Radiation-induced oesophagitis in lung cancer patients. Is susceptibility for neutropenia a risk factor?

Strahlenther Onkol 2012 · 188:564–567
DOI 10.1007/s00066-012-0098-z
Received: 20 October 2011
Accepted: 21 February 2012
Published online: 29 April 2012

D. De Ruysscher[1] · J. Van Meerbeeck[2] · K. Vandecasteele[4] · C. Oberije[1] · M. Pijls[1] · A.M.C. Dingemans[3] · B. Reymen[1] · A. van Baardwijk[1] · R. Wanders[1] · G. Lammering[1] · P. Lambin[1] · W. De Neve[4]

[1] Department of Radiation Oncology (MAASTRO clinic), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center Maastricht (MUMC +), Maastricht
[2] Department of Respiratory Medicine, Ghent University Hospital, Gent
[3] Department of Pulmonology, Maastricht University Medical Center, GROW – School for Oncology and Developmental Biology, Maastricht
[4] Department of Radiation Oncology, Ghent University Hospital, Gent

Radiation-induced oesophagitis in lung cancer patients

Is susceptibility for neutropenia a risk factor?

Acute mucositis is one of the main severe toxicities that occur during and early after concurrent chemotherapy and radiotherapy [1, 2, 3, 4, 5, 6, 7]. On average, between 20% and 30% of patients will suffer from grade 3–4 acute oesophagitis, which requires tube or intravenous (i.v.) feeding. At present, no effective treatments other than symptomatic are of proven value [8, 9, 10].

Prognostic factors that are associated with acute radiation-induced oesophagitis include the overall treatment time of radiotherapy, twice-daily fractionation, mean and maximal oesophageal dose, the volume of the oesophagus that receives a certain dose such as the V55, and by far the most important the concurrent administration of chemotherapy with radiotherapy [11, 12, 13, 14, 15].

In an earlier study, we found that not the dose of chemotherapy was correlated with radiation-induced oesophagitis in concurrent schedules, but the level of neutropenia [16]. Patients with grade 4 neutropenia had an odds ratio of about 20 to develop grade 3 oesophagitis. The grade of neutropenia was an independent prognostic factor together with the mean oesophageal dose for the development of acute oesophagitis. We hypothesized that the level of neutropenia was a surrogate for the biological dose of chemotherapy. However, it could not be ruled out that the genotype/phenotype that is related to susceptibility for chemotherapy-induced neutropenia would also be associated with a higher radiosensitivity of the oesophagus.

We therefore investigated the association between neutropenia during induction chemotherapy and the development of acute radiation-induced during or after subsequent radiotherapy. For comparison, patients treated with concurrent chemoradiotherapy were also studied.

Patients and methods

Patients and treatment

Between February 1, 2006 and September 30, 2008, 119 patients were prospectively included in the two institutions the Maastro Clinic in Maastricht, The Netherlands, and the University Hospital Ghent, Belgium.

The concurrent group comprised

- 34 patients with stage I–III small cell lung cancer from the Maastro Clinic treated with concurrent carboplatin and etoposide and concurrent chest irradiation to a dose of 45 Gy in 30 twice-daily fractions in 3 weeks as previously described [17], and
- 36 patients with stage III non-small lung cancer (NSCLC) treated in Ghent with concurrent cisplatin and etoposide (75 mg/m^2 day 1 and 100 mg/m^2 i.v. on days 1–3, respectively, every 3 weeks for three cycles) and radiotherapy to a dose of 66 Gy in once-daily fractions of 2 Gy, 5 days per week.

The sequential group comprised

- 49 patients with stage III NSCLC treated in Ghent with sequential cisplatin and gemcitabine (75 mg/m^2 day 1 and 1,000 mg/m^2 i.v. on days 1 and 8, respectively, every 3 weeks for three cycles) and radiotherapy to a dose of 66 Gy in once-daily fractions of 2 Gy, 5 days per week.

Radiotherapy dose specification was done according to ICRU 50 recommendations [18].

Patients were seen by the pulmonologist and by the radiation oncologist be-

Tab. 1 Frequency table for Neutropenia and Oesophagitis Grade 3

	Oesophagitis Grade 3	
Neutrophenia	**Present**	**Not present**
High grade	a	b
Low grade	c	d

Tab. 2 Sequential chemotherapy and radiotherapy group: neutropenia before radiotherapy during induction chemotherapy vs. maximal oesophagitis during or after radiotherapy

Neutropenia	Oesophageal toxicity grade 1–3	
	Number	**Percent**
Grade 0	2/4	50
Grade 1	2/3	66
Grade 2	7/11	64
Grade 3	10/16	63
Grade 4	8/15	53

None of the differences are significant.

fore treatment and by one of them weekly during therapy, the first few weeks after the end of treatment until the acute side-effects resolved to grade 1, and thereafter every 3 months the first 2 years, every 6 months from years 3–5 and every year after 5 years. Before and weekly during chemotherapy or radiotherapy, white blood cells and the percentage of neutrophilic granulocytes were measured as specified by the standard protocol during the inclusion period.

Oesophageal toxicity was scored by the treating physician using the CTCAE3.0 (Common Terminology Criteria for Adverse Events, Version 3.0) criteria.

Results are expressed as mean ± standard deviation (SD) and their range. Differences between continuous variables were calculated with Wilcoxon's signed rank test and between proportions by a χ^2 test. An ordinal regression analysis was used to correlate the grade of neutropenia with oesophagitis grade 3 (G3). The odds ratio of oesophageal G3 toxicity versus neutropenia was calculated as (a/b)/(c/d) where a, b, c and d are the numbers of patients according to the frequency table (**Tab. 1**).

Results

A total of 119 patients were included; 63% were male. In the sequential group (n=49), the mean age was 67.1±8.0 years (range 49–83), the mean radiation dose 64.0±10.1 Gy (range 30–70), the mean overall treatment time (OTT) of radiotherapy 43.8±13.6 days (range 16–57), and the mean of the mean esophageal dose (MED) 21.5±11.4 Gy (range 2.7–43.7). In the concurrent group (n=70), the mean age was 60.4±8.7 years (range 42–81), the mean radiation dose 52.1±9.0 Gy (range 45–70), the mean OTT of radiotherapy 32.8±11.3 days (range 45–70) and the mean MED 25.5±7.3 Gy (range 6.0–45.4). The OTT was shorter in the twice a day vs. the once a day concurrent group (23.6±6.1 days (range 18–45 days) vs. 41.6±7.3 days (range 23–51 days); p<0.001). Only the mean MED was not significantly different between the concurrent and the sequential groups (p=0.15), whereas all other differences were significant at a p level<0.001.

The oesophageal toxicities in the concurrent group were grade 0 (G0): 4 (5.7%), G1: 17 (24.3%), G2: 32 (45.7%), G3: 17 (24.3%) and in the sequential group G0: 17 (34.6%), G1: 30 (61.2%), G2: 1 (2.1%), G3: 1 (2.1%). These differences are significant (p<0.001).

Neutropenia in the concurrent group during chemoradiotherapy was very frequent: G0: 1 (1.4%), G1: 8 (11.4%), G2: 13 (18.6%), G3: 19 (27.1%), G4: 29 (41.4%). Neutropenia in the patients receiving sequential chemoradiotherapy was during induction chemotherapy: G0: 4 (8.2%), G1: 3 (6.1%), G2: 11 (22.4%), G3: 16 (32.7%), G4: 15 (30.6%). Patients receiving concurrent chemotherapy and radiotherapy did not have significantly more severe (grade 3+4) neutropenia during their induction phase than those during sequential chemotherapy and radiation (68.5% vs. 63.2%, p=0.54).

During radiotherapy, however, neutropenia was hardly observed in patients who received sequential chemoradiation, with only 2 individuals (4%) with only grade 1 neutropenia. In this patient group, the mean day to develop maximal neutropenia was −52±25.4 (range −163 to −8) days before the beginning of radiotherapy (the first day of radiotherapy being defined as day 1). Maximal oesophagitis developed after a mean of 23.8±11.8 (range 5–48) days after the start of radiotherapy.

In the concurrent group, the odds ratios (OR) of grade 3 oesophagitis vs. neutropenia were as follows: G2 vs. G0/1: 5.60 (95% confidence interval (CI) 1.55–20.26), p=0.009; G3 vs. G0/1: 10.40 (95% CI 3.19–33.95); p=0.0001; G4 vs. G0/1: 12.60 (95% CI 4.36–36.43); p<0.00001 (**Fig. 1**).

There was no correlation between the occurrence of neutropenia during induction chemotherapy and acute oesophagitis during or after radiotherapy alone (**Tab. 2**).

In a univariate analysis, total radiation dose (p<0.001), overall treatment time of radiotherapy (p<0.001), mean oesophageal dose (p=0.038) and neutropenia (p<0.001) were significantly associated with the development of oesophagitis. In a multivariate analysis, only neutropenia remained significant (p=0.023).

Discussion

In this series, we confirm that neutropenia is a very important parameter that is associated with the development of severe oesophagitis during or after concurrent chemoradiotherapy [16]. Patients who received sequential chemotherapy and radiotherapy had the same incidence of severe neutropenia during their induction phase as individuals who were treated with concurrent chemoradiation. However, they did not develop severe oesophagitis when irradiated later. It may be argued that the incidence of oesophagitis was very low in the patient group that received sequential chemotherapy and radiotherapy. However, their total radiation dose, overall treatment time and MED was in the expected range. The MED, which was according to literature and also in our se-

Strahlenther Onkol 2012 · 188:564–567 DOI 10.1007/s00066-012-0098-z

D. De Ruysscher · J. Van Meerbeeck · K. Vandecasteele · C. Oberije · M. Pijls · A.M.C. Dingemans · B. Reymen · A. van Baardwijk · R. Wanders · G. Lammering · P. Lambin · W. De Neve

Radiation-induced oesophagitis in lung cancer patients. Is susceptibility for neutropenia a risk factor?

Abstract

Background. Radiation-induced oesophagitis is a major side effect of concurrent chemotherapy and radiotherapy. A strong association between neutropenia and oesophagitis was previously shown, but external validation and further elucidation of the possible mechanisms are lacking.

Methods and patients. A total of 119 patients were included at two institutions. The concurrent group comprised 34 SCLC patients treated with concurrent carboplatin and etoposide, and concurrent chest irradiation, and 36 NSCLC patients with concurrent cisplatin and etoposide, and concurrent radiotherapy, while the sequential group comprised 49 NSCLC patients received sequential cisplatin and gemcitabine, and radiotherapy.

Results. Severe neutropenia was very frequent during concurrent chemoradiation (grade: 4 41.4%) and during induction chemotherapy in sequentially treated patients (grade 4: 30.6%), but not during radiotherapy (only 4% grade 1). In the concurrent group, the odds ratios of grade 3 oesophagitis vs. neutropenia were the following: grade 2 vs. grade 0/1: 5.60 (95% CI 1.55–20.26), p=0.009; grade 3 vs. grade 0/1: 10.40 (95% CI 3.19–33.95); p=0.0001; grade 4 vs. grade 0/1: 12.60 (95% CI 4.36–36.43); p<0.00001. There was no correlation between the occurrence of neutropenia during induction chemotherapy and acute oesophagitis during or after radiotherapy alone. In the univariate analysis, total radiation dose (p<0.001), overall treatment time of radiotherapy (p<0.001), mean oesophageal dose (p=0.038) and neutropenia (p<0.001) were significantly associated with the development of oesophagitis. In a multivariate analysis, only neutropenia remained significant (p=0.023).

Conclusion. We confirm that neutropenia is independently correlated with oesophagitis in concurrent chemoradiation, but that the susceptibility for chemotherapy-induced neutropenia is not associated with radiation-induced oesophagitis. Further studies focusing on the underlying mechanisms are thus warranted.

Keywords

Oesophagitis · Dysphagia · Radiotherapy · Lung cancer · Toxicity

Bestrahlungsinduzierte Ösophagitis bei Lungenkrebspatienten. Ist Anfälligkeit für Neutropenie ein Risikofaktor?

Zusammenfassung

Hintergrund. Eine durch Bestrahlung induzierte Ösophagitis ist eine Hauptnebenwirkung bei gleichzeitig durchgeführter Chemo- und Strahlentherapie. Ein enger Zusammenhang von Neutropenie und Ösophagitis wurde bereits früher nachgewiesen, eine externe Bestätigung und eine weiterführende Ergründung der zugrundeliegenden Mechanismen fehlen aber noch.

Methoden und Patienten. 119 Patienten aus zwei Einrichtungen wurden in diese Studie aufgenommen. Die Gruppe mit simultaner Strahlen- und Chemotherapie bestand aus 34 SCLC-Patienten, die gleichzeitig mit Carboplantin, Etoposid und einer Brustbestrahlung behandelt wurden sowie aus 36 NSCLC-Patienten, die gleichzeitig Cisplatin und Etoposid und eine Strahlentherapie erhielten. In der anderen Gruppe folgten die Behandlungsschritte nacheinander. Hier bekamen 49 NSCLC-Patienten Cisplatin und Gemcitabin in Folge plus eine Strahlentherapie.

Ergebnisse. Eine schwere Neutropenie trat sehr häufig während gleichzeitiger Chemobestrahlung (Grad: 4 41,4%) und während der Induktions-Chemotherapie bei aufeinanderfolgend behandelten Patienten (Grad 4: 30,6%) auf, nicht aber während der Strahlentherapie (nur 4% Grad 1). In der gleichzeitig behandelten Gruppe waren die Odds Ratios von Stufe 3 Ösophagitis vs. Neutropenie folgendermaßen: Grad 2 vs. Grad 0/1: 5,60 (95%-KI 1,55–20,26), p=0,009; Grad 3 vs. Grad 0/1: 10,40 (95%-KI 3,19–33,95), p=0,0001; Grad 4 vs. Grad 0/1: 12,60 (95%-KI 4,36–36,43), p<0,00001. Es gab keine Korrelation zwischen dem Auftreten von Neutropenie während der Induktions-Chemotherapie und akuter Ösophagitis während oder nach alleiniger Strahlentherapie. In einer univariablen Analyse waren die totale Bestrahlungsdosis (p<0,001), die gesamte Behandlungsdauer der Strahlentherapie (p<0,001), die durchschnittliche ösophageale Dosis (p=0,038) und die Neutropenie (p<0,001) erheblich mit der Entwicklung einer Ösophagitis verknüpft. In einer multivariablen Analyse blieb nur die Neutropenie signifikant (p=0,023).

Schlussfolgerung. Wir bestätigen, dass bei gleichzeitiger Chemobestrahlung, Neutropenie mit Ösophagitis unabhängig korreliert ist, aber die Anfälligkeit für eine durch Chemotherapie induzierte Neutropenie nicht mit einer durch Bestrahlung induzierten Ösophagitis verknüpft ist. Weiterführende Studien, die sich auf die zugrundeliegenden Mechanismen konzentrieren, sind lohnend.

Schlüsselwörter

Ösophagitis · Dysphagie · Strahlentherapie · Lungenkrebs · Toxizität

ries highly associated with oesophagitis, was not significantly different between the sequential and concurrent groups [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15]. The incidence and severity of oesophagitis and of neutropenia in the chemoradiation group are also in line with published data [2, 3, 4, 15, 19].

The finding that neutropenia induced by chemotherapy before radiotherapy was not associated with oesophagitis during radiotherapy implies that the correlation between neutropenia and acute oesophagitis during concurrent chemoradiation may be either due to a higher effective *bio-*

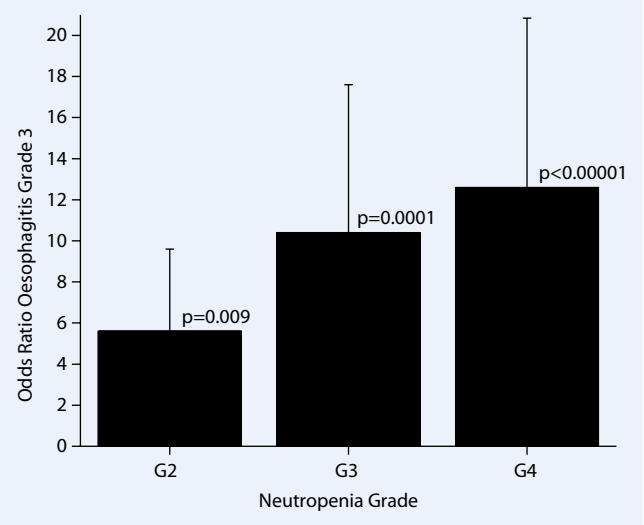

Fig. 1 ◀ Concurrent group. Odds ratios for developing oesophagitis grade 3 (*G3*) as a function of the grade of neutropenia

logical chemotherapy dose which causes more cell kill and hence more toxicity and/or to a higher susceptibility for local infections (e.g. candidiasis) of the oesophagus. If it would be known which microorganisms are surinfecting radiation-induced oesophageal lesions, only the 60% of patients with grade 3 or more neutropenia could receive prophylactic antibiotics and/or anti-mycotic drugs that could decrease symptoms, tube feeding and hospital admissions. An early non-randomised study suggests that the prophylactic use of amphotericin B may indeed be beneficial [10]. However, it remains to be investigated whether this treatment could indeed reduce the incidence of severe oesophagitis, i.e. grade 3–4. This would allow increasing the quality of life of patients [20] and decreasing in-patient care and costs. Clearly, further prospective studies are needed.

Corresponding address

D. De Ruysscher
Department of Radiation Oncology (MAASTRO clinic), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center Maastricht (MUMC +)
Maastricht
The Netherlands
dirk.deruysscher@maastro.nl

Conflict of interest. The corresponding author states that there are no conflicts of interest.

References

1. De Ruysscher D, Faivre-Finn C, Nestle U et al (2010) European Organisation for Research and Treatment of Cancer recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer. J Clin Oncol 28:5301–5310
2. Semrau S, Bier A, Thierbach U et al (2007) 6-year experience of concurrent radiochemotherapy with vinorelbine plus a platinum compound in multimorbid or aged patients with inoperable non-small cell lung cancer. Strahlenther Onkol 183:30–35
3. Gagel B, Piroth M, Pinkawa M et al (2006) Gemcitabine concurrent with thoracic radiotherapy after induction chemotherapy with gemcitabine/vinorelbine in locally advanced non-small cell lung cancer: a phase I study. Strahlenther Onkol 182:263–269
4. Catalano G, Jereczek-Fossa BA, De Pas T et al (2005) Three-times-daily radiotherapy with induction chemotherapy in locally advanced non-small cell lung cancer. Feasibility and toxicity study. Strahlenther Onkol 181:363–371
5. Mizumoto M, Sugahara S, Nakayama H et al (2010) Clinical results of proton-beam therapy for locoregionally advanced esophageal cancer. Strahlenther Onkol 186:482–488
6. Wolff HA, Bosch J, Jung K et al (2010) High-grade acute organ toxicity as positive prognostic factor in primary radio(chemo)therapy for locally advanced, inoperable head and neck cancer. Strahlenther Onkol 186:262–268
7. Semrau R, Temming S, Preuss SF et al (2011) Definitive radiochemotherapy of advanced head and neck cancer with carboplatin and paclitaxel: a phase II study. Strahlenther Onkol 187:645–650
8. Zimmermann FB, Geinitz H, Feldmann HJ (1998) Therapy and prophylaxis of acute and late radiation-induced sequelae of the esophagus. Strahlenther Onkol 174(Suppl 3):78–81
9. Belka C (1998) Oral sucralfate administration for therapy and prevention of radiation-induced esophagitis: results of a placebo-controlled double-blind study. Strahlenther Onkol 174:333–334
10. Wurstbauer K, Merz F, Sedlmayer F (2009) Amphotericin B lozengers: prophylaxis for esophagitis in thoracic radiotherapy: a prospective study. Strahlenther Onkol 185:512–516
11. Ahn SJ, Kahn D, Zhou S et al (2005) Dosimetric and clinical predictors for radiation-induced esophageal injury. Int J Radiat Oncol Biol Phys 61:335–347
12. Rose J, Rodrigues G, Yaremko B et al (2009) Systematic review of dose–volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother Oncol 91:282–287
13. Werner-Wasik M, Yorke E, Deasy J et al (2010) Radiation dose–volume effects in the esophagus. Int J Radiat Oncol Biol Phys 76:86–93
14. Chapet O, Kong FM, Lee JS et al (2005) Normal tissue complication probability modeling for acute esophagitis in patients treated with conformal radiation therapy for non-small cell lung cancer. Radiother Oncol 77:176–181
15. Dehing-Oberije C, De Ruysscher D, Petit S et al (2010) Development, external validation and clinical usefulness of a practical prediction model for radiation-induced dysphagia in lung cancer patients. Radiother Oncol 97:455–461
16. De Ruysscher D, Dehing C, Bremer RH et al (2007) Maximal neutropenia during chemotherapy and radiotherapy is significantly associated with the development of acute radiation-induced dysphagia in lung cancer patients. Ann Oncol 18:909–916
17. Loon J van, De Ruysscher D, Wanders R et al (2010) Selective nodal irradiation on basis of (18)FDG-PET scans in limited-disease small-cell lung cancer: a prospective study. Int J Radiat Oncol Biol Phys 77:329–336
18. ICRU (1993) International Commission on Radiation Units and Measurements Report 50: Prescribing, recording, and reporting photon beam therapy
19. Wurstbauer K, Weise H, Deutschmann H et al (2010) Non-small cell lung cancer in stages I-IIIB: Long-term results of definitive radiotherapy with doses ≥80 Gy in standard fractionation. Strahlenther Onkol 186:551–557
20. Pijls-Johannesma M, Houben R, Boersma L et al (2009) High-dose radiotherapy or concurrent chemo-radiation in lung cancer patients only induces a temporary, reversible decline in QoL. Radiother Oncol 91:443–448