CORRESPONDENCE

Checkpoint Inhibitors—The Diagnosis and Treatment of Side Effects

by Prof. Dr. med. Lucie Heinzerling, MPH; PD Dr. med. Enrico de Toni, Prof. Dr. med. Georg Schett, Dr. med. Gheorghe Hundorfean, and PD Dr. med. Lisa Zimmer in issue 8/2019

Quality, Rather Than Quantity, of Life Is the Crucial Criterion

This important article raises some critical comments and questions (1).

In recent years, oncologists (including myself) have often discussed the ethical meaningfulness of therapies; especially as regards patients' quality of life in the area of conflict that is presented by therapies that often provide an only minimal increase in lifespan for the patient, with increasingly severe adverse effects.

Our ethical responsibility to protect patients from harm seems to have given way to an interpretation according to which only the minimal statistical value seems to matter.

What does even a few weeks' response to treatment mean for a patient if they have to put up with severe side effects for their brief remaining lifespan?

The review article did not include any critical comments on this. Much of what the authors wrote reads like product information from the pharmaceutical industry. In view of the authors' lists of competing interests, this makes a lot of sense.

Of course, studies of the adverse effects of therapy using checkpoint inhibitors will need to be undertaken. But an important aspect of such studies will have to be patients' quality of life.

Why has it not been investigated what happens when the financial resources that these medications consume are invested in comprehensive palliative care for patients with advanced tumor disease? Resources and money are often lacking in this setting.

I am convinced that palliative care that is as generously funded as these uncertain medications would have the same effects in patients' survival, but without the severe adverse effects.

We oncologists should not be blinded by the pseudo-religious cure promises of the pharmaceutical industry, but we should once again put the whole human being at the center of our activities. Treating severe adverse effects of medications is important, but it isn't a task that gives our jobs meaning.

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Conflict of interest statement

The author declares that no conflict of interest exists.

In Reply:

Many thanks for this important contribution to the discussion. We too have asked ourselves how important the marginal benefit for the patient is in view of the adverse effects.

Our study showed that doctors and healthy persons took a more critical view of adverse effects than melanoma patients (1). We asked whether patients would rather live symptom-free for eight weeks (receiving the best possible palliative care) or 16 weeks with moderately severe to very severe adverse effects (the average prolongation of life conferred by ipilimumab); the majority decided on the latter. In the face of a terminal illness, perspectives change and the remaining time left to live becomes more valuable. Documenting quality of life in the context of clinical studies also showed superiority for checkpoint therapy compared with the control arm (2), which is consistent with our own clinical experience. In the meantime data have shown that checkpoint inhibitor therapy in metastatic melanoma leads to long term survival in a proportion of patients without further therapy and adverse effects (3).

Furthermore, adequate management of adverse effects lowers morbidity and mortality. My co-authors and I have therefore taken every opportunity regionally, nationally, and internationally to speak on this subject, even if events were organized by the pharmaceutical industry. The increasing costs of modern oncologic drugs are problematic. In view of notably rising sales it is incomprehensible that the costs for checkpoint inhibitors are not falling drastically, because the manufacturing costs can be assumed to be negligible by comparison to the prices. This is a political problem that our healthcare system urgently needs to get a grip on. With regard to cost effectiveness, primary prevention of skin cancer is certainly the best measure—and too little is done in Germany in this regard. Not treating patients with skin cancer is not an option. Metastatic melanoma in comparatively young patients, with its often rapid progression, requires intensive care and support for patients, especially after the diagnosis has been made or if treatment has failed. It is especially in this phase that too few resources are available, in our opinion.

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CLINICAL SNAPSHOT

Pulmonary Arteriovenous Malformation

A 28-year-old previously healthy woman in the third trimester of pregnancy presented with hemoptysis ("mouth repeatedly full of blood"). Bronchoscopy showed diffuse right bronchial bleeding associated with transient gas-exchange disorder. Clinical examination revealed a low likelihood of pulmonary embolism, duplex sonography of the leg veins was negative, and echocardiography showed no abnormalities. Despite the patient's pregnancy we carried out contrast-enhanced thoracic computed tomography to detect, for example, any pulmonary vascular malformation. A shunt between the right bronchial

1) Aorta; 2) right bronchial artery; 3) right pulmonary vein (upper lobe); 4) shunt

artery and the pulmonary vein, visualized due to suboptimal contrast enhancement, was treated with catheter-assisted coiling. The bleeding ceased, and 10 weeks later the patient gave birth to a healthy girl. Rupture of a pulmonary arteriovenous malformation (PAVM) is a life-threatening event that occurs more frequently during pregnancy. Hormone-induced angiogenesis has been proposed as a possible cause. There have been only few reports of PAVMs from bronchial arteries. In our patient the malformation would probably have gone undetected if the contrast enhancement had not been inadequate. Because of its exposure to contrast medium, the newborn child should undergo thyroid function testing.

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