Analysis of tumor texture on a pre-treatment CT scan predicts treatment outcome in NSCLC patients

Citation for published version (APA):

DOI:
10.1016/S1359-6349(09)71771-9

Document status and date:
Published: 01/01/2009

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher’s website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.tue.nl/taverne

Take down policy
If you believe that this document breaches copyright please contact us at:
openaccess@tue.nl
providing details and we will investigate your claim.

Download date: 28. Feb. 2020
the only metastatic site in 32 (33.5%) pts or were associated with another site in 36 pts (37.5%) and with at least two other sites in 28 (29%) pts. The Karnofsky Performance Status was > 70% in 77 pts (88%). Radical surgery was performed in 9 pts while 4 pts received a stereotactic radiation therapy. 58 (59%) pts received CT after development of BM: 60% of pts just received one line, 26% had two lines, 14% 3 lines or more. 37 pts had synchronous BM, 54% received CT before RT and 57% after, the median time to the beginning WBRT was 3.6 m. The median overall survival after the diagnosis of the primary tumor, the WBRT begins after a median time of 1.15 m. The median overall survival after the diagnosis of BM was 5.7 m [0.4−44.5]. The median overall survival from time of BM diagnosis for all pts was 6.7 m [0.2−69.6]. Median overall survival since the first diagnosis of metastases (watherver the site) was 11.6 m [0.6−69.6].

Conclusion: Our results suggest that in NSCLC pts with synchronous BM, CT may be beneficial and that the sequence with WBRT should be better define.

9056 POSTER
Evaluating the efficacy of zoledronic acid for the prevention of disease progression in patients with non-small cell lung cancer (NSCLC)


Background: Bisphosphonates are effective inhibitors of bone resorption, and outcomes from preclinical and clinical studies have suggested that they have antitumor activity. Preclinical studies of zoledronic acid (ZOL) have demonstrated its ability to induce tumor cell apoptosis, inhibit angiogenesis, inhibit tumor cell adhesion and invasion, decrease tumor cell proliferation, and activate an immune response. Clinical studies in patients with early stage breast cancer suggest that ZOL improves disease-free survival and recurrence-free survival and may improve bone-metastases-free survival. These findings provide the rationale to investigate whether ZOL can prevent disease progression in patients with early stage NSCLC.

Material and Methods: Study 2419 (NCT00172042) is an ongoing, randomized, phase III trial sponsored by Novartis, in patients with stage IIA/B NSCLC who have completed primary treatment (surgery or radiation therapy and chemotherapy) and did not experience disease progression after primary treatment. Patients were randomized within 8 months of diagnosis to treatment with or without ZOL (4 mg q3−4 weeks) for up to 24 months. The primary endpoint of this study is progression-free survival (PFS), which includes disease progression, disease recurrence, and death.

Results: As of January 2009, 407 patients with NSCLC have enrolled and the overall incidence of bone metastases, disease progression, disease recurrence, and death has been evaluated (Table 1).

Table 1: Disease events in patients with NSCLC after primary therapy

<table>
<thead>
<tr>
<th>Bone metastases, n (%)</th>
<th>Ongoing treatment, n = 161</th>
<th>Discontinued treatment, n = 168</th>
<th>Total patients, n = 407</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>110 (58)</td>
<td>115 (69)</td>
<td>225 (55)</td>
</tr>
<tr>
<td>Progression/Recurrence, n (%)</td>
<td>118 (64)</td>
<td>156 (92)</td>
<td>274 (67)</td>
</tr>
</tbody>
</table>

Currently the median follow-up of patients in this study is 12.9 months (range, 0.03−36.2 months). Updated preliminary safety and efficacy results from this trial will be presented.

Conclusions: Study 2419 is an ongoing trial to evaluate the activity of ZOL in delaying disease progression in patients with NSCLC. The available event profile demonstrates the feasibility of this trial, and updated results will be presented. Results from this trial will complement the growing body of evidence of ZOL for preventing disease recurrence in the early breast cancer setting.

9057 POSTER
New dendritic cell immunotherapy approach: randomized phase II study in IIB-IIIA stage non-small cell lung cancer patients

V. Sovonko1, N. Khranovsky2, V. Ganul3, Y. Shvets3, A. Ganul3, V. Silter3, O. Skachkova2, S. Zemchor2, Y. Grinevich4, 1National Cancer Institute, Thoracic Oncology, Kyiv, Ukraine; 2National Cancer Institute, Experimental Oncology, Kyiv, Ukraine; 3National Cancer Institute, Clinical Immunology, Kyiv, Ukraine

Background: Ex vivo-generated dendritic cells (DC) loaded with tumor vaccines have been used as vaccines to improve antitumor immunity in patients with different types of cancer since 1996. Currently, extensive studies to improve the immunotherapy approach based on DC-vaccine have been performed. Great emphasis is paid to finding new more efficient ways to load DC with tumor antigens. Our preclinical findings indicate that the technically heterogenized tumor cells (MHTC) used for DC loading is a very effective and promising approach. We report a phase II trial in non-small cell lung cancer (NSCLC) patients treated with DC pulsed with MHTC, following successful phase I results.

Material and Methods: Seventy-one patients with IIB-IIIA stage NSCLC, ECOG 0−1, without autoimmune disorders were enrolled. 28 patients had received DC-therapy in adjuvant regimen (4−9x10⁶ per injection), 43 patients underwent surgery (lobectomy, pneumonectomy) only. In the trial were used autologous DC of monocytic origin with expression of surface markers CD86 and HLA-DR at least 70%, CD83 – 50% obtained by flow cytometry. Adjuvant therapy with DCs loaded with MHTC was carried out in post-operative period for prevention metastasis development and recurrence of disease. DCs were injected i.v. in 1−2 courses. One course consisted of 5 injections with one-month interval. Groups of comparison were similar by histology forms, stage, age. Clinical and immunological monitoring of DC-vaccine therapy was performed. Special attention was focused on antigen specific antitumor immune response.

Results: DC-immunotherapy was well tolerated without significant toxicity. DC-therapy has improved of 3-year survival of patients. Overall survival of NSCLC patients for 3 year in the group with vaccine therapy was 66% vs 30%. During 3 year follow-up period in a group with DC-vaccine treatment disease progression occurred in 9 patients (32.1%), in a group with surgical treatment alone – in 26 patients (60.5%), 95% of patients showed significant antigen specific immune response after 3–5 DC-vaccinations. In responding to DC-vaccination patients, immunotherapy significantly boosted the IFN-γ and IL-2 producing T-cell response to autologous tumor challenge. Moreover, the increased functionality of T-cells, indicated by increased expression of markers for CTL activation, differentiation and proliferation was revealed.

Conclusions: There was clear evidence of clinical benefit of immunother-apy by DC pulsed with MHTC for NSCLC patients. This approach warrants further study.

9058 POSTER
Analysis of tumor texture on a pre-treatment CT scan predicts treatment outcome in NSCLC patients

E. Rios Velazquez1, J.H. Aerts1, C. Dehing-Oberije1, S. Petit1, H. Eikelder1, D. De-Ruysscher1, A.N. Rie2, P. Lambin1. 1MAASTRO, Radiation Oncology, Maastricht, The Netherlands; 2Eindhoven University of Technology, Biomedical Engineering, Eindhoven, The Netherlands

Background: Early identification of patients at risk of treatment failure is an essential step to improve current treatments. We hypothesized that texture and shape attributes of the tumor on a pre-treatment CT scan correlate with patient outcome. We therefore developed a semi-automated recognition system for prediction of 2-years survival, after radiotherapy based on CT scans image traits.

Methods: 129 patients (38 women and 91 men) with inoperable NSCLC (stage I−III), treated with radical (chemo)-radiotherapy were included in this study. The primary gross tumor volume was delineated on a pre-treatment CT scan and was defined as the region of interest (ROI). A set of 30 image traits assessing gray level intensity and spatial distribution, size and shape of the tumor were extracted. The ROI was automatically divided into five equally sized groups. In a combinatorial feature selection procedure a support vector machine model was built and validated using a five-fold cross validation approach. The model performance was expressed as the mean AUC assessed by the 5-fold cross validation. The combination of variables with the highest classification accuracy was included in the final model. Patient outcome was defined as 2-years survival calculated from the start of treatment.

Results: From the 30 extracted image features, 5 were included in the final predictive model: contrast, mean gray value, kurtosis, long run emphasis and compactness. These features encode textural and shape information
of the tumor region on the pre-treatment CT scan. The AUC of the ROC curve of the final model on the validation set was 0.77 (95% CI, 0.69−0.85).

Results: Our results indicate that meaningful and reliable image traits extracted from the pre-treatment CT scan can predict patient outcome after treatment. The prediction of two year survival with our approach may be an important tool for the analyst in oncology to extract informative CT image traits that can assist them in the decision of treatment choice, allowing them with the possibility of treatment individualization.

9059 POSTER
8473T>C COX-2 polymorphism and susceptibility for lung cancer: a strategy for individualised chemoprevention
A. Pereira1, P. Machado1, A. Araújo2, A. Coelho1, A.L. Teixeira1, R. Medeiros1,1, I.P.O., Medical Oncology Department, Porto, Portugal; 2I.P.O., Molecular Oncology Group, Porto, Portugal

Background: Lung cancer (LC) presents a major health problem in the world, being the most common cause of death from cancer in 2002. Cyclooxygenase-2 (COX-2), normally undetected in physiological conditions, is promptly triggered under inflammatory and tumor promotion conditions, contributing to key steps of carcinogenesis. Up-regulation of COX-2 is believed to be an early event in lung carcinogenesis. It is known to be induced by cigarette smoke condensate in vitro and by the tobacco-specific carcinogen nitrosamine 4-(methylthiynosamin)-1-(3-pyridyl)-1-butanone (NNK) in mice. Furthermore, several epidemiological studies point to a lung cancer chemopreventive effect of non-steroidal anti-inflammatory drugs (NSAIDs), known to suppress COXs enzymes. The 8473T>C COX-2 polymorphism in an AU-rich elements region (3'UTR) might contribute to cancer development by influencing COX-2 mRNA stability. The aim of our study was to assess the influence of this polymorphism in the development of LC.

Material and Methods: This case-control study gathered 1069 individuals: 718 healthy individuals and 351 patients with histopathologically confirmed lung cancer, from the Northern region of Portugal. The 8473T>C COX-2 polymorphism genotypes were determined by Real-Time PCR allelic discrimination technique.

Results: We found no statistically significant differences in the distribution of the 8473T>C polymorphism genotypes between LC cases and controls (P=0.122). However, in a stratified analysis by histological type and gender we observed an increased risk for epidermoid non-small cell lung cancer (OR = 1.47; 95% CI:1.00−2.15) and more interesting, males C allele carriers revealed had an higher susceptibility for epidermoid non-small cell lung cancer (OR = 1.55; 95% CI:1.03−2.33).

Conclusion: The 8473T>C COX-2 polymorphism appears to modulate the genetic susceptibility for epidermoid non-small cell lung cancer, especially in males. This genetic profiling based higher-risk group definition may help shift the balance between use of COX-2 inhibitors chemoprevention that is currently hampered by the adverse gastrointestinal and cardiovascular side effects.

9060 POSTER
Cyclin D1 and Non-Small Cell Lung Cancer: a role of CCND1 gene variants in lung carcinogenesis
R. Catarino1, A. Coelho1, A. Araújo2, A. Nogueira1, R. Medeiros1,1, I.P.O., Medical Oncology Department, Porto, Portugal; 2I.P.O., Institute of Oncology, Medical Oncology, Porto, Portugal

Background: In most industrialised countries, lung cancer is the main cause of cancer death and has a poor prognosis. Non-small cell lung cancer (NSCLC) accounts for approximately 75% of cases. Experimental evidence suggests that lung cancer development and progression can be linked to an increased proliferation rate. Cyclin D1 (CCND1) has been described as having a pivotal role in the carcinogenesis of lung carcinoma. CCND1 is a key regulator of the G1/S phase of the cell cycle and its altered activity is associated with the development of several human cancers.

Patients and Methods: We analysed the A870G CCND1 polymorphism by PCR-RFLP in genomic DNA isolated from peripheral blood of 1535 cases and controls of 1238 healthy individuals. Statistical analysis was performed using the computer software SPSS for Windows (version 13.0). Chi-square analysis was used to compare categorical variables and a 5% level of significance was used in the analysis. The odds ratio (OR) and its 95% confidence interval (CI) were calculated as a measurement of the association between CCND1 genotypes and cancer risk. Logistic regression analysis was used to calculate the adjusted OR (aOR) and 95% CI for the influence of CCND1 genotypes in the risk of cancer.

Results: Our results demonstrate that patients carrying the GG CCND1 genotype present an increased risk for the development of NSCLC (OR = 1.57; 95% CI 1.17−2.10, P = 0.003). This genetic susceptibility was even more evident when considering the epidermoid histological type (OR = 1.84, 95% CI 1.30−4.07, P = 0.005). Multivariate logistic regression analysis adjusted by gender, age and tobacco smoke confirmed this association, indicating that individuals carrying two G-alleles present an increased risk of 2.7-fold for the development of lung cancer (aOR = 2.68; 95% CI 1.54−4.69, P = 0.001).

Conclusions: In conclusion, our results may be important in the definition of a biological predictive profile for the development of NSCLC within our population. Furthermore, the knowledge of the mechanisms involved in NSCLC carcinogenesis may help to identify targets for the development of chemoprevention or therapeutic strategies.

9061 POSTER
Impact of zoledronic acid on follow-up duration in lung cancer patients with bone metastasis in a US managed care plan
S. Kaura1, S. Thayer2, 1Novartis Pharmaceuticals Corporation, Health Economics Oncology, USA; 2i3 Innovus, Health Economics and Outcomes Research, San Francisco, USA

Background: For lung cancer patients with bone metastasis, skeletal complications including fractures are common and cause considerable morbidity, reduce quality of life, and reduce survival. This study was designed to assess the impact of zoledronic acid (ZOL), an intravenous bisphosphonate (iVBP), in patients with solid tumor cancers, including lung cancer.

Methods: A claims-based analysis using commercial and Medicare Advantage data from over 45 US managed care plans was used to evaluate the relation between treatment persistence and follow-up duration in patients treated with ZOL compared with those who were not (non-iVBP). A secondary analysis assessing the effect of time to treatment with ZOL will also be conducted. Persistence was defined as the absence of a >45 day gap between ZOL treatments. Index date was set at bone metastasis or first ZOL fill. Age 18+ with a lung cancer and a bone metastasis diagnosis between 01/01/01 and 12/31/06, continuous enrollment in the health plan for 6 months pre-index, with no evidence of bone metastasis or iVBP in the pre-index period was required. Patients were followed until disenrollment (including mortality) or end of study (12/31/07). ANOVA tests were used to compare follow-up duration, a proxy for survival, between ZOL persistence groups.

Results: The study sample included 10,513 lung cancer patients; 1,729 in the ZOL cohort and 8,784 in the non-iVBP cohort. Mean age was 62.4 years (±11.24) and 59.0% of patients were male. 78.5% of patients were commercial enrollees. Mean Charlson was 4.67(±2.95). Treatment persistence groups included in the analysis were 31−90 days (N = 475), 91−180 days (N = 239), 181−365 days (N = 133), >366 days (N = 44).

Persistent use of ZOL was associated with longer follow-up duration. There was a statistically significant difference (p<0.001) in the unadjusted mean follow-up duration for the non-iVBP cohort, 216 days (±304), compared with 236 (±233; 95% 90−90 days persistence group); 330 (±259; 91−180 days); 425 (±373; 181−365 days); and 729 days (±418; >366 days).

Conclusions: This study showed that in cancer patients with lung cancer and bone metastasis, patients with longer periods of persistence with ZOL achieved the better outcomes in terms of longer follow-up duration in the health plans.

9062 POSTER
The value of day 8 blood count in treatment decisions when using oral vinorelbine in non-small cell lung cancer (NSCLC) patients
A. Faria1, J.S. Myerson1, M. Puglisi2, N. Starling1, S. Ashley1, S. Popat1, M.E.R. O’Brien1, 1Royal Marsden Hospital, Medical Oncology, Sutton, United Kingdom; 2Royal Marsden Hospital, Medical Oncology, London, United Kingdom

Background: Chemotherapy regimens most used in our NSCLC patients are intravenous (IV) cisplatin/carboplatin and IV/oral vinorelbine on day 1, 215 ± 237; 181−365 days); and 729 days (±418; >366 days).

Results: We reviewed the clinical files of the last 100 NSCLC patients treated with vinorelbine and two courses were identified. Evidently, where d8 vinorelbine was omitted, delayed, or given with dose reduction, and reasons for these actions were recorded.