Patterns of prescribing radiotherapy and bevacizumab in nationwide practice – analysis of 101 designated cancer care hospitals in Japan

Yoichiro Tsukada1,2*, Fumiaki Nakamura3, Momoko Iwamoto1, Atsuro Terahara2 and Takahiro Higashi1

1Division of Health Services Research, Center for Cancer Control and Information Services, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104–0045, Japan
2Department of Radiology, Toho University Omori Medical Center, Tokyo, Japan
3Department of Public Health/Health Policy, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan
*Corresponding author: Division of Health Services Research, Center for Cancer Control and Information Service, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104–0045, Japan. Tel: +81-3-3547-2511 (ext. 1606); Fax: +81-3-5565-2322; Email address: yotsukad@ncc.go.jp

ABSTRACT

Radiotherapy and bevacizumab are each effective in treating patients with advanced cancer, but their concurrent use may cause serious adverse events (SAEs). Whereas sequential administration can theoretically reduce the risk of SAEs while maintaining the anticancer effects, this hypothesis remains unconfirmed, leading to variations in practice. To elucidate current practices, the patterns of care received by patients in Japan with regard to these two therapies were assessed in a large database of a hospital-based cancer registry linked with insurance claims. This database contained information on 106,057 patients diagnosed with seven major cancers in 2011 and the care they received up to the end of 2012. In total, 335 patients from 101 hospitals in the database were treated with both radiotherapy and bevacizumab. Of these patients, 50.8% had lung cancer, and 51.3% had Stage IV cancer. Of the 335 patients, 75 (22.4%) received these therapies concurrently. In patients treated sequentially, the time from the last dose of bevacizumab to the start of radiotherapy was most frequently 4–5 weeks (12.4%), whereas the time from the end of radiotherapy to the start of bevacizumab was most frequently 1–2 weeks (10.6%). The cumulative proportions of patients in these two groups receiving sequential therapies within 3 weeks were 19.0% and 26.1%, respectively. Many practices appeared to avoid the concurrent use of bevacizumab and radiation, but some provided concurrent therapy. Additional data are required to determine whether the avoidance of concurrent use should become a standard of care.

KEYWORDS: adverse effects, bevacizumab, radiation-sensitizing agents, radiotherapy, Vascular Endothelial Growth Factor A

INTRODUCTION

Neoplastic angiogenesis is essential for tumor growth [1]. Vascular endothelial growth factor (VEGF) is a heparin-binding growth factor expressed in tumor cells and adjacent endothelial cells of blood vessels, and is a key for inducing angiogenesis [1, 2]. Bevacizumab (Avastin®; Genentech, Inc.; South San Francisco, CA), an anti-VEGF monoclonal antibody approved for use by the US Food and Drug Administration (FDA) in 2004, inhibits tumor angiogenesis and the growth and proliferation of human tumor cell lines [3, 4]. Although bevacizumab alone cannot permanently control tumor growth in most patients [5], combinations of bevacizumab with systemic chemotherapy have improved outcomes in patients with a wide range of advanced or metastatic cancers, including colorectal cancer (CRC) [6], non–small-cell lung cancer (NSCLC) [7, 8], breast cancer [9] and renal cancer [10]. In Japan, bevacizumab was approved in July 2015 for patients with inoperable advanced or recurrent CRC, non-squamous NSCLC, breast cancer, ovarian cancer, and malignant glioblastoma. Moreover, clinical trials have assessed combinations of bevacizumab with radiotherapy in patients with several types of cancer, including rectal cancer [11], breast cancer [12], NSCLC [13], cervical cancer [14], and brain tumors [15, 16].
Bevacizumab, however, has been associated with several complications, such as intestinal perforation and delayed wound healing [17]. Because bevacizumab may delay wound healing, the FDA has recommended that bevacizumab be discontinued at least 28 days prior to elective surgery, and that this agent should not be restarted within 28 days after surgery and until the surgical wound has completely healed [18]. Furthermore, several clinical trials have reported that concurrent use of radiation therapy and bevacizumab may be associated with serious adverse events (SAEs) [19–22]. The FDA issued a Drug Warning against combined use in 2007 [19]. In real-world practice settings, however, conditions may arise necessitating simultaneous radiotherapy and bevacizumab. For example, CRC patients with liver metastases being treated with systemic chemotherapy and bevacizumab may experience severe abdominal pain arising from the tumor mass, and may therefore be considered for radiotherapy of the liver to control these symptoms [23]. At present, there are no professional guidelines for the use of simultaneous or sequential radiotherapy and bevacizumab, including the interval between the two treatments.

As a first step to understanding the type and frequency of SAEs associated with radiotherapy and bevacizumab, we analyzed the percentages and characteristics of cancer patients in Japan who were treated with both radiotherapy and bevacizumab, both simultaneously and sequentially, using a nationwide database.

MATERIALS AND METHODS

Data source

The database used was one that compiled health claims data linked to the Hospital-Based Cancer Registry (HBCR) from designated cancer care hospitals (DCCHs) and several hospitals that were not designated, but played a similar role in their communities and voluntarily submitted their data. This database was developed to measure process-of-care quality indicators for gastric, colorectal, breast, lung, liver, cervical and prostate cancer. In total, 178 hospitals joined the project: 173 of the 397 DCCHs and 5 other hospitals in 2011, and information on 106,057 patients was collected.

The insurance claims data were derived from an ongoing evaluation required of the hospitals that participate in a per-diem payment system (PDPs) based on diagnosis procedure combination (DPC) groups (DPC/PDPS) in the national health insurance scheme. The DPC/PDPS program was launched in 2002 and was adopted by secondary and tertiary care hospitals in Japan [24]. It includes unique identification codes for hospitals and patients, diagnoses, and the codes for all procedures and prescriptions supplied to each patient, as well as their dates. Although DPC/PDPS payments apply only to inpatient care, the evaluation collected the same information on outpatient care. This study included both inpatient and outpatient data.

The HBCR data contained information on cancer patients newly diagnosed, treated and followed up at the participating hospitals. The DCCHs, which are designated by the Ministry of Health, Labour and Welfare to provide specialized cancer care across communities in Japan, are required to submit their data annually to the National Cancer Center [25]. The entire HBCR database covered ~70% of all newly diagnosed cancer patients in 2011 [25]. The data contain information on cancer patients and their clinical profiles, including clinical and pathological tumor-node-metastasis (TNM) stages, topology (site), histology codes of the International Classification of Diseases for Oncology, third edition (ICD-O-3), diagnosis and first-course treatment with dates of care.

The database collected insurance claims for at least one year, from each patient’s first visit in 2011 to the hospital registered in the HBCR database, through December 2012. This study was approved by the Institutional Review Board of the National Cancer Center.

Targeted patients

The database was searched for patients who received both external-beam radiotherapy (including intensity-modulated radiotherapy) and bevacizumab during the study period. Patients who received only stereotactic body radiotherapy (SBRT) were excluded, because the fees for SBRT were lump-sum payments and the dates of SBRT were unclear on some insurance claims data.

Endpoints

Patients who received both radiotherapy and bevacizumab concurrently or sequentially were identified and classified into three groups: (i) a concurrent treatment (C) group, in which patients received concurrent radiotherapy and bevacizumab; (ii) a sequential bevacizumab–radiotherapy (B–R) group, in which the first dose of radiotherapy was delivered after the last dose of bevacizumab; and (iii) a sequential radiotherapy–bevacizumab (R–B) group, in which the first dose of bevacizumab was administered after the last irradiation. The characteristics of the three groups were compared, including cancer site, stage, and number of radiation fractions. Patients were subdivided into those who received <21 radiation fractions, generally considered palliative therapy, and ≥21 radiation fractions, generally considered therapy with curative intent. The cut-off of 21 was set based on the results of previous studies investigating palliative radiotherapy regimens [23, 26–29]. In the two sequential treatment groups, the intervals in weeks from the last day of radiotherapy to the first day of bevacizumab and from the last day of bevacizumab to the first day of radiotherapy were determined.

Intermittent irradiations at intervals of ≤30 days apart were categorized as belonging to a single course of radiotherapy, whereas intervals between two irradiations of >30 days were regarded as belonging to different courses of radiotherapy. If a patient underwent two or more courses of radiotherapy, the course nearest in time to bevacizumab treatment was considered. Stages were recorded according to the Union for International Cancer Control (UICC) TNM codes (UICC TNM classification of malignant tumors, 6th edition). Pathological stage was normally defined as each patient’s final stage, although clinical stage was used when pathological stage was not known. Stata® version 13.1 software (StataCorp, College Station, TX) was used for all data analyses.

RESULTS

Of the 106,057 cancer at 178 hospitals, 20,703 received radiotherapy, and 2447 received bevacizumab, with 335 patients at 101 hospitals receiving both. Table 1 shows the characteristics of these 335 patients. Of these, 170 (50.8%) had lung cancer, 172 (51.3%) had Stage IV disease, and 38 (11.3%) were >75 years old. A total of 75 patients (22.4%) were treated concurrently, including two who received two courses of concurrent treatment, and 260 (77.6%) were treated sequentially, including 137 who received bevacizumab...
Table 1. Characteristics of patients treated with radiotherapy and bevacizumab (n = 335)

| Patient characteristics | Number of patients, n (%) |
|-------------------------|----------------------------|
| Treated concurrently    | 75 (22.4)                  |
| Treated sequentially    | 260 (78.6)                 |
| Mean (±standard deviation) age, years | 62.2 (±11.1) |
| <75 years, n (%)        | 297 (88.7)                 |
| ≥75 years, n (%)        | 38 (11.3)                  |
| Sex: female, n (%)      | 106 (31.6)                 |
| Sites of cancer, %      |                            |
| lung                    | 171 (51.0)                 |
| rectal                  | 89 (26.6)                  |
| colon                   | 37 (11.0)                  |
| breast                  | 28 (8.4)                   |
| others                  | 10 (3.0)                   |
| UICC stage, n (%)       |                            |
| 0                       | 1 (0.3)                    |
| I                       | 18 (5.4)                   |
| II                      | 27 (8.1)                   |
| III                     | 102 (30.5)                 |
| IV                      | 172 (51.3)                 |
| unknown                 | 15 (4.5)                   |

followed by radiotherapy (B–R group), 142 who received radiotherapy followed by bevacizumab (R–B group), and 19 who received bevacizumab both before and after radiotherapy. The 335 patients received 356 courses of radiotherapy. Table 2 shows details of tumor sites, stages, and radiotherapy fractions per course. In all three groups, the most frequent subgroup consisted of patients with Stage IV lung cancer who were irradiated with <21 fractions.

Intervals from bevacizumab to radiotherapy

Figure 1 shows the proportion of patients in the B–R group by weekly intervals from the last administration of bevacizumab to the first dose of radiotherapy. The most common interval was 4–5 weeks (17 patients, 12.4%), although 26 patients (19.0%) started radiotherapy within 3 weeks after the last dose of bevacizumab.

Intervals from radiotherapy to bevacizumab

Figure 2 shows the proportion of patients in the R–B group by weekly intervals from the last dose of radiotherapy to the first dose of bevacizumab. The most common interval was 1–2 weeks (15 patients, 10.6%), with 37 patients (26.1%) starting bevacizumab within 3 weeks after the last dose of radiotherapy.

**Discussion**

This study showed that about only one-fifth of the cancer patients in Japan who were treated with both radiotherapy and bevacizumab received the two concurrently. In most patients, the interval between finishing one treatment and starting the other was several weeks, indicating that many practices throughout Japan avoided concurrent treatment with radiotherapy and bevacizumab treatment. To our knowledge, this is the first study to assess patterns of radiotherapy and bevacizumab treatment in cancer patients. These patterns may be associated with the occurrence and numbers of SAEs, as well as with factors affecting the occurrence of SAEs.

Several clinical trials have reported SAEs in patients concurrently treated with radiotherapy and bevacizumab [20–22]. For example, one study analyzed SAEs in two independent Phase II clinical trials in patients with limited small-cell lung cancer and locally advanced NSCLC [20]. In the first trial, in which patients received chemoradiation therapy with concurrent bevacizumab, two of 29 patients experienced tracheoesophageal fistula (TEF) formation, one resulting in death, and another patient died from an aerodigestive hemorrhage. In the second trial, two of five patients experienced TEF formation after chemoradiation therapy with concurrent bevacizumab. In a Phase I trial, four of six patients with inoperable Stage III NSCLC who received induction chemotherapy followed by concurrent thoracic radiotherapy with bevacizumab developed pulmonary toxicities [21]. All three trials were terminated early due to these SAEs [20, 21].

Recent in vitro studies reported that bevacizumab can sensitize cancer cells to radiotherapy, resulting in downregulation of VEGF expression, inability to repair double-strand breaks in DNA, and normalization of tumor microvessels, resulting in tumoricidal effects [30, 31]. The combination of anti-VEGF antibody, irradiation, and bleomycin in mouse models resulted in enhanced intestinal injury with severe epithelial ulcerations during the acute phase, and lung fibrosis during the late phase [32]. Anti-VEGF antibody inhibits VEGF signaling pathways required for wound-healing processes following normal tissue damage by radiation, suggesting caution in treating patients with combinations of targeted agents and radiotherapy.

Our findings showed that intervals of several weeks elapsed between bevacizumab and radiation treatment in many sequentially treated patients. These intervals tended to be longer in the B–R than in the R–B group, perhaps to avoid the adverse events associated with any remaining bevacizumab. However, about one-fifth of patients in the B–R group started radiotherapy within 3 weeks, the estimated half-life time of bevacizumab in the human body [18]. Moreover, about one-fourth of the patients in the R–B group started bevacizumab within 3 weeks after finishing radiotherapy. A Phase III trial that showed that the addition of improved overall survival in patients with advanced cervical cancer and a history of cisplatin-based chemoradiation therapy utilized a wash-out period of at least 3 weeks from the last dose of radiotherapy to remove potential deleterious effects of these previous treatments [33]. Furthermore, more than 10% of our patients were ≥75 years old, and
large numbers of patients in all three groups had Stage IV lung cancer and were irradiated with fewer than 21 fractions. These characteristics suggest that this treatment was mainly used for palliative purposes, including symptom management, in patients with advanced cancers, and that these patients were at higher risk of SAEs than patients in better overall condition who received regular therapy. Further studies, analyzing SAEs and their risk factors, are required to determine the standards of care in these patients, balancing the risks and benefits of treatment.

Our study had several limitations. First, our analyses used an insurance claims database. The claims data did not include the site or the total dose of irradiation, suggesting the need for further studies to assess these factors. Second, we classified radiotherapy courses into two groups, with a cut-off of 21 fractions. Although some patients may have been misclassified, we believe this analysis is useful in gaining insight into the purposes of radiotherapy. Third, our analysis included data from patients with seven major types of cancer treated at 178 hospitals, including 173 DCCHs, suggesting that these results may not have been representative of cancer patients throughout Japan. However, the database included 106,057 patients, about one-fifth of those newly diagnosed in 2011 with these seven major types of cancer in Japan [34], suggesting that our findings represent a trend of care practices in Japan. Finally, we analyzed patients with seven major types of cancer, suggesting that these findings may not be applicable to patients with other types of cancer, such as ovarian cancer and brain tumors.
In conclusion, many oncology practices in Japan appeared to avoid concurrent treatment with bevacizumab and radiotherapy. Further studies are needed to determine whether the avoidance of concurrent use should become the standard of care.

We thank Kaoru Konno for her technical assistance in the project, as well as the participating hospitals that submitted insurance claims data. The results of this study were presented in part at the 27th Annual Meeting of the Japanese Society for Radiation Oncology.
FUNDING
This work was supported by the National Cancer Center Research and Development Programs (Grant number H25-A-21). Funding to pay Open Access publication charges for this article was also provided by this grant.

REFERENCES
1. Nishida N, Yano H, Komai K, et al. Vascular endothelial growth factor c and vascular endothelial growth factor receptor 2 are related closely to the prognosis of patients with ovarian carcinoma. Cancer 2004;101:1364–74.
2. Leung DW, Cachianes G, Kuang WJ, et al. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 1989;246:1306–09.
3. Ferrara N, Hillan KJ, Novotny W, et al. Bevacizumab (avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. Biochem Biophys Res Commun 2005;333:328–35.
4. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. Clin Ther 2006;28:1779–802.
5. Nieder C, Wiedenmann N, Andratschke NH, et al. Radiation therapy plus angiogenesis inhibition with bevacizumab: rationale and initial experience. Rev Recent Clin Trials 2007;2:163–8.
6. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–42.
7. Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.
8. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. J Clin Oncol 2009;27:1227–34.
9. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012;366:299–309.
10. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370:2103–11.
11. Landry JC, Feng Y, Cohen SJ, et al. Phase 2 study of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: ECOG 3204. Cancer 2013;119:1521–7.
12. Pernin V, Belin L, Cottu P, et al. Radiotherapy associated with concurrent bevacizumab in patients with non-metastatic breast cancer. Breast 2014;23:816–20.
13. Spigel DR, Hainsworth JD, Farley C, et al. Tracheoesophageal (TE) fistula development in a phase ii trial of concurrent chemoradiation (CRT) and bevacizumab (B) in limited-stage small-cell lung cancer (LS-SCLC). J Clin Oncol (Meeting Abstracts) 2008;26:7554.
14. Schefter T, Winter K, Kwon JS, et al. RTOG 0417: Efficacy of bevacizumab in combination with definitive radiation therapy and cisplatin chemotherapy in untreated patients with locally advanced cervical carcinoma. Int J Radiat Oncol Biol Phys 2014;88:101–5.
15. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014;370:709–22.
16. Levy C, Allouache D, Lacroix J, et al. REBECa: a phase I study of bevacizumab and whole-brain radiation therapy for the treatment of brain metastasis from solid tumours. Ann Oncol 2014;25:2351–6.
17. Miles D: Management of toxicity in patients receiving therapy with bevacizumab. Eur J Cancer Suppl 2008;6:29–39.
18. U.S. Food and Drug Administration. Highlights of Prescribing Information: United States. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf (29 Jun 2015, date last accessed).
19. Genentech, Inc. Important Drug Warning Regarding Avastin® (Bevacizumab). U.S. Food and Drug Administration. http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153953.pdf (26 Jun 2014, date last accessed).
20. Spigel DR, Hainsworth JD, Yardley DA, et al. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. J Clin Oncol 2010;28:43–8.
21. Lind JS, Senan S, Smit EF, et al. Pulmonary toxicity after bevacizumab and concurrent thoracic radiotherapy observed in a phase I study for inoperable stage III non-small-cell lung cancer. J Clin Oncol 2012;30:e104–8.
22. Crane CH, Ellis LM, Abbruzzese JL, et al. Phase I trial evaluating the safety of bevacizumab with concurrent radiotherapy and capcitabine in locally advanced pancreatic cancer. J Clin Oncol 2006;24:1145–51.
23. Gasent Blesa JM, Dawson LA. Options for radiotherapy in the treatment of liver metastases. Clin Transl Oncol 2008;10:638–45.
24. Sato M, Tateishi R, Yasunaga H, et al. Mortality and morbidity of hepatocarcinoma, radiofrequency ablation, and embolization for hepatocellular carcinoma: a national survey of 54,145 patients. J Gastroenterol 2012;47:1125–33.
25. Higashi T, Nakamura F, Shibata A, et al. The national database of hospital-based cancer registries: a nationwide infrastructure to support evidence-based cancer care and cancer control policy in Japan. Jpn J Clin Oncol 2014;44:2–8.
26. Trey J, Back MF, Shakespeare TP, et al. The role of palliative radiation therapy in symptomatic locally advanced gastric cancer. Int J Radiat Oncol Biol Phys 2007;67:385–8.
27. Fairchild A, Barnes E, Ghosh S, et al. International patterns of practice in palliative radiotherapy for painful bone metastases: evidence-based practice? Int J Radiat Oncol Biol Phys 2009;75:1501–10.
28. Rodrigues G, Macbeth F, Burmeister B, et al. Consensus statement on palliative lung radiotherapy: Third International Consensus Workshop on Palliative Radiotherapy and Symptom Control. Clin Lung Cancer 2012;13:1–5.
29. Hoyer M, Swaminath A, Bydder S, et al. Radiotherapy for liver metastases: a review of evidence. Int J Radiat Oncol Biol Phys 2012;82:1047–57.
30. Gao H, Xue J, Zhou L, et al. Bevacizumab radiosensitizes non-small cell lung cancer xenografts by inhibiting DNA double-strand break repair in endothelial cells. Cancer Lett 2015;365:79–88.
31. Zhuang HQ, Yuan ZY, Wang P. Research progress on the mechanisms of combined bevacizumab and radiotherapy. *Recent Pat Anticancer Drug Discov* 2014;9:129–34.

32. Mangoni M, Vozenin MC, Biti G, et al. Normal tissues toxicities triggered by combined anti-angiogenic and radiation therapies: hurdles might be ahead. *Br J Cancer* 2012;107:308–14.

33. Tewari KS, Sill MW, Long HJ III, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med* 2014;370:734–43.

34. Center for Cancer Control and Information Service, National Cancer Center. Current cancer statistics: Japan (in Japanese). http://ganjoho.jp/reg_stat/statistics/stat/summary.html (25 Jun 2015, date last accessed).