Chemotherapy and radiation therapy are standard care in cancer treatment; however, both have numerous adverse side effects because they affect healthy as well as cancerous cells. The side effects, including decreased white blood cell count, nausea, hair loss, and fatigue, can be severe enough that patients may decide to forgo treatment. Targeted therapies are treatments that focus on specific molecules in cancerous cells and avoid disruption of healthy cells. Telomeres, the ends of chromosomes, are possible targets. In healthy cells, telomeres become shorter with each cell division, limiting the number of divisions that a normal cell can undergo. Many cancer cells have telomerase activity, which rebuilds telomeres after each cell division and confers immortality to cancer cells. Telomerase is an enzyme normally present to a significant degree only in the cells of developing fetuses. Treatments that target the telomerase enzyme itself or the chromosomal telomeres are being developed and tested in early clinical trials. This article focuses on several approaches to telomere-targeted therapy.

Telomere-Based Cancer Treatment: Emerging Targeted Therapies

Michele Chen, APRN-BC, and Sandra W. McLeskey, RN, PhD

Telomeres, the ends of chromosomes, are composed of long, repeating sequences of DNA (see Figure 1). In normal somatic cells, the ends of telomeres cannot be replicated prior to cell division, when the rest of the chromosome is duplicated (Allsopp & Weissman, 2002). Therefore, daughter cells' chromosomes are minutely shorter than those of the parent cell after normal cell division. Cell division results in progressive shortening of each chromosome, such that after a finite number of cell divisions, telomeres become too short and the cell cannot divide further; this state is called senescence (Serrano, 2010). However, an enzyme called telomerase that rebuilds the telomere after each cell division is present in embryonic cells and in most cancer cells. Reports have shown telomerase activity in 80%–90% of cancer cells (Harley, 2008). Because the chromosomal length is maintained, cells with telomerase activity are immortal, meaning they can divide indefinitely. If the telomerase enzyme were prevented from working, cancer cells may undergo senescence and fail to divide further; therefore, the development of therapies that target telomeres or telomerase is an active research area. Figure 2 lists definitions of terms.

Research is focusing on using telomerase activity or telomere length as a prognostic and diagnostic indicator. Analysis of the activity level of telomerase may give insight to the likelihood of recurrence of a particular cancer because higher levels of telomerase activity have been correlated to higher chances of tumor recurrence (Tatsumoto et al., 2000). Therefore, knowledge of telomerase activity level or telomere length in patients with cancer may help healthcare providers plan appropriate treatment to combat cancer progression.

At a Glance

- When telomeres are too short, cells stop dividing, become senescent, and may enter apoptosis or programmed cell death.
- Telomerase inhibition, active immunotherapy, and telomere-disrupting agents all aim to shorten telomeres and induce senescence in cancer cells.
- To date, telomere-targeting agents are being tested in clinical trials to determine dosage, toxicity, and effectiveness.

Telomeres and Telomerase

Blackburn and Gall (1978) discovered the existence of tandem repeats (5'-CCCCAA-3') located at the ends of ribosomal genes in the protozoan Tetrabymena thermophila.
Greider and Blackburn (1985) discovered telomerase activity in *Tetrahymena thermophila*, as well as the occurrence of tandem repeats of T-T-G-G-G-G on the native telomeric primers. Suppression of telomerase activity decreased telomere length and cell growth arrest in human tumors (Hahn et al., 1999). Telomere length determined the timing of cell death: the longer the length of the existing telomere, the longer the time until degradation of the telomere and eventual apoptosis following telomerase inhibition (Xu & Blackburn, 2007). Since researchers have discovered the importance of telomerase suppression, multiple studies have shown the efficacy of telomerase suppression and inhibition of tumor growth.

**Biology of Telomeres**

In the cell cycle process, a cell that has recently undergone mitosis increases in size, replicates its chromosomes, and prepares for subsequent mitosis. Chromosomal replication is necessary because each daughter cell must receive a complete set of chromosomes to be identical. During chromosomal replication, old chromosomes are used as templates to direct the synthesis of new chromosomes, such that each new chromosome is a complementary copy of an old one. Mitosis is the end point of the cell cycle, during which one complete set of chromosomes is segregated into each daughter cell.

The enzyme that replicates chromosomes, DNA polymerase, cannot copy the DNA of an old chromosome at its tip (i.e., the telome). The inability to copy the telomere will have no consequence for several cell divisions because the telomere is composed of tandem repeats. The new chromosome will be slightly shorter than the old one (by about 150 base pairs) and contain fewer repeats in its telomere. However, after many cell divisions, the telomere eventually will become short enough that further cell division would disrupt the integrity of the chromosome. At that point, the cell must stop dividing and enter senescence. Researchers believe that in normal somatic cells, telomeres have a multifunctional task: (a) to protect chromosome ends from recombining or degrading, (b) to help control recognition of dividing chromosomes, and (c) to secure chromosomes with the appropriate nuclear format to facilitate DNA replication (de Lange, 1998). The shortening of telomeres is thought of as a mitotic clock in which countdown occurs until cellular senescence is signaled (Allsopp et al., 1992). In addition, the extreme shortening of telomeres activates expression of the tumor suppressor gene TP53, which causes cell-cycle arrest and apoptosis (Smogorzewska & de Lange, 2002).

**Telomerase**

Telomerase is a complex enzyme containing a human telomerase reverse transcriptase (hTERT) RNA component and a protein component, human telomerase reverse transcriptase (hTERT). The presence of hTERT is necessary for telomerase activity; the telomere end caps do not lengthen without hTERT activation (Bodnar et al., 1998). Usually, hTERT expression is repressed in a normal cell because of the chromosomal configuration. When hTERT expression is activated, the protein becomes part of a ribonucleoprotein complex that replaces the 5’-TTAGGG-3’ repeat with 5’-CUACCCUAAC-3’ (Liu, 1999). Cell senescence, cell-cycle arrest, and apoptosis will not occur with activation of telomerase; therefore, the cell is free to divide continually. This attainment of cellular immortality is a hallmark sign of carcinogenesis (Novak, Jensen, Garbe, Stamper, & Futscher, 2009). In many types of cancer cells, telomerase activity is present and represents one part of the complex pathway through which tumorigenesis can be initiated and maintained. Although telomerase activation does not cause cancer by itself, researchers believe it is a compounding factor (Sauna, Kimchi-Sarfaty, Ambudkar, & Gottesman, 2007).

**Telomeres and Telomerase in Cancer**

Cancer cells acquire the ability to proliferate unremittingly. In this process, cancer cells frequently lose their differentiated appearance and behavior and become more embryonic. Three...
main events typically spark tumorigenesis: failure of the DNA repair system, inhibition or loss of tumor suppressor genes, and activation of oncogenes (Lopez-Serra et al., 2006; Rennstam, Baldetorp, Kytola, Tanner, & Isola, 2001; Wu et al., 2005). However, initiation of telomerase activity seems to accompany many genetic changes that occur (Harley, 2008).

Researchers are attempting to take advantage of the difference in telomerase activity in normal somatic cells and cancerous cells. Analysis of telomerase activity, particularly the presence of hTERT, is an area of interest because of its potential use as a diagnostic marker. Telomerase activity typically is present early in carcinogenesis (Saldanha, Andrews, & Tollesbol, 2003). If caught early enough in the cancer process, the cancer cells may be treated at a less aggressive stage while they are still dividing. Sensitive tests such as TRAP (telomerase repeat amplification protocol) may help recognize the beginning stages of carcinogenesis (Sarsero, Merino, & Yanofsky, 2000). However, additional testing is needed before TRAP becomes available.

**Telomerase Inhibition**

A concern for any new systemic cancer therapy is whether the treatment will affect noncancerous cells while targeting cancer cells. Telomerase inhibition, when merged with different anticancer treatments, may be more efficacious with minimal risks because telomerase inhibition targets differences in telomerase activity in cancerous and somatic cells (Andrews & Tollesbol, 2007). Telomerase activity is high in cancerous cells but is absent in most types of somatic cells. Telomerase inhibition attempts to cause cancer cell apoptosis (Noreen, Heinrich, & Moelling, 2009; Terme et al., 2009). However, hematopoietic stem cells, intestinal crypt cells, and endometrial cells do express some telomerase and may be adversely affected by telomerase-suppression therapy. Research in this area has shown that those cells express telomerase sporadically at lower levels and have longer telomeric lengths; therefore, they are not as susceptible to telomerase inhibition as cancerous cells (Cunningham, Love, Zhang, Andrews, & Tollesbol, 2006; Thornley et al., 2002).

Another concern is whether a significant lag time in telomeric erosion and ultimate senescence will occur after therapy is initiated. The lag time is an issue if cancer progression is allowed to continue and the cancer cells evolve to tumors that will downregulate expression of hTERT, ultimately avoiding apoptosis. A small therapeutic window may be available for therapy because telomere length must be short for apoptosis to occur in a manageable time frame (Barwell et al., 2007). Barwell et al. (2007) surmised that using telomerase suppression as anticancer therapy on specific cancers may be difficult initially; years of research will be needed to assess which cancers express increased telomeric activity and shortened telomere length and which cancers will respond favorably to telomerase-suppression therapy (Phatak & Burger, 2007). However, studies have shown that rapid tumor cell senescence and apoptosis follow initiation of telomerase inhibition (Li et al., 2004; Li, Crothers, Haqq, & Blackburn, 2005). In addition, traditional chemotherapeutic medications may be used to shorten

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**Table 1. Clinical Trials of Telomere-Based Cancer Treatments**

<table>
<thead>
<tr>
<th>AGENT AND STUDY</th>
<th>CANCER TYPE</th>
<th>INCLUSION CRITERIA</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geron Corporation, 2009</td>
<td>Multiple myeloma</td>
<td>Failed standard therapy twice</td>
<td>Telomerase activity in the bulk tumor fraction of bone marrow from two patients decreased after GRN163L treatment by 78% and 48%, respectively. Telomerase activity in the myeloma stem cell-containing fraction of their bone marrow declined by 33% and 63%, respectively.</td>
</tr>
<tr>
<td>Hochreiter et al., 2006; National Institutes of Health, 2009a</td>
<td>Solid tumors, specifically breast cancer</td>
<td>Failed standard therapy once for metastatic disease</td>
<td>In vivo studies showed that GRN163L inhibited tumor-cell growth in all breast cancer cell lines, and tumor growth and lung metastases were suppressed for four weeks. In addition, GRN163L did not affect telomerase activity in normal mammary cells or endothelial cells.</td>
</tr>
<tr>
<td>Lin et al., 2005; National Institutes of Health, 2009b</td>
<td>Chronic lymphoproliferative disease, specifically B-cell leukemia or small cell leukemia</td>
<td>Failed standard therapy once</td>
<td>Preliminary data showed effective inhibition of B-cell leukemia on exposure of GRN163L.</td>
</tr>
<tr>
<td>GRN163L</td>
<td>Action mechanism: The direct binding of GRN163L to the hTR site promotes a competitive inhibition of telomerase activity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRN163L</td>
<td>Acute myelogenous leukemia</td>
<td>Failed standard therapy once</td>
<td>Initial data showed tolerance of therapy along with slightly stronger T-cell (particularly CD4+-cell) immune responses to telomerase. In the initial trial, 19 of 20 patients responded to therapy, with T cells exhibiting antitelomerase activity.</td>
</tr>
<tr>
<td>GV1001</td>
<td>Lung carcinoma; pancreatic carcinoma</td>
<td>Failed standard therapy once</td>
<td>Phase I and II trials demonstrated T-cell response in more than 50% of patients without substantial clinical toxicity.</td>
</tr>
</tbody>
</table>

hTERT—human telomerase reverse transcriptase; hTR—human telomerase
the lag time. For example, paclitaxel is a chemotherapeutic agent that can shorten telomeres by reducing telomeric repeats (Multani, Ozen, Imam, Wallace, & Pathak, 1999). Therefore, combination therapy with standard chemotherapeutic agents and telomerase-inhibition therapy may be a viable option for future use.

**Prospective Treatments**

To date, clinical trials of telomere- and telomerase-targeting agents are underway for initial safety and efficacy testing (see Table 1). Each treatment aims to cause suppression by attacking the telomerase from a different angle.

**Telomerase Inhibition**

The telomerase enzyme inhibitor GRN163L, developed by the Geron Corporation, targets hTERT with the goal of causing cancer cell senescence and apoptosis. GRN163L is a synthetic, short piece of DNA, with sequences complementary to the template region of hTERT (Goldblatt et al., 2009). GRN163L binds to hTERT because of the complementarity, thus preventing the binding of hTERT. For in vitro studies and clinical trials, researchers chose cancers with high telomerase activity levels and short telomere length, such as lung cancer, breast cancer, and Barrett esophageal adenocarcinoma (Fauce et al., 2008). In vitro results showed that GRN163L inhibited telomere lengthening, which made the cells less aggressive and more differentiated in their behavior. The drug prevented tumor formation in animal studies (Dikmen et al., 2005). In a preclinical study of GRN163L with breast cancer, the researchers tested various tumor subtypes including estrogen receptor-positive, estrogen receptor-negative, HER2+, BRCA1, and doxorubicin-resistant breast cancer cells. In all breast cancer subtypes, GRN163L effectively inhibited telomerase activity, which ultimately showed a significant reduction in colony formation in tissue culture and tumor growth and metastasis in mice (Hochreiter et al., 2007). Small molecules that will stabilize G-quadruplexes are in development (Harley, 2008). Advantages of the treatment include rapid cell death and the ability to use a small-molecule complex that binds to the human leukocyte antigen class II molecules and stimulates the formation of CTL complexes (Kyte, 2009). GRNVAC1 is a viral vector that has almost a full-length TERT segment encoded in its mRNA, which is processed into a membrane-associated protein by dendritic cells infected with the vector (Shay & Keith, 2008).

Either technique results in immunotherapy that specifically attacks the tumor cells expressing TERT (Brunsvig et al., 2006; Su et al., 2005). Advantages of active immunotherapy include positive lifelong results with periodic boosting, minimal side effects because of small boosting dosages, and the possibility of prophylactic vaccinations. Disadvantages include enormous manufacturing challenges to produce a gene-based treatment (Harley, 2008).

**Telomere-Disrupting Agents**

Telomere-disrupting agents consist of small molecules that stabilize the G-quadruplexes of telomeres. G-quadruplexes are looped structures made by the nucleic acid sequences that compose the telomeric repeat (GGTTAG) (Patel, Phan, & Kuryavyi, 2007) (see Figure 3). G-quadruplexes adversely affect telomere function; stabilization of the structures results in telomere uncapping, which causes rapid dissociation and degradation of hTERT and entry into apoptosis (Kelland, 2007). Small molecules that will stabilize G-quadruplexes are in development (Harley, 2008). Advantages of the treatment include rapid cell death and the ability to use a small-molecule complex to deliver the telomerase enzyme to the tumor cells.

**Immunotherapy**

Active telomerase-based immunotherapy draws from the concept that an immunologic response occurs from the body in reaction to an invading antigen, such as telomerase-positive cells. Some cancers have telomerase-specific cytotoxic T lymphocytes (CTLs) (Filaci et al., 2006). The CTLs express CD8 and CD4 antigens, which help the immune system mount a response to antigen-specific activation. Initial studies have tested immunotherapy vaccine administration with breast, pancreatic, renal, lung, and prostate cancer, melanoma, and acute myeloid leukemia. To date, the most promising products are GV1001 and GRNVAC1. GV1001 is a telomerase reverse transcriptase (TERT) reporter complex that binds to the human leukocyte antigen class II molecules and stimulates the formation of CTL complexes (Kyte, 2009). GRNVAC1 is a viral vector that has almost a full-length TERT segment encoded in its mRNA, which is processed into a membrane-associated protein by dendritic cells infected with the vector (Shay & Keith, 2008).

Either technique results in immunotherapy that specifically attacks the tumor cells expressing TERT (Brunsvig et al., 2006; Su et al., 2005). Advantages of active immunotherapy include positive lifelong results with periodic boosting, minimal side effects because of small boosting dosages, and the possibility of prophylactic vaccinations. Disadvantages include enormous manufacturing challenges to produce a gene-based treatment (Harley, 2008).
drug that might be active orally; a disadvantage is the drug may disrupt normal cell telomere structures (Harley, 2008). In human tumor xenograft studies in mice, G-quadruplex therapy demonstrated rapid cell senescence in the xenografts with minimal signs of toxicity (Gowan et al., 2002; Gunaratnam et al., 2009; Kelland, 2007). To date, those agents have not reached clinical trials.

**Telomere Prognostics**

Through the study of telomere length in normal cells, researchers believe they can determine a person’s risk of developing certain types of cancer. For instance, shorter telomere length in peripheral blood lymphocytes has been associated with high-risk occurrence of lung, kidney, head, neck, and bladder cancers (Wu et al., 2003). Shorter telomeres typically are associated with more aggressive tumors (Bisoffi, Heaphy, & Griffith, 2006). Patients with acute promyelocytic leukemia who had short telomeres had poor prognosis, increased relapse rate, and decreased survival rate (Ghaffari, Shayan-Asl, Jamialahmadi, Alimoghaddam, & Ghavamzadeh, 2008). In patients with Ewing sarcoma, short telomere length was associated with a 5.3-fold risk of relapse compared to patients with a longer telomere length (Avigad et al., 2007). To date, all available prognostic tests are under investigation and are not available for general use.

**Nursing Implications**

If the science of telomerase inhibition is translated into everyday practice, oncology nurses probably will use it as a cancer treatment in the future. As telomere-based drugs make their way into clinical trials, many nurses will use them before they are approved. Nurses will need education on administration, side effects, and patient teaching for telomere-based treatment. Nurses are obligated to understand the drugs they administer so they can inform patients about what is being done and why (Young, 2009).

**Conclusion**

Telomerase activation is an essential part of the tumorigenesis process that has been linked to the deleterious action of causing cell immortality. As the tumor cell constantly divides, the genetic instability fostered by short telomeres engenders the emergence of a more aggressive tumor phenotype (Samper, Flores, & Blasco, 2001). However, telomerase is active in 80%–90% of all tumors, has low activity in hematopoietic cells (Wang et al., 2005), and is not active in most normal somatic cells. Therefore, therapy can be aimed at attacking active telomerase in tumor cells while sparing most of the healthy somatic cells.

Multiple clinical trials are ongoing for different telomerase therapies, including telomerase inhibitors, active immunotherapy, and telomere-disrupting agents, all with potential advantages and disadvantages. Telomerase suppression therapy may become an adjunctive therapy to traditional cancer treatment; additional research is needed before telomere-based cancer therapy becomes a reality.

**References**


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