Acceleration of Telomere Loss by Chemotherapy Is Greater in Older Patients with Locally Advanced Head and Neck Cancer

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Abstract

Purpose: Chronic viral infection and combinations of chemotherapeutic drugs have been reported to accelerate telomere erosion. Here, we asked if chemoradiotherapy, using the single agent cisplatin, would accelerate telomere loss in head and neck cancer patients, and whether loss was linked to smoking status, age, gender, or stage of disease at diagnosis.

Experimental Design: Blood samples were collected from 20 patients with squamous cell cancer of the head and neck before, during, and after chemoradiotherapy. Following DNA isolation from peripheral blood mononuclear cells, telomere length was measured by terminal restriction fragment analysis.

Results: Chemoradiotherapy increased the rate of telomere erosion >100-fold. Telomere length before treatment in chemoradiotherapy patients was similar to age-matched controls. Although smokers began with significantly shorter telomeres, smoking status did not affect chemoradiotherapy-induced attrition, nor did gender or stage of disease. We also make the novel observation that a significantly greater telomere loss occurred in response to treatment in older patients, with those younger than 55 years losing an average of 400 bp of telomeric DNA compared with the 880 bp lost by those over 55 years.

Conclusions: The lack of telomere length difference before treatment suggests that shortened telomeres may not be a risk factor for development of head and neck cancer in the age range we examined. Chemoradiotherapy caused a severe telomere length reduction in all patients. The significant difference seen in the elderly (P = 0.018) suggests that chemoradiotherapy may have more severe effects on the replicative capacity of blood cells in older patients.

Eukaryotic chromosome ends consist of specialized structures called telomeres that are critical to chromosome integrity. In vertebrates, the DNA component of telomeres consists of the hexamer T2AG3 repeated thousands of times. Attrition of these repeats occurs as cells divide, primarily due to the end-replication problem and to the accumulation of oxidative damage within telomeric DNA (1, 2). The concept that telomeres represent cellular “clocks” for predicting proliferative potential and limiting proliferative life span (3) reinforces the importance of examining situations in which unusually rapid shortening might occur. Under normal circumstances, the rate of lymphocyte telomere loss in vivo varies between 15 and 55 bp per year in adults (4) with more rapid losses seen earlier in life. Various disease states and chronic stresses, such as Down’s syndrome and HIV infection, significantly accelerate the loss of telomeric DNA in lymphocytes. Viral infection can increase losses by >5-fold (5–8), resulting in premature senescence of the immune system (9) from which patients do not fully recover.

Randomized controlled clinical trials have shown that concurrent chemoradiotherapy confers a survival benefit over radiation alone in patients with locally advanced head and neck cancer (10). Although the optimal concurrent chemotherapy regimen and schedule remains controversial, the use of lower doses of cisplatin given more frequently seems tolerable and achieves overall survival and locoregional control rates comparable with other chemoradiotherapy combinations (11, 12). Chemotherapy results in cycles of injury and repair that may play a role in telomere shortening due to both effects in the single-stranded regions of telomeres and as a consequence of increased cell replication. Cisplatin, a very commonly used cytotoxic agent, has a broad range of antitumor activity and was found to show the largest enhancement in cell killing after irradiation (13). In addition, in active form, it is able to react with nucleophilic sites to form DNA adducts (14). The N7 position of guanine is the primary target for cisplatin, and the principal adducts formed occur at adjacent deoxyguaninines (GpG) and are 1,2-intrastrand cross-links. The adducts formed...
by platinum agents result in the very efficient inhibition of DNA replication, RNA transcription, cell cycle arrest, or apoptosis, even at levels 60-fold lower than saturation (14). Measurements of adduct profiles in patients that were treated with cisplatin have shown that tumor response and a favorable outcome is correlated to an increased level of 1,2-intrastrand cross-links (15, 16). Telomeric repeats found in vertebrates are an excellent target for cisplatin. As long as two or more tandem guanines are present, cisplatin targeting to DNA occurs at its highest level (17). The telomeric 6-bp repeat (TTAGGG) contains two potential GG sites for every 12 nucleotides (or 16.7% of all dinucleotide pairs in telomere repeats). That value is ~2.6-fold higher than would be predicted to occur at random. In contrast to cisplatin, little is known about the effect of radiation on telomere shortening.

Few studies have examined changes in telomere length throughout cycles of cytotoxic agents; however, significant changes in mean telomere length have been found as a result of a variety of combination chemotherapies and/or radiation (18–22). In patients with non-Hodgkin’s lymphoma, various combination chemotherapy regimens resulted in a telomere length reduction of ~500 bp in five patients that had blood draws pretreatment and posttreatment (19). In 37 patients with previously untreated advanced stage, aggressive non-Hodgkin’s lymphoma, the use of a high-dose sequential chemotherapeutic regimen followed by autologous stem cell transplantation resulted in a significant loss of telomere length in peripheral blood progenitor cells (18). No difference was observed in telomere length between peripheral blood progenitor cells collected before treatment and after the first high-dose cycle. However, the 1,000-bp loss of telomere length seen after the second high-dose regimen was maintained even 4 years after treatment was completed. The authors attribute the large reduction to increased proliferative stress of stem cells undergoing two consecutive treatments. In a separate study, combination chemotherapy was given to 24 pediatric patients with acute lymphoblastic leukemia and solid tumors (20, 22). In acute lymphoblastic leukemia patients, the rates of attrition in lymphocytes and granulocytes were 480 and 360 bp/y, respectively. The reported rate of loss in solid tumor patients was considerably higher (~1,200 bp/y), and no difference was seen between the rates of telomere loss in bone marrow mononuclear cells compared with peripheral blood mononuclear cells.

The studies above reported mean terminal restriction fragment (TRF) length after patient treatment with combination chemotherapy. These studies attribute possible exhaustion of replicative capacity to telomere loss resulting from the use of a combination chemotherapy. In our study, we examined telomere loss in patients with locally advanced squamous cell cancer of the head and neck or nasopharyngeal carcinoma receiving cisplatin and concurrent radiotherapy. We find that chemoradiotherapy induces a high but variable level of accelerated telomere loss that unexpectedly showed a novel and significant correlation to the age of the patients.

Materials and Methods

This project was approved by the Conjoint Health Research Ethics Board of the University of Calgary, Calgary, Alberta (Sept 2003) and conforms to the Tri-Council and International Conference on Harmonisation’s Guidelines and with the Helsinki Declaration. Twenty cancer patients were enrolled between September 2003 and December 2004. All patients signed informed consent. Eligible patients had locally advanced squamous cell cancer of the head and neck or nasopharyngeal carcinoma treated with concurrent chemoradiotherapy or radiotherapy alone. The radiation treatment consisted of 70 Gy in 35 daily fractions, delivered from Monday through Friday. Chemotherapy consisted of single agent cisplatin (20 mg/m²) given i.v. daily for 4 days during the 1st and 5th week of radiation. Patients who had previous chemotherapy or a prior diagnosis of cancer were excluded from the study. Blood samples were collected at three different time points: before initiation of treatment, at day 28 (before the second chemotherapy cycle), and at the completion of all chemotheraphy and radiation. Ninety age-matched noncancer control subjects were used to compare various external factors with subject telomere length (and with initial telomere length of cancer patients). These subjects were recruited from the Calgary, Alberta area through random digit dialing and agreed to provide one blood sample along with personal information collected through an in-person interview. To ensure accurate comparison with the cancer group, demographic characteristics of those 90 individuals, such as smoking status and pack-years, were used to further reduce control subject numbers before statistical analysis (pack-year cutoffs were >5 and >15).

Telomere length was analyzed as reported previously (4). In summary, peripheral blood mononuclear cells (PBMC) were isolated from whole-blood samples using a Ficoll-Hypaque gradient. Cells were lysed, and DNA was extracted using a phenol/chloroform extraction method. DNA was then stored at −20°C until digestion. Five micrograms of DNA were digested with restriction endonucleases (RsaI and HindIII) for which there are no recognition sites within the telomeric repeats. Aliquots of digested DNA were electrophoresed through a 1% loading gel for quantification for 100 V-h, then through a final 0.6% gel along side molecular weight markers, for 700 V-h. Gels were denatured, neutralized, and dried for 2 hours before hybridization in 5× SSC containing 4 × 10⁶ cpm of [³²P]-end-labeled telomere probe [(CCCTAA)n] at 37°C. Following 18 hours of incubation, gels were washed in 2× SSC at 48°C thrice, dried, and exposed to Kodak film for up to 1 week. Autoradiograms were photographed and analyzed using Image 1 freeware available from the NIH (http://rsb.info.nih.gov/ij). The weighed center of mass of each plot profile (excluding background signal) was generated for each sample and is shown graphically in Fig. 1. Numerical values generated from these histograms were compared with values of a known molecular weight standard, results of which reveal the mean TRF length. The TRF procedure (including the DNA isolation step from PBMCs) was repeated in triplicate for each sample to ensure reproducibility. In addition, to eliminate any additional interassay variability, all of the collection time points from each patient were run on the same gel (i.e., before, during, and after). Data analyses were done using the SPSS statistical software (version 12.0 for Windows), and patient demographics and clinical data were collected from the clinic chart. Relationships among telomere length, age, and gender were assessed by single and multiple linear regression analysis. Age was divided into two equal-sized groups to compare possible changes between young and old individuals. Repeated measures analysis and factorial ANOVA were used to examine differences between the time points and assess the between-subject and within-subject effects.

Results

The mean TRF lengths from PBMCs of 20 cancer patients before treatment were compared with the mean TRF data from 90 age-matched noncancer control subjects. Linear regression analysis of mean telomere length in each group to age, before treatment, showed that at patient age increased (before treatment) a reduction of 38 bp/y was seen in the cancer
patients and 26 bp/y in the noncancer subjects. No significant difference was seen between the means of each group before or after adjusting for age or gender (chemoradiotherapy and radiotherapy patients: 7.06 kb, n = 20; noncancer subjects: 7.01 kb, n = 90). In addition, after further selecting the noncancer subjects to match demographic characteristics close to the cancer group (pack-years >5 and >15), no significant differences were seen (mean, >5-6.99 kb, n = 36; mean, >15-6.91 kb, n = 18). These data show that in our group of head and neck cancer patients, telomere length before treatment is not significantly different from that found in the controls without cancer. One of the pretreatment factors did have an effect on the mean TRF of cancer patients: the number of pack-years that an individual had smoked (calculated by multiplying the number of packs per day by the number of years the individual has smoked). This had a negative influence on the starting mean TRF of each sample. DNA from each sample was digested on separate occasions and run individually on three separate gels.

The demographics and raw mean telomere length data from patients are shown in Table 1. An autoradiogram that represents telomere length distributions from a subset of the cancer patients is shown. All of the samples were analyzed using a fully blind protocol (with the exception that all three draws from each patient had to be loaded on the same gel, to eliminate additional inter-gel variability, but identities of sample donors were unknown). After mean TRF data were generated from all of the patients, repeated measures analyses were done. A highly significant difference was seen after chemoradiotherapy (P < 0.0001). Differences in the shape of the distributions, the median, and the mean are shown in the Box-and-whisker plot in Fig. 2A.

To assess possible external factors that might have contributed to the changes seen in mean TRF throughout treatment, various repeated measures analyses were done. In brief, repeated measures ANOVA allows us to examine multiple dependent variables that were measured at different times (i.e., mean TRF values from a before, during, and after chemoradiotherapy blood draw). In addition, it allows for the investigation of between-subject effects (such as differences between males and females) and within-subject effects (such as differences in mean TRF between individuals or treatment time points). The model assumes that factors involved have a linear relationship to the dependent variable (i.e., mean TRF), and the error cutoff of 0.05 was used. Following analysis of the data seen in Table 1, it was evident that certain factors contributed to the telomere length differences seen throughout cisplatin treatment. As was mentioned earlier, the time at which the draw was taken (i.e., pretreatment, during, or posttreatment) significantly affected mean TRF (P < 0.0001). An average rate of loss of 330 bp per time point (660 bp total) was seen in all chemoradiotherapy patients (mean: pretreatment, 7.13 kb; during, 6.81 kb; posttreatment, 6.47 kb; n = 19), whereas corresponding loss of telomeres for this 28 day time frame is 2 to 5 bp for healthy controls (4). The cross-sectional nature of our healthy control subset prevented a calculation for the rate of loss in that group.

The only other circumstance where the change in telomere length was influenced by a tested variable was when patients were divided into two equal-sized age groups, those under 55 years of age and those 55 years or older (Fig. 2B). Factorial ANOVA analyzing the initial versus final mean TRF from each patient between age groups determined that there was a significant difference in the final means and rate of loss between the two subsets (P = 0.018). In patients under 55 years of age, a loss of 400 bp was seen (means: pretreatment, 7.07; during, 6.85; posttreatment, 6.67; n = 9), whereas patients >55 years showed a loss of 880 bp during treatment (means: pretreatment, 7.18; during, 6.78; posttreatment, 6.30; n = 10). It is also interesting to note that the initial mean telomere length of the older group was longer than that of the younger group (7.18 versus 7.08 kb) despite the fact that the mean age of the 55 and older group was 61 (versus 50 in the young group). This difference, however, was not large enough to reach statistical significance and thus may be due to random variation because individuals at the same ages show broad ranges of telomere lengths (4).

Factors such as disease stage (P = 0.944), smoking status (P = 0.283), number of pack-years (P = 0.269), patient response (complete remission versus partial remission versus no response; P = 0.537), and total cisplatin dose received (144 mg/m² to 400 mg/m², P = 0.598) did not show significant changes with respect to mean TRF loss, despite the fact that large differences (such as number of pack-years) between patients did exist. In summary, these data show that chemoradiotherapy induces a significant decrease in the length of telomeres in PBMCs, and that this effect is much more evident in the patients over the age of 55.

Fig. 1. Changes in mean telomere length in PBMCs after chemoradiotherapy. Southern blot analysis showing TRF distributions at three collection points (before treatment, during treatment, and after treatment) from five head and neck cancer patients receiving chemoradiotherapy plus radiation therapy. Five micrograms of digested genomic DNA from each sample were separated by electrophoresis and hybridized to a radiolabeled telomere-specific probe. Samples represent patients 5, 7, 6, 19, and 9 (left to right, respectively; see in Table 1). M is the radiolabeled HindIII-digested lambda DNA (molecular weight marker) and is used to determine the mean TRF of each sample. DNA from each sample was digested on separate occasions and run individually on three separate gels.
**Discussion**

Mean TRF length has been reported to be shorter in solid tumors than in surrounding normal tissues by up to 2.8 kb (23). In numerous hematologic disorders, a significant mean TRF reduction is seen in patients versus age-matched controls in peripheral blood mononuclear cells (5, 20, 24, 25). In studies where telomere length was measured in the PBMCs of solid tumor patients that receive more intensive treatment protocols, greater telomere shortening was seen per unit time than in leukemia patients where less intensive treatment protocols were employed (20). Our linear regression analysis results suggest that no mean TRF difference is seen in locally advanced head and neck cancer patients at diagnosis compared with individuals without cancer, suggesting that cancer itself does not alter telomere length in PBMCs. Both patient and noncancer control groups displayed similar rates of telomere loss (as seen through regression analysis) and similar distribution (even after age adjustments), suggesting that cancer itself does not alter telomere length in PBMCs, and that shortened telomeres may not be a risk factor for the development of head and neck cancer, at least at the telomere length and age ranges that we are analyzing. These data differ from a large recent study of four cancer populations that reported shorter telomeres in head and neck, bladder, lung, and renal cell cancer patients compared with untreated controls (26). However, the telomere length measurement methods used in that study were not consistent between the various cancer types. Our study is limited by a relatively small sample size; thus, small differences in pretreatment telomere lengths might not have been identified.

Of the pretreatment characteristics that were analyzed, the number of cigarette pack-years did seem to significantly affect the mean TRF of patients at diagnosis (in contrast to the control group). Our data suggest that environmental exposure to cigarette smoke (and the carcinogens associated with smoking) was shown to accelerate telomere shortening in PBMCs. Similar effects were also realized in the control group, but only after selecting for individuals with the highest pack-year values (pack-years >15). Lack of effect seen in the >5 pack-year group and the total control group could be attributed to the low number of smokers with a high number of pack-years in the control set (mean pack-years: 20.7 in control, 34.25 in patients). This finding is not unexpected due to the fact that cigarette smoke increases the risk of heart disease, lung cancer, and microbial infections (27) and thus might be expected to increase turnover of cellular components of the immune system. In support of this idea, tobacco smoke has also been linked with a reduction in the proliferative capacity of lymphocytes (28).

This study is the largest longitudinal series investigating telomere length changes with concurrent chemoradiotherapy. In our original study design, we had planned to collect samples from patients receiving radiotherapy alone as treatment for locally advanced head and neck cancer. However, we

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NOTE: Patient information of individuals enrolled in our study since the Fall of 2003. The staging system used to determine the disease stage at the time of diagnosis summarizes information from the tumor-node-metastasis classification system (35), which describes the anatomic extent of the cancer. Stage II is representative of cancers with a primary tumor size (T) of 2 (out of 4), regional lymph node involvement (N) of 0 (out of 3), and distant metastases (M) of 0 (out of 1). Stage III is representative of cancers with a tumor-node-metastasis of T1-4,N1-2c, and M0, whereas stage IVA is representative of cancers with a tumor-node-metastasis of T1-4,N1-2c, and M0. Smoking status is divided among nonsmokers, former smokers (quit over 3 months ago), and current smokers. Pack-years was calculated by multiplying the number of packs per day by the number of years the individual has smoked. Best response to treatment was classified as a complete response, partial response, minor response, stable, or progressive disease. Mean TRFs (pretreatment, during treatment, after treatment) are also shown for each patient that was enrolled.

Abbreviations: CR, complete response; PR, partial response; NA, not available.

*Patient 20 was treated with radiotherapy alone.
encountered poor recruitment among head and neck cancer patients receiving radiotherapy alone. The single patient enrolled that was treated with radiotherapy alone did not show telomere loss (Table 1, patient 20). In the absence of a larger group of patients treated with radiotherapy alone, it is not possible to ascertain how much radiation may have contributed to the accelerated telomere loss in patients by an unknown mechanism.

The mechanisms by which cisplatin accelerates telomere loss are not known, but the G-rich nature of telomeric DNA lends itself to the preferential binding of cisplatin, due to a higher frequency of guanine-guanine and adenine-guanine repeats (29). Following adduct formation, cells likely continue to proliferate, albeit at a slower rate. If a permanent cell cycle arrest occurred, cell death would likely occur before division and cisplatin-based telomere reduction. In the absence of immediate cell death and arrest, the largest telomere length losses might be seen as a consequence of damage to telomeric DNA being transmitted to the cell populations derived from lymphocytes in the form of shorter telomeres. DNA damage recognition and repair efficiency varies between memory and naive cells and between young and old cells (30). The absolute numbers of memory T cells in the cell population increase with age (31), and it is important to note that memory cells in the young also have a lower efficiency of DNA repair capacity compared with naive cells. In elderly individuals with a higher proportion of memory T cells, the reduced ability to repair damaged DNA might contribute to greater telomere loss. For example, under circumstances where DNA repair is less than adequate for both naive and memory cells, such as in the elderly (30), DNA strands containing adducts might go unrepaired, potentially leading to greater telomere losses in the T-cell population. In addition, combination chemotherapy involving cisplatin has been shown to lower plasma antioxidant levels (32). Oxidative damage is an important factor involved in telomere shortening in normal human somatic cells (33). An increase in oxidative damage due to cisplatin in patients (an effect likely exaggerated in the elderly) might help contribute to the severe telomere losses that are seen.

Recent work examining the effect of chemotherapeutic agents on the telomere length of cells in the immune system have usually involved the grouped analysis of subsets of patients undergoing a variety of combination chemotherapy treatments for a group of different cancers (18–22). In contrast, patients in this study were more homogenous with respect to age, tumor type, and gender (Table 1), which should allow us to better define what aspects of treatment may affect telomere length. A dramatic loss of telomere length was seen during chemoradiotherapy treatment (mean loss of 660 bp over an 8-week span). Assuming an average annual loss of 30 bp/y in the absence of treatment in subjects of a similar age (4), the telomere loss seen in 8 weeks equates to 22 years of attrition seen in control subjects, or an ~145-fold acceleration of telomere loss. Furthermore, the individuals over the age of 54 had a treatment-related loss more than twice that of individuals between the ages of 44 and 54. By analogy with these losses seen during chronic infection by various agents, this could clearly affect the efficiency of the immune system to respond to subsequent challenges and suggests that the use of chemotherapeutic drugs in the elderly should be further examined for possible secondary effects. No other factors examined, such as stage of disease or total milligrams of cisplatin received, were seen to affect the rate of telomere loss in patients. One question our data raise is why more elderly cancer patients undergo a greater loss of telomeric sequences in their PBMC population than do younger patients. Because lymphocyte populations lose the ability to efficiently replicate in response to mitosis with age (34), one possibility might be that remaining cells in the elderly, while still able to undergo limited replication, may be devoid of any telomerase activity, underscoring the natural telomere attrition induced by chemotherapy-induced cell replication. This mechanism could also be exacerbated by...
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