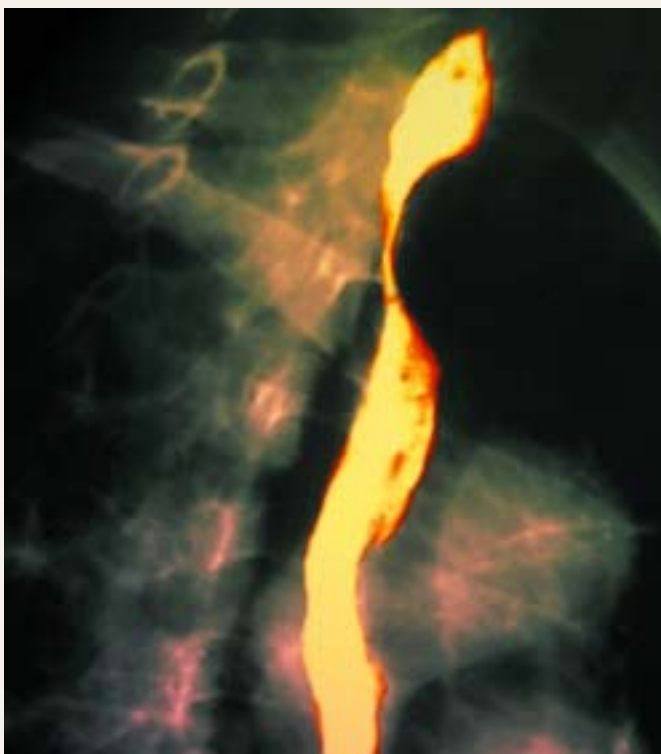


Serine protease inhibition: Potential uses beyond control of blood loss

MECHANISM OF ACTION AND MANAGEMENT OF LARGE TUMOR RESECTIONS IN THORACIC SURGERY

This supplement is based on a symposium entitled "The Role of Aprotinin in the Management of Large Tumor Resections in Thoracic Surgery: Understanding the Mechanism of Action" held during the 83rd annual meeting of the American Association for Thoracic Surgery, May 4, 2003, in Boston.



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LEARNING OBJECTIVES

- Review the mechanism of interaction between aprotinin and coagulation and plasminogen activator pathways, and its potential interaction with malignant cells
- Evaluate the use of aprotinin and its benefit of reducing blood loss and potentially decreasing lung injury in large thoracic tumor resections
- Describe the ability of aprotinin to inhibit serine proteases, which may result in inhibition of tumor metastasis
- Assess the safety of aprotinin and risk of thrombotic events and hypersensitivity reactions in both cardiothoracic and noncardiothoracic surgery from administration of half-dose versus full-dose aprotinin.

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Cardiothoracic surgeons

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Overview: A changing paradigm for treatment of neoplastic disease

Once characterized by a "search-and-destroy" approach, management of neoplastic disease no longer consists primarily of modalities such as radical surgery, chemotherapy, and radiotherapy. Increasingly, physicians who treat patients with cancer have access to target-specific strategies that modify molecular or genetic characteristics, promote angiogenesis, or use growth factors or cell-cell interactions.

The interaction between tumor cells and the coagulation and fibrinolytic systems suggest other potential treatments for neoplastic disease. Evidence indicates that certain tumor cells intensify activation of the coagulation and fibrinolytic systems to achieve rapid growth and metastasis. Serine protease inhibitors act at various points in the hemostatic, fibrinolytic, and inflammatory pathways. Therefore, it is not surprising that the agents have been investigated for their potential roles in inhibiting the processes required for tumor invasion and metastasis.¹

Potential benefits: From CABG to tumor resection

This publication will review current uses of serine protease inhibitors in both the surgical setting and management of neoplastic disease. By way of comparison, other agents with similar properties also will be discussed.

Aprotinin (Trasylol®, Bayer Corporation, West Haven, CT) is a nonspecific serine protease inhibitor. The single-chain polypeptide, which comprises 58 amino-acid residues, has been shown to inhibit numerous serine proteases in a dose-dependent manner (*Figure 1*).² It is currently the only serine protease product approved in the United States to reduce perioperative blood loss in patients undergoing cardiopul-

COVER ILLUSTRATION: Digitally color-enhanced x-ray taken in the left posterior oblique view shows an esophageal tumor in the narrowed portion of the esophagus near the top of the image.

monary bypass during coronary artery bypass graft surgery (CABG).³

The benefits of aprotinin in this and other surgical settings are well documented. They include decreased perioperative blood loss, fewer transfusions and explorative operations for bleeding, and a blunted systemic inflammatory response.²

In cancer patients undergoing tumor-related or other surgery, treatment with aprotinin, as expected, decreases blood loss and transfusion requirements. However, because aprotinin inhibits processes fundamental to the inflammatory response, it may also inhibit tumor growth and metastasis.²

APROTININ AND BLOOD CONSERVATION

The overall importance of blood conservation has been well documented. The shortage of donor blood makes conservation during surgery even more desirable. The risks associated with blood transfusions include bacterial and viral infections and increased mortality. In the general population, the 3 most common causes of transfusion-related deaths are bacterial infections, mis-transfusion, and transfusion-related acute lung injury. In cancer patients, blood transfusion increases the rate of relapse and risk of mortality. In some studies, blood transfusion been identified as an independent risk factor for increased relapse and mortality.^{4,5}

Aprotinin decreases platelet dysfunction through inhibition of the fibrinolytic system and preservation of platelet membrane-binding functions. Platelet dysfunction is believed to be the primary cause of bleeding following CABG. Decreased transfusion requirements have been observed in patients undergoing both primary and reoperative cardiac, orthopedic, and transplant surgery.

Blood loss in surgery for malignant tumors

Several studies have shown that aprotinin also

FIGURE 1 Aprotinin, a serine protease inhibitor

Binds with human serine proteases:

- Trypsin
- Plasmin
- Plasma kallikrein
- Tissue kallikrein
- Elastase
- Urokinase
- Thrombin

decreasing
affinity



decreases transfusion requirements in patients undergoing surgery for malignant tumors including hepatic tumors, meningioma, femoral osteosarcoma, and adenocarcinoma.⁶⁻⁸

In one study, high-dose aprotinin was evaluated in a prospective, randomized, double-blind study of 97 patients with primary malignant, metastatic, or benign hepatic tumors. The investigators reported that, compared with placebo,

In cancer patients, blood transfusion has been identified as an independent risk factor for increased relapse and mortality

high-dose aprotinin (loading dose of 2×10^6 kallikrein activation units [KIU], followed by 5×10^5 KIU/h infusion, plus a 5×10^5 KIU bolus for every 3 red blood cell [RBC] units transfused) significantly decreased intraoperative blood loss, number of patients transfused, and the total transfusion requirement (*Table 1*).⁸ Aprotinin administration remained significantly correlated with blood loss after adjusting for underlying disease, age, preoperative hematocrit, repeat surgery, type of surgery, duration of clamping, and postoperative D-dimer level.

Aprotinin also decreased blood loss in

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TABLE 1 Blood loss and transfusion requirements in patients undergoing elective liver resection

	Aprotinin (n=48)	Placebo (n=49)	P-value
Intraoperative blood loss (mL)*	1217 ±966	1653 ±1221	0.048
Patients transfused (%)	17	39	0.02
RBC requirements (RBC packs)	30	77	0.15

*mean ± standard deviation RBC, red blood cell

patients, with and without cancer, undergoing orthopedic surgery. Aprotinin (1 X 10⁶ KIU loading dose followed by 5 X 10⁵ KIU/h; n=12) compared with placebo (n=11) significantly reduced total blood loss (1783 vs 5305 mL; *P*<0.05) and blood transfusions (3 vs 7 units of packed RBCs; *P*<0.05) following orthopedic surgery for removal of infected hardware or tumor resection.⁹ Results were similar in a study that compared high-dose aprotinin (4 X 10⁶ KIU loading dose followed by

Aprotinin decreases secretion of such inflammatory mediators as interleukin, neutrophil elastase, and tumor necrosis factor

1 X 10⁶ KIU/h; n=18), low-dose aprotinin (2 X 10⁶ KIU loading dose followed by 5 X 10⁵ KIU/h; n=22), and placebo (n=18) in patients undergoing major orthopedic surgery.⁹ High-dose aprotinin administration compared with placebo significantly decreased postoperative drainage (625 vs 1190 mL; *P*<0.05), total measured bleeding (1715 vs 2795 mL; *P*<0.05), total calculated bleeding (607 vs 1073 mL of RBC units, hematocrit 100%; *P*<0.05 and 2023 vs 3577 mL of whole blood, hematocrit 30%; *P*<0.05), and postoperative (32% vs 28%; *P*<0.05) and postoperative day 2 hematocrit (31% vs. 27%).

Low-dose aprotinin compared with placebo significantly decreased postoperative drainage

(590 vs 1190 mL; *P*<0.05) and postoperative day 2 (29% vs 27%; *P*<0.05) hematocrit. High-dose aprotinin compared with placebo also decreased the number of homologous (0 vs 2 RBC units; *P*<0.05) and homologous and autologous (2 vs 4 RBC units; *P*<0.05) RBC units transfused and the number of patients exposed to transfusions (4 vs 11 patients;

P<0.05). No significant differences among the aprotinin groups were reported.

Deep venous thrombosis was not increased in patients receiving aprotinin. One patient in the placebo, 3 patients in the low-dose aprotinin, and 0 patients in the high-dose aprotinin group had a deep venous thrombosis on venogram.⁹

Finally, in 100 patients who underwent surgery for intracranial meningioma or vestibular schwannoma, high-dose aprotinin (3 X 10⁴ KIU/kg body weight loading dose, followed by 1 X 10⁴ KIU/kg/hr until end of surgery or a maximum of 8 hours) compared with placebo also decreased blood loss (508 vs 1014 mL; *P*=0.028).⁷

EFFECTS ON ANTI-INFLAMMATORY PATHWAY

Aprotinin in *in vitro* and *ex vivo* models modulated several processes in the inflammatory pathway including reduced levels of proinflammatory cytokines² and inhibition of complement factors,¹⁰ the potent proinflammatory properties of kallikrein,^{11,12} neutrophil transmigration through the vascular endothelium,^{13,14} and thrombin-induced platelet activation.¹⁵

Multiple clinical studies conducted in patients undergoing CABG have documented the anti-inflammatory effects of aprotinin. The drug was shown to decrease secretion of several inflammatory mediators including interleukin-6, -8, and -10, polymorphonuclear neutrophil elastase, and tumor necrosis factor-alpha. Additionally, aprotinin blocked expression of CD11b/CD18 adhe-

sion molecules located on white blood cells.²

Inflammatory pathways: Postsurgical adverse events

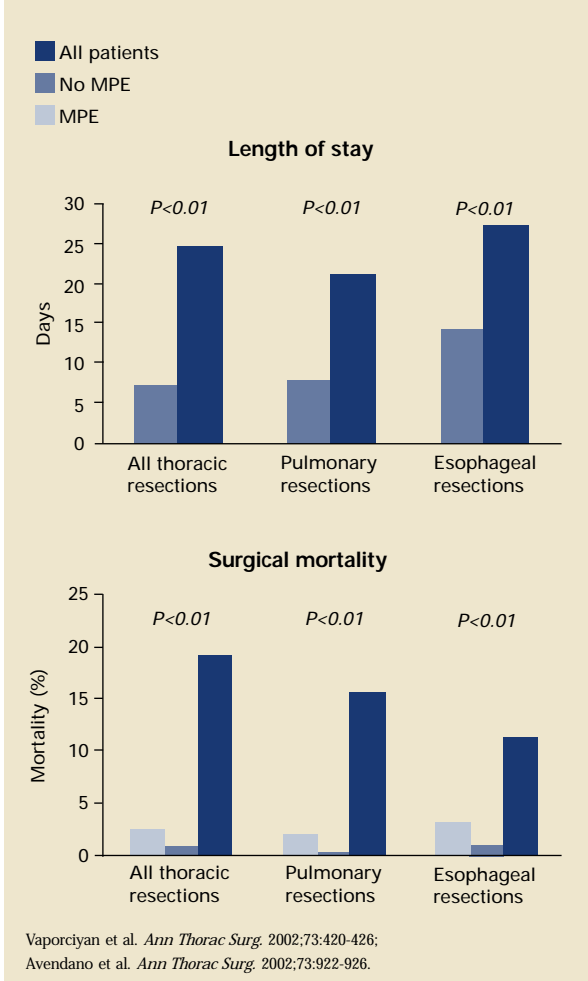
Both cellular and humoral components link the coagulation and inflammatory pathways, as is evident in patients with systemic inflammatory response syndrome or disseminated intravascular coagulation. Initiating events of the systemic inflammatory response syndrome include major surgery or trauma, sepsis, and cardiopulmonary bypass.

The ultimate outcome of the systemic inflammatory response can be multiorgan dysfunction (manifested as coagulopathy), myocardial dysfunction, or a major pulmonary event such as acute lung injury, acute respiratory distress syndrome, or pneumonia. Data from CABG patients shows that inflammatory mediators are increased in patients with acute lung injury.

A major pulmonary event is a significant problem following intrathoracic resection of malignant disease increasing both length of stay and mortality (Figure 2). Patients who had a major pulmonary event following pneumonectomy for primary lung cancer had a 20-fold increase in mortality compared with patients who did not (39.3% vs 2.1%; $P<0.001$).¹⁶ Aprotinin administration may inhibit inflammation through multiple pathways and ultimately decrease the risk of a major pulmonary event.

Clinical studies conducted in adult and pediatric patients requiring cardiopulmonary bypass have also documented decreased lung injury with aprotinin therapy.^{17,18} In a prospective, randomized study of 20 patients, aprotinin significantly reduced the increase in malondialdehyde levels seen with cardiopulmonary bypass ($P=0.048$ vs placebo). Histologic examination of lung tissue and neutrophil counts also showed positive effects of aprotinin therapy.¹⁷ Similarly, in a randomized, placebo-controlled study of 60 pediatric patients who underwent cardiopulmonary bypass,

FIGURE 2 Impact of postoperative major pulmonary events (MPE)



aprotinin administration significantly improved post-operative oxygenation ($P<0.05$) and decreased time on mechanical ventilation ($P<0.05$).¹⁸

APROTININ AND TUMOR PROGRESSION AND METASTASIS

As mentioned, aprotinin appears to oppose tumor progression and metastasis through inhibition of serine proteases. Components of the coagulation and fibrinolytic pathways that are

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TABLE 2 Tumor types based on coagulation and fibrinolytic pathway activity

Type I

Generate thrombin, do not express uPA

- Small cell lung cancer
- Renal cell carcinoma
- Malignant melanoma

Type II

Do not generate thrombin, express uPA

- Non-small cell lung cancer
- Colorectal cancer
- Prostate cancer
- Breast cancer

uPA, urokinase-type plasminogen activator

known to play roles in tumor progression and metastasis include tissue factor, fibrin, fibrinogen, factors VIIa, Xa, and XIIa, platelets, thrombin, and urokinase-type plasminogen activator (uPA).

The degree of coagulation and fibrinolytic pathway activation varies with tumor type and is classified according to the dominant pathway;

Activation of the coagulation and fibrinolytic pathways may play a role in tumor progression and metastasis

type I tumors generate thrombin but do not express uPA whereas type II tumors express uPA but do not generate thrombin (Table 2). Patients with type I tumors may benefit from treatment with a thrombin inhibitor such as warfarin or heparin; patients with type II tumors may benefit from a uPA inhibitor such as aprotinin.

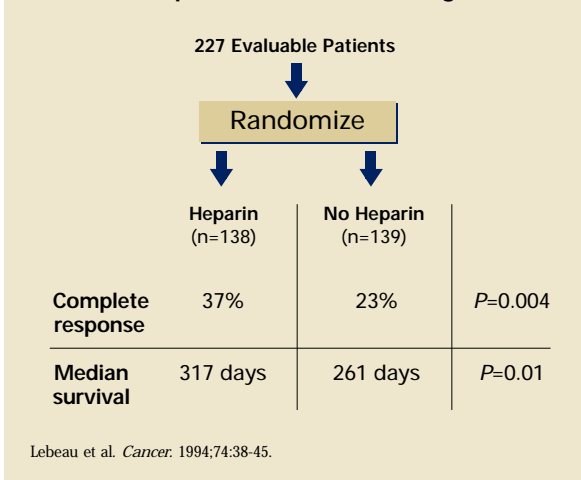
Type I tumors: Potential benefits of warfarin and heparin

Thrombin enhances tumor growth; promotes mito-

sis, angiogenesis, cell motility, cell adhesion, and chemotaxis; stimulates growth factors; enhances platelet activation; mediates oncogene expression; and activates nuclear transcription factor. *In vitro* studies utilizing immunohistochemical techniques have identified thrombin in small cell lung cancer, renal cell carcinoma, and malignant melanoma cells.² Numerous studies have demonstrated the beneficial effects of heparin or warfarin anticoagulation in patients with small cell lung cancer,¹⁹⁻²² melanoma,²³ and breast and pelvic cancer.²⁴

In a large small cell lung cancer study of thrombin inhibition, 328 patients were randomized to receive either methotrexate, doxorubicin, cyclophosphamide, and lomustine (MACC); MACC plus warfarin; or mitomycin, etoposide, cisplatin, and hexamethylmelamine (MEPH) alternating with MACC (MEPH/MACC).¹⁹ Complete and partial response rates were significantly higher in MACC plus warfarin patients (17% and 50%) than in MACC (8% and 43%) or MEPH/MACC (10% and 38%) treated patients ($P=0.012$). Both failure free and overall survival were longer in MACC plus warfarin patients (6.6 and 9.3 months) than in MACC (5.0 and 7.9 months), and MEPH/MACC (5.0 and 7.9 months) patients; however, the differences were not significantly different ($P=0.054$ and $P=0.098$). Similar results were noted in 2 smaller studies of unfractionated heparin or warfarin to patients with small cell lung cancer (Figures 3 and 4).^{21,22}

A pilot study evaluating the effects of low-molecular-weight heparin (LMWH) on malignant melanoma also reported beneficial effects.²³ Of 27 patients enrolled in the study, 18 patients received LMWH and 9 received LMWH and chemotherapy with dacarbazine, cisplatin, carmustine, and tamoxifen; radiation; or a combination of chemotherapy and radiation. The authors reported that survival for patients treated with LMWH was at least as good as, if not better than, current best treatment for malignant melanoma. Finally, short-course LMWH compared with unfractionat-

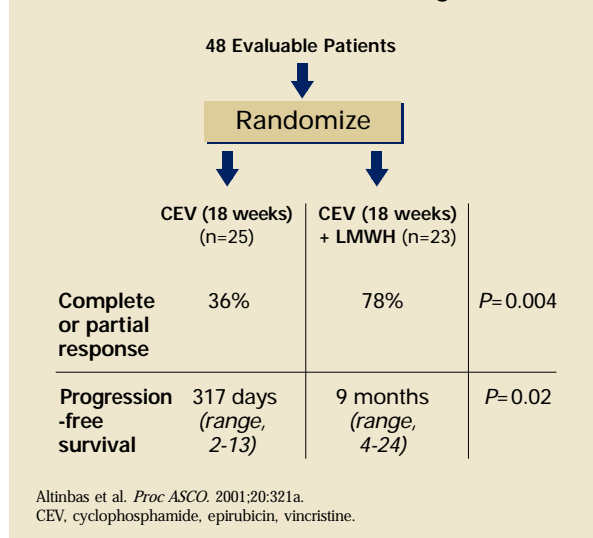
FIGURE 3 Heparin and small cell lung cancer

ed heparin appeared to improve survival following breast and pelvic cancer surgery; however, a significant survival advantage at 650 days was evident only in patients with pelvic cancer.²⁴

Type II tumors: Potential benefits of aprotinin

Normal physiologic processes that involve the uPA-plasmin system include clot lysis, wound healing, embryogenesis, and tissue remodeling. Tumor processes that involve the uPA-system include tumor cell growth, invasion, and metastasis. The role of uPA in tumor progression has been evaluated both *in vitro* and in cancer models. *In vitro*, insertion of the uPA gene into cells with a low malignancy potential increases their malignancy potential and converts them into highly invasive cells.²⁵ Augmentation of cells with uPA *in vitro* decreases cell adhesiveness, rounded morphology, anchorage-dependent growth, contact inhibition, and loss of intracellular actin cables and increases lectin agglutinability, cell motility, and angiogenesis.

Expression of uPA in tumors has been identified as a marker of poor prognosis in a variety of cancers including breast, prostate, colorectal, and non-small-cell lung cancer. High uPA levels are correlated with other markers of poor prognosis

FIGURE 4 LMWH and small cell lung cancer

such as advanced tumor stage, lymph node involvement, absence of hormone receptors, vascular invasion, increased invasiveness and metastasis, and rapid disease recurrence. Additionally, high uPA concentrations are an independent marker of poor prognosis and are associated with more rapid disease recurrence and shortened disease-

Aprotinin improved survival when administered perioperatively to patients undergoing tumor resection

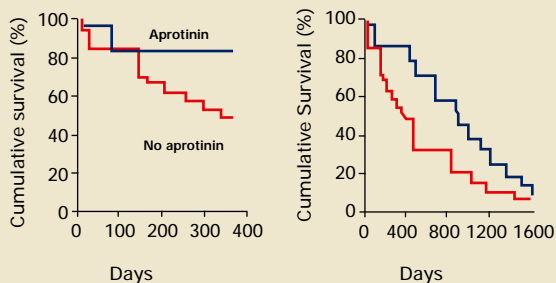
free and overall survival.² Current evidence suggests that uPA expression at tumor cell margins facilitates the migration of tumor cells through tissues to form distant metastases.

In animal models of malignancies, treatment with aprotinin resulted in decreased tumor size, invasion, and metastasis, and increased survival.²⁵⁻²⁸

In a study of prophylactic treatment to prevent head and neck cancer recurrence and metastasis, administration of aprotinin in conjunction with radiation, microwave hyperthermia, and

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FIGURE 5 Aprotinin and survival after resection of hepatic metastases



Lentschener et al. *Fibrinol Proteol.* 1999;13:39-45.

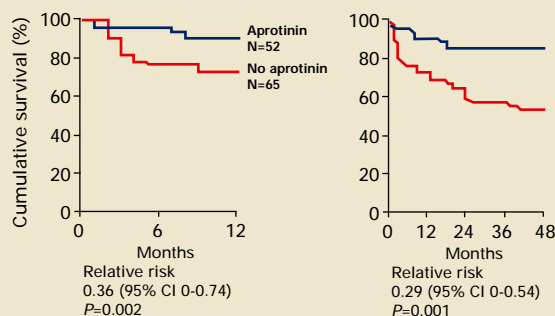
interferon increased the 3-year survival rate by 37%, decreased tumor recurrences by 39%, and decreased regional metastases by 8.4% compared with radiation with or without microwave hyperthermia.²⁹ Patients received aprotinin injections every 3 to 4 months for 3 years.

Aprotinin also improved survival when administered perioperatively to patients undergoing

Currently, aprotinin therapy is used as prophylactic therapy before and during surgery

tumor resection. Survival was prolonged in a randomized, placebo-controlled study of patients who received aprotinin (2 X 10⁶ KIU loading dose, followed by 5 X 10⁵ KIU/h, plus 5 X 10⁵ KIU bolus for every 3 transfused RBC units) following elective liver resection for metastatic colorectal cancer. At 1-year follow-up, significantly more patients had died in the placebo group than in the aprotinin group ($P=0.029$) (Figure 5), but this beneficial effect was no longer statistically significant at 5-year follow-up.³⁰ The loss of a significant difference at 5 years was attributed to the short duration of aprotinin therapy--only metastases originating from the intra-

FIGURE 6 Aprotinin and survival after esophagectomy



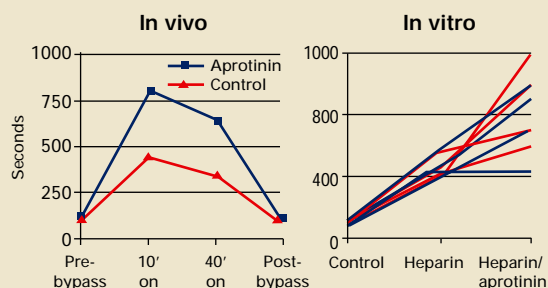
Zimblar et al. *ASA* 2002. Abstract A1187 (www.asa-abstracts.com).

operative release of tumor cells appeared to have been curtailed by the drug. An additional finding of this study was decreased plasmin activity in aprotinin-treated patients as demonstrated by a significantly smaller increase in D-dimer levels ($P=0.01$ vs placebo).

Aprotinin therapy also prolonged survival in a study of 117 patients who underwent surgical resection of esophageal cancer. At 1-year follow-up, more patients who did not receive aprotinin had died and by 18 months, the survival advantage for aprotinin was significant ($P<0.01$) (Figure 6).³¹ Interestingly, the mean survival time was 32.9 months (no additional deaths) for patients who received aprotinin and 34.6 months (8 additional deaths) for patients who did not receive aprotinin. The authors suggested this difference might be attributed to fewer stage 1 procedures (21% vs 35%) and lower age (62.2 vs 65.1 years) in the aprotinin group.

At MD Anderson Cancer Center, aprotinin is given to patients with a high likelihood of massive blood loss during tumor resection. Patients who receive aprotinin tend to have large pleural (e.g., mesothelioma), mediastinal (e.g., large thymus/thymic carcinomas), or vascularized tumors. Aprotinin is also given to patients with

FIGURE 7 Effect of aprotinin on activated clotting time



Royston D. *J Cardiothorac Anesth.*1989;3:80.

tumors involving a large pleural or peritoneal surface area and in patients undergoing reoperative procedures in the chest. At first, aprotinin was as rescue therapy at MD Anderson, meaning patients received aprotinin therapy after surgical incision. Currently, aprotinin therapy is used as prophylactic therapy that is administered before and during surgery. Initial experience with prophylactic aprotinin therapy has been positive and blood loss and perioperative morbidity appear to be less than would be expected in this patient population.²

DOSE-DEPENDENT EFFECTS

Regardless of its use, aprotinin produces specific dose-dependent effects.^{2,3} Inhibition of the fibrinolytic system occurs at lower doses; plasmin is inhibited at a concentration of approximately 50 KIU/mL.² Inhibition of the coagulation and inflammatory systems occurs with higher aprotinin doses: The serine proteases kallikrein, elastase, urokinase, and thrombin are inhibited at an aprotinin concentration >200 KIU/mL.³²

Full-dose effects on CABG patients

The effects of full-dose aprotinin have been observed following CABG or repeat CABG. In general, patients receiving full-dose aprotinin (2 X 10⁶ KIU loading dose, 2 X 10⁶ KIU added to circulating pump-prime, and 500,000 KIU/h continu-

TABLE 3 Monitoring anticoagulation with aprotinin

- Maintain celite-based ACT values at 750 seconds
OR
- Maintain kaolin-based ACT values at 480 seconds
OR
- Give additional heparin in a fixed-dosage regimen
OR
- Use heparin/protamine titration, which does not rely on contact activation

ACT, activated clotting time

ous intravenous infusion during surgery) had less thoracic drainage and required fewer units of donor blood, platelets, and fresh frozen plasma than patients receiving half-dose aprotinin (1 X 10⁶ KIU loading dose, 1 X 10⁶ KIU added to circulating pump prime, and 250,000 KIU/h contin-

The risk of deep venous thrombosis does not appear to be increased when aprotinin is given during orthopedic surgery

uous intravenous infusion during surgery). Similar findings have been noted when aprotinin has been added to pump-prime only, or placebo.³

Prophylactic, high-dose aprotinin in patients with malignant tumors

Prophylactic, high-dose aprotinin therapy is recommended for perioperative management of malignant tumors.² High-dose aprotinin not only reduces blood loss due to plasmin inhibition but also decreases inflammation resulting from kallikrein inhibition. Aprotinin doses >3 X 10⁶ KIU were typically administered to patients prior to surgical resection of malignant tumors in published reports.^{30,31}

At MD Anderson Cancer Center, aprotinin was

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initially administered as rescue therapy after surgical resection had begun. Aprotinin is currently recommended as prophylactic therapy that is initiated before surgical resection. The full dosing schedule is utilized in selected patients. All patients should receive 1 mL of aprotinin test dose at least 10 minutes prior to the loading dose to test for allergic reactions.

Aprotinin decreases intraoperative blood loss and the inflammatory response ... and inhibits tumor progression and metastasis

Safety data

The majority of safety information for aprotinin therapy has been obtained from studies that enrolled cardiothoracic surgery patients. Their results suggest that aprotinin is safe, well tolerated, and associated with a lower mortality risk, in comparison with placebo.²⁵ However, the risk of thrombosis and hypersensitivity reactions merits further discussion.

Thrombosis and whole blood clotting times.

Aprotinin does not appear to increase the risk of thrombosis in patients undergoing CABG. However, appropriate anticoagulation and anticoagulation monitoring are essential because the agent prolongs whole blood clotting time.

Coadministration of aprotinin and heparin requires care: The degree of anticoagulation may be overestimated if activated clotting time (ACT) is used (*Figure 7*). Recommendations for monitoring heparin anticoagulation using the ACT test are based on the type of test utilized (*Table 3*). The risk of deep venous thrombosis does not appear to be increased in patients, including those with cancer, who receive aprotinin during orthopedic surgeries.^{6,33}

Hypersensitivity. As aprotinin is a protein molecule, hypersensitivity reactions may occur during

and following administration, as stated in the prescribing information. The manufacturer recommends a 1-mL test dose prior to administering the loading dose. Aprotinin should be discontinued in patients who experience a hypersensitivity reaction. Reactions include skin eruptions, itching, dyspnea, nausea, and tachycardia. Additionally, fatal anaphylactic shock with circulatory failure can occur.

The risk of a hypersensitivity reaction increases with aprotinin reexposure. The incidence of hypersensitivity reactions is <0.1% in patients with no prior exposure, 5.0% in patients with previous aprotinin exposure during the past 6 months, and 0.9% in patients with previous exposure at least 6 months earlier.³⁴

CONCLUSIONS

Unlike older cancer therapies, many new cancer therapies are target-specific; for example, those agents that inhibit thrombin (e.g., heparin, warfarin) and those that inhibit uPA (e.g., aprotinin). The beneficial effects of aprotinin administration in patients undergoing CABG are well known and include decreased blood loss and transfusion requirements. The beneficial effects of aprotinin in patients undergoing surgical resection of a malignant tumor are less well known and appear to be mediated through the drug's effects on the hemolytic, fibrinolytic, and inflammatory pathways. Results from clinical studies demonstrate that aprotinin decreases intraoperative blood loss and the inflammatory response. Results from *in vitro*, animal, and small clinical studies suggest that aprotinin inhibits tumor progression and metastasis. To maximize the effects of aprotinin in patients undergoing tumor resection, aprotinin should be administered at full dose prior to surgical incision. Additional studies evaluating the effects of aprotinin on blood loss, the inflammatory response, and tumor progression and metastasis are needed to further define the role of aprotinin in patients undergoing malignant tumor resection.

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CME EXAM AND EVALUATION

Serine protease inhibition: Potential uses beyond blood control

To receive CME accreditation, circle the correct response, complete the program evaluation and registration form, and then submit this form to Medical Education Resources. Certificates will be mailed to the address listed below. Please allow 3 weeks for processing.

- Serine proteases play a role in which of the following pathways?
 - Hemostatic
 - Fibrinolytic
 - Inflammatory
 - All of the above
- Aprotinin inhibits which of the following?
 - DNA methyltransferase
 - Serine protease
 - Serotonin
 - All of the above
- Aprotinin is currently approved in the United States for which of the following?
 - Reduction in perioperative blood loss and blood transfusions in patients undergoing cardiopulmonary bypass
 - Reduction in major pulmonary events following intrathoracic resection
 - Inhibition of the systemic inflammatory response
 - All of the above
- Which of the following statements is TRUE?
 - Aprotinin administration increases the risk of thrombosis in patients undergoing CABG
 - Aprotinin prolongs the activated prothrombin clotting time
 - An aprotinin test dose should be administered to all patients prior to receiving the drug
 - All of the above
- Which of the following statements is TRUE?
 - Type 1 tumors inhibit thrombin formation
 - Type 1 tumors may be inhibited by administration of aprotinin
 - Type 2 tumors express urokinase-type plasminogen activator (uPA)
 - All of the above
- Normal physiologic processes in which the uPA-plasmin system plays a role include
 - Clot lysis
 - Wound healing
 - Embryogenesis
 - All of the above
- Which of the following statements is TRUE?
 - Aprotinin prolongs survival following surgical resection of breast cancer
 - Aprotinin should be administered as rescue therapy
 - Aprotinin prolongs survival following surgical resection of esophageal cancer
 - All of the above
- Which of the following is an example of type I tumors?
 - Non-small cell lung cancer
 - Colorectal cancer
 - Malignant melanoma
 - All of the above
- Which of the following is the primary cause of bleeding following CABG?
 - Platelet dysfunction
 - Red-blood cell dysfunction
 - Residual anticoagulant effects
 - Thrombin inhibition
- In vitro* and *ex vivo* studies indicate that aprotinin
 - Reduces cytokines
 - Inhibits complement factors
 - Inhibits kallikrein
 - All of the above

PROGRAM EVALUATION

Please check the box that best reflects your opinion on the statements below, using the rating scale defined at right.

	Strongly disagree 1	Disagree 2	Agree 3	Strongly agree 4
1. The program objectives were met	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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