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Oral Leukoplakia Cancer Development Diagnosis

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Abstract

The fundamental understanding of carcinogenesis has increased thanks to our 10-year translational study using the oral premalignant lesion (OPL) model. Despite the fact that retinoids have demonstrated effectiveness in this paradigm, a significant portion of our OPL patients develop malignancy, particularly after treatment is stopped. We have created the first complete method for determining the cancer risk of OPL patients based on our 10-year OPL study. Cellular and molecular biomarkers, epidemiological parameters and medical/demographic factors are all included in this method for assessing cancer risk.

Seventy patients with advanced OPL were enrolled in a chemoprevention trial between 1988 and 1991 that involved an induction with high dose isotretinoin (1.5 mg/kg/day for three months), followed by nine months of maintenance treatment with either low dose isotretinoin (0.5 mg/kg/day) or -carotene (30 mg/d; total treatment time, one year). Using exploratory data analysis, logrank testing, Cox proportional hazard modelling, and recursive partitioning, we evaluated the connection between cancer risk variables and time to cancer development.

After treatment, upper aerodigestive tract malignancies appeared in 22 of our 70 patients (31.4%), with a median follow-up of 7 years. The annual incidence of cancer was 5.7%. OPL histology, cancer history, and three of the five biomarkers we evaluated are the most effective predictors of cancer risk (chromosomal polysomy, p53 protein expression, and loss of heterozygosity at chromosome 3p or 9p). The best predictors of the development of cancer in the multivariable Cox model are histology (P = 0.0003) and the combined biomarker score of chromosomal polysomy, p53, and loss of heterozygosity (P = 0.0008). Micronuclei and the retinoic acid receptor were not linked to an increased risk of developing cancer.

We have successfully illustrated a method for thoroughly evaluating cancer risk in OPL patients. A panel of three biomarkers and traditional medical/demographic factors can be combined to identify high risk patients in our sample. Future research will be required to confirm this finding. It is possible to develop more effective chemoprevention trials and molecular targeting studies with the identification of high risk patients.

Keywords: Carcinogenesis; Oral premalignant lesion; Isotretinoin; Logrank testing; Aero-digestive tract malignancies; Chromosomal polysomy

Introduction

Long thought to increase the chance of developing oral cancer, oral leukoplakia is a premalignant lesion. Despite the fact that the cause of oral leukoplakia is not entirely known, these lesions are frequently linked to carcinogenic exposures, such as those from using tobacco, alcohol, or, particularly in Southeast Asia, betel nuts (usually chewed) [1]. The lesion's histology is related to the likelihood that it may develop into a malignant leukoplakia. Depending on how long the follow-up period is the total malignant transformation rates for dysplastic lesions range from 11 to 36%. A recent study with an average follow-up of 11.6 years revealed that proliferative verrucous leukoplakia has a malignant transformation rate as high as 70.3%.

We began a chemoprevention trial of an induction phase of 3-month high dose isotretinoin (13-cis-retinoic acid) followed by a 9-month maintenance phase of low dose isotretinoin or- carotene in subjects with OPLs in 1988 on the basis of compelling data demonstrating retinoid activity in preventing cancers of the upper aero-digestive tract. 70 patients signed up for the trial [2]. It has been documented that the high dose initiation and low dose maintenance of isotretinoin in this trial were both effective. In this translational trial, we prospectively collected tissue samples for biomarker analysis to characterise the molecular/cellular biology of leukoplakia to examine correlations between biomarker expression and short-term response (p53, RAR-, and micronuclei), and to assess the utility of these biomarkers for long-term outcome prediction (RAR-; LOH at 3p, 9p, and chromosome polysomy).

The primary goal of the current report is to provide comprehensive cancer risk assessment tools for patients with oral leukoplakias, taking into account all collected variables, including medical-demographic variables, epidemiological factors, and cellular-molecular biomarkers. This is done with the help of accumulating data and follow-up of this pivotal chemoprevention trial [3]. Our objective is to develop risk models that will make it easier to assign suitable interventions based on the unique cancer risk or disease process of OPL patients. We also looked at whether the short-term intervention affected cancer prevention or cancer treatment. It is possible to create more effective, better focused chemoprevention studies with fewer participants and/or shorter length by selecting high risk leukoplakia patients [4]. We can design better mechanism-based prevention studies with more information of biomarkers and the impact of chemopreventive drugs on the oral carcinogenesis pathway.

The field urgently requires systematic statistical approaches to be able to analyse and integrate the explosion in technology and biomarker data as translational chemoprevention study advances and more

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and more marker information (for example, from chip technology) is gathered from smaller and smaller tissue specimens (biopsies and brushings) [5]. These methods are required for chemopreventive biomarker analyses, and they must be able to take into account the real-world problem of lacking or used-up tissue samples or unhelpful results (e.g., with LOH in the present study). Our study serves as an example of a methodical framework-model for analysing translational data and serves to highlight the statistical complexity of such data.

Individuals and Methods

A clinical study's design and eligibility requirements

Participants in the trial had to have advanced OPLs, which were classified as dysplastic lesions, widespread, symptomatic hyperplastic lesions, or hyperplastic lesions in high-risk oral sites like the ventral-lateral tongue or FOM. If they had been free of the disease for at least two years at the time of trial admission, patients with past cancer were eligible.

There were two phases of the investigation. In the first stage, patients who met the criteria and gave their consent received a high-dose isotretinoin induction regimen (1.5 mg/kg/day) for three months. When lesions progressed during the induction phase, patients were taken out of the research and given alternate therapies. Patients who had non-progressing or responsive lesions were randomised to undergo a 9-month maintenance therapy with low dose isotretinoin (0.5 mg/kg/day) or -carotene (30 mg/day) in the second phase of the trial. Our earlier publication included a more in-depth examination of patient eligibility and trial design [6].

Analysis of biomarkers

Five biomarkers were to be analysed as part of the study design: p53, RAR-, CP, LOH, and micronuclei. In our earlier studies, we gave thorough details of the laboratory processes used to conduct these biomarker analyses. In accordance with the protocol, biopsies from patients' primary index OPLs were collected during their planned clinic visits at baseline, three months, and one year [7]. All accessible and evaluable tissue samples were used for the biomarker tests in this investigation. Several factors had an impact on sample evaluation (e.g., dropout, loss to follow-up or patient refusal). Since only 20–30 sections of 4 m can be extracted from each biopsy tissue block, the necessity for histological analysis and unanticipated and planned biomarker analyses have worn out some tissue samples over time [8]. The most common cause of inevaluable samples was tangential specimen cutting, which left insufficient epithelial cells in the basal and/or parabasal layers for analysis. To our understanding, there was no logical reason why some data were missing. Most samples that are accessible are regarded as being suitable for biomarker analysis.

Analysis of the data

Time to cancer development is the main outcome of the research and analysis we discuss here. The likelihood of a cancer-free survival was calculated using the Kaplan-Meier estimate. The impact of single and multiple factors on predicting the development of cancer was examined using the logrank and Cox proportional hazards model. To assess the predictive impact of numerous biomarkers, a composite score of biomarkers was created. The illustration of the relationship between numerous factors and the construction of models were made easier by exploratory data analysis utilising event charts and scatter plot matrices [9]. To offer a different approach for categorising patients according to their likelihood of developing cancer, recursive partitioning using RPART with exponential scaling for survival data was used. Every reported P has two sides.

Results

Gain, monitoring and the development of cancer

At the University of Texas M. D. Anderson Cancer Center, 70 patients were included in the trial between January 1988 and March 1991. 59 of these patients were randomised to either low dose isotretinoin (n = 26) or -carotene (n = 33) maintenance since their lesions had improved or stabilised after the 3-month induction therapy [10]. Patients were voluntarily followed off-protocol after the study's completion in 1992. In August 1997 and September 1998, respectively, systematic telephone follow-up and chart reviews were carried out. This report covers all the activities as of December 31, 1998, including the most recent follow-up. A total of 22 patients (31.4%) had upper aerodigestive tract malignancies by December 1998. Seven years was the median follow-up (the range was 0.2-10.6 years), and 75% of patients had at least five years of follow-up [11]. With a mean of 4.0 years and a median of 3.1 years among patients who had new malignancies, the range of time to malignancy was 0.2 to 10.1 years. The annual incidence rate of upper aerodigestive tract cancer was 5.7%. The tongue-FOM, buccal mucosa, gingiva, palate, lip, larynx, and oesophagus were among the new cancer sites. With the exception of one tongue-related in situ squamous cell carcinoma, they were all invasive carcinomas. Anal squamous cell carcinoma, which was not the cancer end goal specified for our study, was discovered in one more patient.

Discussion

To better control oral cancer, it is essential to be able to identify oral leukoplakia patients who are at a higher risk of developing the disease. The highest risk patients could be identified and given more aggressive treatment options and thorough follow-up. During a 10-year follow-up in our study, 31.4% of leukoplakia patients got cancer. This outcome is in line with reports of OPLs developing cancer. The study's time to cancer onset ranged from 2.8 months to 10.1 years [12]. According to field carcinogenesis, 41% of newly discovered malignancies appeared in places unrelated to previous cancer or leukoplakia locations. Leukoplakia is a premalignant lesion, but it also serves as a warning sign for higher cancer risk throughout the upper aerodigestive tract.

We have discovered clinical and molecular-cellular factors after ten years of translational assessments that seem to place leukoplakia patients at higher risk of developing malignancy [13]. Despite the fact that smoking and drinking are risk factors for OPLs, they were not linked to a higher risk of cancer in our group. The presence of moderate-to-severe dysplastic OPLs and/or a history of past cancer in our patients seem to be associated with a higher chance of developing cancer, according to data that concur with widely accepted medical wisdom and numerous published papers. However, these pathological risk markers and cancer history are not very accurate cancer predictors. In order to produce a more accurate risk profile, we evaluated the prediction power of five cellular or molecular biomarkers that may supplement the medical history and pathological variables.

According to our OPL data, expressions of three of these five biomarkers-high CP, high p53 protein accumulation in the parabasal layer, and LOH at 3p or 9p-were linked to an increased chance of developing cancer. The total score of these three markers was more accurate in predicting the probability of developing cancer than the individual scores of any one of the markers [14]. Additionally, combining data from genotypic and phenotypic biomarkers can

increase the accuracy of cancer development predictions. Therefore, it appears that integrating integrated data from a panel of biomarkers along with histological analysis of the OPL can increase the accuracy of cancer risk assessment. Additionally independent predictors of cancer risk were the composite biomarker score and histology. The risk of cancer increased with the number of abnormalities in the histology or related biomarker expressions. The multivariable Cox regression analysis and the recursive partitioning method supported the same conclusions. These findings support the idea of multistep carcinogenesis and call for additional research to comprehend the underlying mechanism.

One of our patients was "statistically" diagnosed with cancer as a result of our biomarker model study (a 65-year-old male former smoker and current alcohol drinker). His hyperplastic histology (tongue OPL) and lack of a history of cancer indicated that he was typically low risk. Our risk model, however, showed a higher probability of developing cancer (CP of 24%, parabasal p53 labelling score of 0.71, and LOH at both 3p and 9p). The patient (still asymptomatic) agreed to visit the clinic for an unscheduled biopsy-pathological procedure in December 1998 at the time of the planned phone call (September 1998), which revealed an aggressive squamous cell carcinoma in the tongue [15]. This cancer diagnosis (9.7 years after trial enrolment) was the sole consequence of the information from our predictive model. Some patients with leukoplakia experience a protracted delay in the development of malignancy, opening a window for medical intervention, such as chemoprevention. We also assumed the patient was cancer free in September 1998 (the date of our systematic/scheduled phone contact/follow-up) and redone the analysis to minimise any potential bias caused by the patient's unplanned follow-up clinic visit.

Only tissue samples from the one-year therapy period were able to be collected in our investigation due to the clinical trial design. During the follow-up period, there were no prearranged follow-up appointments or scheduled biopsies. As a result, we were unable to trace the carcinogenesis pathway or examine longer-term biomarker changes. This restriction may contribute to the failure of RAR- and micronuclei expressions to predict cancer risk [16]. Our study did not give adequate follow-up data to confirm or deny either scenario, but it is possible that loss of RAR- or an increase in micronuclei preceded the development of cancer. Future designs for chemoprevention trials should incorporate planned follow-ups and biopsies both during and after the treatment period. In order to track patterns of biomarker changes over time, this will provide standard follow-up and assessments of all patients. To fully comprehend multistep carcinogenesis, long-term follow-up of chemoprevention study participants will be necessary.

The next step in cancer control, which involves developing more powerful and/or long-lasting chemopreventive therapies inside the carcinogenic pathway of those at higher cancer risk, requires improving our capacity to forecast the onset of cancer. The most exciting recent advances in chemoprevention, which entail molecular targeting approaches of agent development, align with our approach to molecular-cellular risk modelling. Chemoprevention research in general and OPL research in particular is moving forward quickly in terms of molecular targeting, as demonstrated, for instance, by research targeting p53.

A proven, transferable, and conclusive risk assessment approach is not attempted to be presented in this research. Instead, it tries to show how useful different statistical modelling techniques may be for learning more about how cancer develops while still working within the limitations of a study's design, patient population, missing data, etc. Despite these drawbacks, the data set (gathered by a skilled team of researchers from a prospective National Cancer Institute randomised trial) nevertheless serves as the most complete and developed translational data-with 10 years of data collection-that we are aware of [17]. The Cox model, together with the use of event charts, scatter plot matrices, and recursive partitioning, provides logical modelling procedures for the hazards connected to the development of cancer. The present findings on particularly predicting head and neck cancer must be confirmed by other studies because, as we are aware, this pretty detailed data set is still quite small. Despite these limitations, we think that the current methodological and analytical approach will significantly advance the creation of cancer predictors in the future, not just for the head and neck but for other locations as well. Our statistical modelling strategy can also assist in addressing the expanding translational chemoprevention issue of examining ever-increasing amounts of biomarkers and biomarker data obtained (through chip technology, for example) from incredibly small tissue specimens.

Conclusion

In light of the limitations of a translational chemoprevention study, this paper outlines a successful method of comprehensive cancer risk assessment in OPL patients. We showed that a panel of three biomarkers and medical-demographic factors can both be used to identify high risk patients. An on-going, extensive, long-term chemoprevention experiment sponsored by the National Cancer Institute is testing the validity of our biomarker risk modelling technique in patients with OPLs. The use of biomarkers will help identify high risk patients, including those with lower risk histology, by increasing the sensitivity of histology in predicting the development of cancer. Researchers and physicians can provide each person with the most effective, personalised cancer preventive measures using quantitative cancer risk assessments.

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