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Fatalism Is Not Justified when Evaluating the Critically Ill Elderly

To the Editor:

With interest we read the article by Iwashyna and colleagues describing and discussing spurious inferences about long-term outcomes with respect to severe sepsis and geriatric conditions (1). Their line of thought is intriguing and may also influence our perception on whether or not to admit critically ill elderly patients. We and others have shown that patients with severe sepsis have a decreased health status when compared with a general matched healthy population (2). Moreover, the premorbid condition was a strong predictor for final outcome. Recently, we demonstrated that critically ill octogenarians already have an impaired health-related quality of life preceding critical illness, but their long-term impaired health-related quality of life is recovering to baseline values over time (3). This suggests that we have to consider carefully the health status before considering whether ICU admission would be of potential benefit for an elderly patient, but that we should not be too fatalistic in making this decision. Iwashyna and coworkers pointed this out quite eloquently. Because the number of critically ill elderly people will increase in the next decennium, the suggested line of reasoning may be important for all health care workers dealing with the critically ill. This will almost certainly have impact on the needed number of ICU beds, critical care physicians, nurses, and other ICU staffing.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Published 2012 by the American Thoracic Society

Reply

From the Authors:

The evolving research on survivorship complicates the already complex art of patient-centered decision making for the critically ill. Several groups have now presented data showing frequent problems among survivors of critical illness—some new, some preexisting, some likely the acute recognition of chronic processes. Our study (1) and others' studies have implications for practice, as patients may be less willing to accept treatment with modest risks of cognitive impairment and disability than they would the same risk of death (2). But given the difficulties of conveying prognostic information to families (3), and our lack of nuanced and accurate risk-prediction tools in most cases, it is not yet clear how a humane and evidence-based physician should incorporate these data.

We agree with Drs. Spronk and Hofhuis that a blanket fatalism is not justified in evaluating the older and oldest critically ill. But more so, we would argue that fatalism is not justified when considering the challenges of ICU survivors. Instead, a new challenge has been identified for critical care physicians and our collaborators. In our opinion, a crucial and underappreciated opportunity is collaborating with and organizing survivors of critical illness and their families into full partners (4). Their knowledge of the survivorship experience is necessary in clarifying present care needs and priorities for future research, many of which fall outside the disease-based medical model. We also must rigorously test innovative and diverse interventions. In some cases, these interventions will involve preventing new problems; in others, helping patients and their caregivers better adapt to and accommodate new problems; and in others, treating long-standing but previously unrecognized problems. We need a portfolio of new therapies to match the diverse challenges our older adult survivors face.

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Supported by NIH grants K08 HL091249 (T.J.I.), K08 AG031837 (C.C.), and K12RR023250 (G.N.). The funders played no role in the design, interpretation, or decision to publish the analysis presented here.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the U.S. government.

Author Contributions: All authors contributed to all aspects of this letter to the editor.

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Favorable Effect of Sorafenib in a Patient with Neurofibromatosis-associated Pulmonary Hypertension

To the Editor:

Neurofibromatosis type 1 (NF1) is an autosomal dominant disease that is caused by mutations in *Nf-1*. *Nf-1* works as a tumor suppressor gene that regulates a proto-oncogene, *Ras*. Some patients with NF1 suffer from pulmonary arterial hypertension (PAH); the current classification for PAH (Dana Point classification) categorizes NF1-associated PAH as pulmonary hypertension with unclear multifactorial mechanisms (1). In recent years, some tyrosine kinase inhibitors, especially imatinib mesylate (2), have been regarded as promising drugs for severe PAH. Sorafenib is one of these tyrosine kinase inhibitors, and a small pilot study has already reported its tolerability and potency in treating PAH (3). In addition, sorafenib is expected to act simultaneously as a specific therapy against NF1-induced peripheral nerve sheath tumors by suppressing the mitogen-activated protein kinase (MAPK) cascade (4). A recent report indicated that the degenerated pulmonary vasculature in NF1-associated PAH is affected by NF1 vasculopathy (5). Studies also revealed that the regulation of *Ras* by *Nf1* plays a critical role in vascular smooth muscle proliferation (6). Sorafenib is an oral inhibitor of multiple kinases, including *Raf-1*: the downstream target of *Ras* in the MAPK cascade. We hypothesized that sorafenib would have novel therapeutic potential in NF1-associated PAH by suppressing MAPK cascade activities.

We evaluated the safety and efficacy of sorafenib in a patient with refractory NF1-associated PAH. The patient was a 36-year-old female who was diagnosed with NF1 when she was 23 years old. She had typical café-au-lait spots and neurofibromas, but lacked bone lesions or schwannomas. She was diagnosed with PAH when she was 30 years old due to progressing dyspnea on effort and leg edema. She initially received prostacyclin infusion therapy to treat the severe PAH, but she was compelled to stop because of frequent catheter-related infections. Phosphodiesterase 5 inhibitor and endothelin receptor antagonist therapy were initiated following the failure of prostacyclin infusion therapy. However, her PAH became refractory and difficult to manage. During the previous 12 months, the pulmonary vascular resistance increased from 754 $\text{dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$ with 39 mm Hg of mean pulmonary artery pressure to 1,447 $\text{dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$ with 55 mm Hg of mean pulmonary artery pressure. Her 6-minute walking distance also declined from 355 m to 257 m, and the New York Heart Association functional class worsened from II to III. In this distressed situation, we decided to administer sorafenib at a dose of 100 mg once per day increasing to 200 mg after 4 weeks following a domestic ethical committee approval in Keio University.

Author Contributions: This manuscript has been read and approved by all the authors. Y.T.: study manager; T.O.: gathered clinical data; M.K.: gathered clinical data; M.S.: gathered clinical data; T.S.: medical advisor; K.F.: physician in charge.

Following 3 months of sorafenib administration without severe adverse events, reexamination of right heart catheterization revealed novel improvement of pulmonary arterial pressure (55 to 39 mm Hg) and pulmonary vascular resistance (1,447 to 1,063 $\text{dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$) (Figure 1), despite the small decrease in cardiac index (2.2 to 2.0 $\text{L}/\text{min}/\text{m}^2$), which was not correlated with the decrease in left ventricular ejection fraction. Furthermore, the patient's symptoms and exercise tolerance showed great improvement with respect to New York Heart Association classification (class III to I) and 6-minute walking distance (257 m to 330 m). No adverse effect other than mild nausea was observed during the administration.

As we had expected, sorafenib was effective as a novel therapy for refractory NF1-associated PAH. We achieved pulmonary hemodynamic and functional improvements despite the small decrease in cardiac index, which was not correlated with the decrease in left ventricular ejection fraction. As previously reported (3), the decrease in cardiac index was related to blood volume shifts caused by concurrent vasodilating therapy that induced distribution of blood to the skin vasculature.

In conclusion, this case indicates that sorafenib is a favorable and well-tolerated therapy for refractory NF1-associated PAH. It is the first tailor-made PAH treatment directed at the signal transduction mechanism of proliferation.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Figure 1. Time course of hemodynamic and exercise capacity before and after the administration of sorafenib. Pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP) attained by right heart catheterization and 6-minute walking distance (6MWD) are shown. The horizontal arrow above the graph indicates the administration period of sorafenib.