with biopsy-negative LSILs; however, the difference was not significant ($P = 0.25$). The IgG reactivity to HSV2 was similar between the two groups ($P = 0.82$). At least two