Ecteinascidin-743 (ET-743) (Yondelis™, PharmaMar, Madrid, Spain) is a new antineoplastic agent currently under active clinical investigation. This agent is of particular interest because of its unique mechanism of action and activity in tumor types that are considered generally unresponsive to standard chemotherapy agents. This article describes the drug and its nursing implications.

**Mechanism of Action**

ET-743 is a DNA-binding agent first isolated from the marine organism Ecteinascidia turbinata (a “sea squirt”), although it now is manufactured in the laboratory (Corey, Gin, & Kania, 1996). ET-743 binds to the DNA base guanine at the minor groove (i.e., narrow bend in DNA) of the molecular structure (Pommier et al., 1996) and causes the molecule to bend toward the DNA major groove (i.e., wide bend in DNA). This process alters the normal structure of the DNA molecule (Zewail-Foote & Hurley, 1999) (see Figure 1). The drug is composed of 3-tetrahydroisoquinolone subunits (A, B, and C) that are bound to each other. Subunits A and B bind to the DNA base guanine. Subunit C, which does not interact with guanine, appears to be important in the drug’s cytotoxic mechanism of action (Sakai, Jares-Erijman, Manzanares, Elipe, & Rinehart, 1996). After ET-743 binds to DNA, subunit C protrudes from the DNA molecule and may affect the binding of proteins required for regulating DNA activity; this, in turn, impairs the cell’s ability to function, including the process of transcription (Bonfanti et al., 1999; Friedman, Hu, Kolb, Gorfajn, & Scotto, 2002). Additionally, ET-743 creates DNA adducts (i.e., nucleotide crosslinks that prevent the DNA strands from separating). These adducts stimulate the cell in attempting to repair the nucleotide excision repair defect, which results in the cell’s death because of DNA strand breaks (Takebayashi et al., 2001). This is a newly described drug mechanism of action and only affects cells with transcribed genes (Friedman et al.). In addition, ET-743 is unique in its ability to inhibit the activity of the multidrug resistance gene (Jin, Gorfajn, Faircloth, & Scotto, 2000; Scotto, 2002), which confers resistance to many antineoplastic agents. Because of its activity in DNA transcription, the drug appears to be most effective in the growth, portion of the cell cycle (Erba et al., 2001). Arrest of cells at synthesis and growth/mitosis also occurs and promotes apoptosis (Gajate, An, & Mollinedo, 2002).

**Preclinical Studies**

Transplanted xenografts of human ovarian cancer, melanoma, non-small cell lung cancer, and soft tissue sarcoma (STS) are sensitive to ET-743 (Curigliano et al., 2001; Hendriks et al., 1999; Li et al., 2001; Valoti et al., 1998). STS cell cultures are less responsive to ET-743 than standard chemotherapeutic agents, such as doxorubicin and methotrexate (Li et al.). Nonsarcoma cell cultures are less responsive to ET-743 (Li et al.). ET-743 has been combined with various antineoplastic agents to treat tumor cells in vitro and in vivo (Faircloth, Grant, & Hornicek, 2001; Li et al.). Additive cytotoxicity was demonstrated with ET-743 and cisplatin, docetaxel, doxorubicin, navelbine, and dacarbazine against a variety of cell types. A high degree of cytotoxicity was observed with lung and breast cell lines when ET-743 was combined with docetaxel (Barrera et al., 1999). In xenograft models, doxorubicin administered before ET-743 was more effective than single-agent ET-743 in chrodrosarcoma, fibrosarcoma, and osteosarcoma (Faircloth et al.). Animal toxicology studies indicate that myelosuppression and hepatotoxicity would be expected toxicities for ET-743 alone or in combination with other agents (Jimeno et al., 1996).

Submitted September 2002. Accepted for publication November 3, 2002. (Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Clinical Journal of Oncology Nursing or the Oncology Nursing Society.)

Digital Object Identifier: 10.1188/03.CJON.313-319

Jeanne Held-Warmkessel, MSN, RN, AOCN®, APRN, BC

Ecteinascidin-743 (ET-743) is a marine-derived antineoplastic agent undergoing clinical trials to evaluate its use in the treatment of a variety of solid tumors. After the completion of the phase I studies, the agent subsequently was investigated in phase II trials for efficacy in a variety of tumor types. Ongoing phase I evaluation continues with other antineoplastic agents. Side effects of ET-743 include myelosuppression, hepatotoxicity, and nausea and vomiting. Liver function test monitoring is crucial and useful in predicting other serious toxicities. Nursing care issues and patient education are discussed in this article.

**Key Words:** clinical trials, DNA-binding proteins, neutropenia, nausea, vomiting