Acta Oncologica, 2009; 48: 325–327

informa
healthcare

EDITORIAL

Follow up your unexpected clinical observations!

OLAV DAHL

Section of Oncology, Institute of Medicine and Department of Oncology, Haukeland University Hospital, University of Bergen, N5021 Bergen, Norway

Progress in clinical oncology is often ascribed progress in laboratory medicine alone which then is transferred to the patients. This is frequently termed translational medicine. However, frequently the clinical use of a drug or method is a two way process, with accumulation of new knowledge and facts at the bedside which has to be taken into account before the final progress can appear. Recently it has become clear that the term targeteted therapy sometimes may not be as targeted as initially expected, based on *in vitro* work or animal studies, as experience shows new side effects and complications due to a broader effect of the targeted therapy than initially thought of [1].

Gastric cancer remains a great challenge, especially in Asia, despite a very substantial decline in incidence in Western countries, probably partly related to reduced use of salted food and eradication of infection with Helicobacter pylori strains [2–5]. Ten years ago the main scientific controversy in gastric cancer treatment was the extent of surgical lymph node dissection: The extended surgery done by Japanese surgeons in contrast to less lymph node dissections in most Western countries [6]. Another long standing controversy has been the role of adjuvant therapy. In USA the use of adjuvant radiation therapy has been advocated, based on a study which has been somewhat controversial due to the type of surgery chosen [7]. However, only R0 resections of primary gastric cancer is currently a curative option [8]. Recently the Magic study using primary (neoadjuvant) chemotherapy and postoperative chemotherapy, demonstrating a survival benefit of 13% [9]. A similar non-significant observation has been reported in a French study using postoperative chemotherapy, which was prematurely closed due to slow accrual and problems with toxicity due to a higher cisplatin dose [10]. Therefore adjuvant perioperative chemotherapy is now accepted in many European countries for Stage II and III patients.

In parallel with this progress in localized gastric tumours, several chemotherapy regimens are now available for palliation of metastatic disease [11–15]. Despite some differences in toxicity, more easily administered regimens now exist for patients with metastases from gastric cancer in relative good performance status at start of therapy.

Gastric cancer may be easy to follow by gastroscopy, endoscopic ultrasound examination or by CT or MR imaging, but frequently the disease is difficult to monitor due to dissemination within the bowel cavity accompanied with ascites, or due to a more disseminated growth pattern instead of discrete easily measurable nodules. In such cases elevation of the carcinoembryonic antigen (CEA) and sialylated Lewis blood group antigen CA19-9 [16]serum markers before therapy are considered indications for poor prognosis [17]. Serial measurements during chemotherapy, is also useful as a decline denotes tumour regression and a rise means tumour progression in the patients with initially raised markers. In this issue of Acta Oncologica, Kim et al. demonstrate that the monitoring of disease response by these markers should be carefully assessed [18]. For the first time they report that chemotherapy for gastric cancer can induce a surge of the serum markers CEA and CA 19-9, defined as an initial increase by more than 20% and then decline with more than 20% together with at least stable disease after the RESIST criteria [19]. The phenomenon could reflect that more effective chemotherapy can release the markers from drug sensitive cells as they are destructed. Unfortunately the current markers are only useful for a minority of gastric cancer patients, but the finding is important as a transient rise within a frame of 7–8 weeks hereto has been regarded as an indication of tumour progression or

(Received 30 November 2008; accepted 11 January 2009)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860902740915

chemotherapy resistance. That a rise in markers following first courses of chemotherapy indicates release form destructed tumour cells and a positive tumour response, is therefore important knowledge to avoid premature conclusions on a failure, which could lead to termination of a potentially beneficial therapy. This may also reflect increased expression of CEA due to the treatment with 5-fluorouracil as demonstrated in cell cultures [20–22]. However, a transient increase in CEA may also be related to liver toxicity from fluorouracil [23]. Kim et al. did not report liver function tests in their paper.

In testicular cancer the use of the serum markers alpha-fetoprotein, AFP, and human chorionic gonadotropin-β, HCGβ, have proved to be important for monitoring the therapy efficacy. Due to the rapid regression after start of therapy, a transient therapy induced increase of markers is well known as a surge [24,25]. It is also well known that initiation of therapy for breast cancer can induce a CEA surge reaction [26–29]. Measurement of serum CEA is currently widely used as a method to monitor response of colorectal cancer. For CEA we started relatively early with a combination of fluorouracil and folinate together with oxaliplatin (Nordic FLOX) [30,31]. We were able to report objective regression in about half of the patients. I had a patient who I noticed a rise in CEA before the outpatient visit, and this was discussed and a change in therapy was proposed. However, the patient and his wife reported an improved clinical condition during chemotherapy and we therefore awaited the scheduled CT scan which showed a nice decrease of his liver metastases. When we retrospectively assessed a series of 27 patients on the same regimen, another four (15%) had a CEA surge [32,33]. In fact our small, observational study led to a change in the ASCO recommendations for use of biomarkers in colorectal cancer [34]. Our findings were confirmed in a series of 89 patients where ten (11%) exhibited a CEA surge after initiation of chemotherapy [22]. However, a recent paper presented the use of serial recording of CEA after start of chemotherapy for colon cancer without taking into account the surge phenomenon which may affect 10–15% of the patients, potentially leading to false conclusions [35,36]. In the next issue of ASCO recommendations for use of markers in gastrointestinal cancer, therefore also the recommendations on use of markers in gastric cancer should be changed.

In Acta Oncologica we generally do not any longer accept case reports. However, clinicians should have an open mind for phenomena not previously reported. If there are several similar original observations, we would like to see a detailed description of the phenomenon, its frequency and not the least a statement of the potential consequences for treatment of patients in a letter to the editor. With all the new drugs coming into the clinics and particularly by a fast track approach, the clinicians should be carefully observing their patients.

References

[1] Dahl O, Borkamo ED, Fluge O. Current status of anti-vascular therapy and targeted treatment in the clinic. Int J Hyperthermia 2008;24:97–110.

[2] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.

[3] Sjodahl K, Jia C, Vatten L, Nilsen T, Hveem K, Lagergren J. Salt and gastric adenocarcinoma: A population-based cohort study in Norway. Cancer Epidemiol Biomarkers Prev 2008; 17:1997–2001.

[4] Sorbye H, Kvinnsland S, Svanes K. Effect of salt-induced mucosal damage and healing on penetration of N-methyl-N'-nitro-N-nitrosoguanidine to proliferative cells in the gastric mucosa of rats. Carcinogenesis 1994;15:673–9.

[5] Nguyen LT, Uchida T, Murakami K, Fujioka T, Moriyama M. Helicobacter pylori virulence and the diversity of gastric cancer in Asia. J Med Microbiol 2008;57:1445–53.

[6] Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H, Hada M, et al. Should systematic lymph node dissection be recommended for gastric cancer? Eur J Cancer 1998;34: 1480–9.

[7] Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–30.

[8] Lello E, Furnes B, Edna TH. Short and long-term survival from gastric cancer. A population-based study from a county hospital during 25 years. Acta Oncol 2007;46:308–15.

[9] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.

[10] Bouche O, Ychou M, Burtin P, Bedenne L, Ducreux M, Lebreton G, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801). Ann Oncol 2005;16:1488–97.

[11] Cunningham D, Chua YJ. East meets west in the treatment of gastric cancer. N Engl J Med 2007;357:1863–5.

[12] Ragnhammar P, Hafstrom L, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in colorectal cancer. Acta Oncol 2001;40:282–308.

[13] Dupont J, Jensen HA, Jensen BV, Pfeiffer P. Phase I study of short-time oxaliplatin, capecitabine and epirubicin (EXE) as first line therapy in patients with non-resectable gastric cancer. Acta Oncol 2007;46:330–5.

[14] Foukakis T, Lundell L, Gubanski M, Lind PA. Advances in the treatment of patients with gastric adenocarcinoma. Acta Oncol 2007;46:277–85.

[15] Oh SY, Kwon HC, Seo BG, Kim SH, Kim JS, Kim HJ. A phase II study of oxaliplatin with low dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFOX-4) as first line therapy for patients with advanced gastric cancer. Acta Oncol 2007;46:336–41.

[16] Tempero MA, Uchida E, Takasaki H, Burnett DA, Steplewski Z, Pour PM. Relationship of carbohydrate antigen

19-9 and Lewis antigens in pancreatic cancer. Cancer Res 1987;47:5501–3.

[17] Catalano V, Graziano F, Santini D, D'Emidio S, Baldelli AM, Rossi D, et al. Second-line chemotherapy for patients with advanced gastric cancer: Who may benefit? Br J Cancer 2008;99:1402–7.

[18] Kim H, Lee K-W, Kim Y, Oh D-Y, Kim J, Im SA, et al. Chemotherapy-induced transient CEA and CA 19-9 surges in patients with metastatic or recurrent gastric cancer. Acta Oncol 2009;48:385–90.

[19] Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: A review of validation studies on tumour assessment. Eur J Cancer 2006;42:1031–9.

[20] Aquino A, Formica V, Prete SP, Correale PP, Massara MC, Turriziani M, et al. Drug-induced increase of carcinoembryonic antigen expression in cancer cells. Pharmacol Res 2004;49:383–96.

[21] Prete SP, Turriziani M, Massara MC, De Rossi A, Correale P, De Vecchis L, et al. Combined effects of 5-fluorouracil, folinic acid and oxaliplatin on the expression of carcinoembryonic antigen in human colon cancer cells: Pharmacological basis to develop an active antitumor immunochemotherapy. J Exp Clin Cancer Res 2008;27:5.

[22] Ailawadhi S, Sunga A, Rajput A, Yang GY, Smith J, Fakih M. Chemotherapy-induced carcinoembryonic antigen surge in patients with metastatic colorectal cancer. Oncology 2006;70:49–53.

[23] Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA. Hepatic toxicity associated with fluorouracil plus levamisole adjuvant therapy. J Clin Oncol 1993;11: 2386–90.

[24] Horwich A, Peckham MJ. Transient tumor marker elevation following chemotherapy for germ cell tumors of the testis. Cancer Treat Rep 1986;70:1329–31.

[25] Vogelzang NJ, Lange PH, Goldman A, Vessela RH, Fraley EE, Kennedy BJ. Acute changes of alpha-fetoprotein and human chorionic gonadotropin during induction chemotherapy of germ cell tumors. Cancer Res 1982;42:4855–61.

[26] Kiang DT, Greenberg LJ, Kennedy BJ. Tumor marker kinetics in the monitoring of breast cancer. Cancer 1990; 65:193–9.

[27] Loprinzi CL, Tormey DC, Rasmussen P, Falkson G, Davis TE, Falkson HC, et al. Prospective evaluation of carcinoembryonic antigen levels and alternating chemotherapeutic regimens in metastatic breast cancer. J Clin Oncol 1986;4: 46–56.

[28] Mughal AW, Hortobagyi GN, Fritsche HA, Buzdar AU, Yap HY, Blumenschein GR. Serial plasma carcinoembryonic antigen measurements during treatment of metastatic breast cancer. JAMA 1983;249:1881–6.

[29] Sonoo H, Kurebayashi J. Serum tumor marker kinetics and the clinical course of patients with advanced breast cancer. Surg Today 1996;26:250–7.

[30] Sorbye H, Dahl O. Nordic 5-fluorouracil/leucovorin bolus schedule combined with oxaliplatin (Nordic FLOX) as first-line treatment of metastatic colorectal cancer. Acta Oncol 2003;42:827–31.

[31] Sorbye H, Glimelius B, Berglund A, Fokstuen T, Tveit KM, Braendengen M, et al. Multicenter phase II study of Nordic fluorouracil and folinic acid bolus schedule combined with oxaliplatin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2004;22:31–8.

[32] Sorbye H, Dahl O. Carcinoembryonic antigen surge in metastatic colorectal cancer patients responding to oxaliplatin combination chemotherapy: Implications for tumor marker monitoring and guidelines. J Clin Oncol 2003;21: 4466–7.

[33] Sorbye H, Dahl O. Transient CEA increase at start of oxaliplatin combination therapy for metastatic colorectal cancer. Acta Oncol 2004;43:495–8.

[34] Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol ;24 2006;24:5313–27.

[35] Iwanicki-Caron I, Di Fiore F, Roque I, Astruc E, Stetiu M, Duclos A, et al. Usefulness of the serum carcinoembryonic antigen kinetic for chemotherapy monitoring in patients with unresectable metastasis of colorectal cancer. J Clin Oncol 2008;26:3681–6.

[36] Fakih MG. Carcinoembryonic antigen monitoring in metastatic colorectal cancer: Words of caution. J Clin Oncol 2008;26:e7.