Time to Move Beyond Retrospective Analyses for Thymic Neoplasms and Conduct a Prospective Multi-Institutional Clinical Trial

To the Editor:

Congratulations to Singhal and colleagues [1] for reporting the important University of Pennsylvania experience regarding the question of adjuvant radiotherapy after resection of Masaoka stages I and II thymomas. Their results along with prior observations [2, 3] and the accompanying discussion by Dr Wright of the Massachusetts General Hospital thoracic surgery group, clearly call for a prospective study of both early-stage and locally advanced thymic neoplasms. The lack of prospectively validated consensus recommendations on the optimal approach for thymomas is suboptimal for our patients [4]. However, the last paragraph of their report states that a prospective trial may not be doable for stage II patients "given the small number of patients involved and the long-term follow-up that would be required" to show any difference. This assumption may not be absolute.

Our multidisciplinary pediatric oncology colleagues have been very successful in prospectively studying rare solid tumors such as rhabdomyosarcoma, Wilms' tumor, and neuroblastoma. More recently, the thoracic surgery community, building on the prior hypothesis-generating work of select multidisciplinary academic thoracic oncology programs [2], successfully led the development, completion, and analysis of the first prospective multiinstitutional protocol for superior sulcus (Pancoast) tumors [5, 6]. This phase-II intergroup and surgeon-led study basically established a new standard of care on which to build future studies. More importantly, it has shown that an uncommon subset of non–small cell lung cancer can be prospectively studied within a North American cooperative group mechanism.

As both a medical and radiation oncologist with a commitment to thoracic oncology, I can appreciate the challenge that the article by Singhal and co-workers and its accompanying discussion broach. It is likely that a concerted effort will be put forth by the thoracic surgery–led Thoracic Committee of the American College of Surgeons Oncology Group, to prospectively study early-stage as well as locally advanced thymic neoplasms in parallel phase-II studies. Such studies would need to have the following features: uniform pretreatment imaging; written guidelines regarding surgical approach (including processing and orientation of the en bloc specimen for the pathologist after resection as well as mandatory guidelines on describing the extent of tumor adherence to surrounding structures [ie, phrenic nerve] in the dictated operative report); central review by a dedicated pathologist well versed in mediastinal tumor specimen analysis; tissue banking for future translational research studies (ie, gene microarray chip analysis); and, if radiotherapy is included in the schema of any prospective study; formal radiotherapy guidelines that include mandatory three-dimensional conformal techniques. Furthermore, such a study may present an opportunity to validate at least one of the staging systems that populate the literature on these tumors [4, 7].

The American College of Surgeons Oncology Group appears to be the forum that currently is poised to conduct phase II studies. Pending agreement from our European and Asian thoracic surgery colleagues, possibly a phase-III trial end point can be addressed. Until the multidisciplinary thoracic oncology community, albeit led by forceful academic surgeons, as suggested by Dr Wright, moves forward, clinicians will be left only with hypothesis-generating retrospective data from select high-powered institutions [1, 3, 7–10]. The present currency regarding lack of prospective modern clinical trial data for thymic neoplasms can be addressed. In this regard, we need only consider the recent experience with superior sulcus (Pancoast) tumors and the long-standing historical approach to pediatric tumors. How refreshing it is for today's thoracic oncologists when seeing a patient with a Pancoast tumor to no longer have to quote the data from Shaw and Paulson from nearly a half a century ago [11]!

Charles R. Thomas, Jr, MD

Department of Radiation Oncology
University of Texas Health Science Center at San Antonio
7979 Wurzbach Rd
San Antonio, TX 78229
e-mail: cthomas@ctrc.net

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Reply

To the Editor:

We have been convinced by Dr Thomas' eloquent letter in support of using the American College of Surgeons Oncology Group (ACOSOG) mechanism to organize multiinstitutional trials addressing outstanding issues surrounding thymic neoplasms. Perhaps we *were* too pessimistic regarding the possibility of such trials being completed in this important area. With the rapidly gathering momentum of ACOSOG's Thoracic Com-

mittee, there is now little doubt that such work can be successfully carried out. We could not agree more with your assessment that such studies should be done.

After receiving your letter, in fact, we contacted Dr David Harpole at ACOSOG to look into beginning the process of initiating such studies. What we discovered is that Dr Thomas, along with Dr Cameron Wright of Massachusetts General Hospital and Dr Geoffrey Graeber of West Virginia University, has already undertaken this process, and two thymic studies are under development.

As members of a center that sees a large volume of thymic work, we look forward to participating in these trials and helping to assure the most scientifically rigorous evaluation possible of our therapies for thymic neoplasms.

Joseph B. Shrager, MD
Larry R. Kaiser, MD

Section of General Thoracic Surgery
University of Pennsylvania Health System
Hospital of the University of Pennsylvania
4th Floor Silverstein
3400 Spruce St
Philadelphia, PA 19104
e-mail: jshrag@mail.med.upenn.edu

Argatroban as a Heparin Substitute in Cases of Heparin-Induced Thrombocytopenia

To the Editor:

We read with great interest the review by Warkentin and Greinacher [1] on heparin-induced thrombocytopenia and cardiac operations. We comment on the final paragraph: "Although the direct thrombin inhibitor argatroban has been used successfully for CPB [cardiopulmonary bypass] anticoagulation in dogs, experience with its use in humans is limited to cardiovascular procedures not requiring CPB. . . . Thus, it cannot be recommended for use in CPB."

Argatroban is a unique synthetic direct thrombin inhibitor developed in Japan. It does not need antithrombin III as a cofactor, and it is nonantigenic. The anticoagulant effect is concentration dependent. Argatroban binds to both free and clot-bound thrombin and exhibits no interaction with platelets or heparin antibodies. In addition, activated clotting time (ACT) can be used to monitor the anticoagulant effect [2, 3]. The drug is excreted through the hepatobiliary, not the renal, route. Monitoring the anticoagulant effect of argatroban is superior to and simpler than monitoring the same effect of recombinant hirudin, bivalirudin, or danaparoid. The only clinical disadvantage is that there is no neutralizing agent, such as protamine sulfate for heparin sodium. However, the fact that the plasma half-life of argatroban is as short as 15 to 30 minutes compensates for this disadvantage.

We [3] investigated argatroban as a potential anticoagulant in place of heparin in studies of CPB in an experimental model and confirmed that the use of argatroban as an anticoagulant in conjunction with a heparin-coated cardiopulmonary circuit is safe, reduces the activation of coagulation and fibrinolytic systems, and preserves platelet count. In addition, we [2] used argatroban in various clinical situations; for anticoagulation after operation for continuous hemofiltration, during replacement of the descending aorta using a standard left heart bypass technique, for percutaneous cardiopulmonary support, and during vascular surgical procedures. This experience confirmed that argatroban is useful as an anticoagulant in cardiovascular surgery and as a heparin substitute without side effects such as postsurgical bleeding complications or effects on fibrinolytic activities or platelet functions. On the basis of these results, we [4] judged argatroban to be a safe anticoagulant during surgical procedures requiring CPB and used it in this way with good results in a patient who had antithrombin III deficiency. Edwards and associates [5] reported the successful use of argatroban, similar to our protocol, and ACT monitoring in a patient with heparin-induced thrombocytopenia who underwent CPB. Further clinical investigation of protocols and determination of the optimal ACT level are needed. However, we believe argatroban is a first-choice substitute for heparin in patients with heparin-induced thrombocytopenia.

Kojiro Furukawa, MD

Department of Thoracic and Cardiovascular Surgery
Saga Medical School
5-1-1 Nabeshima
Saga, Japan
e-mail: furukawa@bcm.tmc.edu or
furukawk@post.saga-med.ac.jp

Hitoshi Ohteki, MD

Department of Cardiovascular Surgery
Saga Prefectural Hospital
Koseikan
1-12-9 Mizugae
Saga, Japan

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Reply

To the Editor:

Drs Furukawa and Ohteki challenge our statement that argatroban "cannot be recommended for use in CPB [cardiopulmonary bypass] operations." They cite anecdotal experiences with this direct thrombin inhibitor for cardiac surgery in humans [1–3]. However, these reports describe only two instances of argatroban use during conventional CPB for surgical procedures on the heart [2, 3] (other examples of its use included anticoagulation therapy after a cardiac operation, CPB for continuous hemofiltration, bypass during operation on the descending aorta, and off-pump surgery [1]). Only one of the two cases involved a patient with suspected heparin-induced thrombocytopenia, and that patient required 51 units of blood products during the early

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