Sorafenib in Thyroid Cancer Patients: Learning From Toxicity

Thomas et al. [1] have recently published a review article addressing the use of sorafenib in metastatic thyroid cancer. Results concerning efficacy are of importance, but in our opinion the safety results deserve some comments. As highlighted by the authors, this review showed frequent dose reductions because of toxicity consistent with the findings of the phase III DECISION trial [2] and contrasting with the safety of sorafenib in other cancer populations. In the phase III TARGET trial of sorafenib in renal-cell carcinoma (RCC) patients, doses were reduced and interrupted only in 13% and 21%, respectively, of patients receiving sorafenib [3]. This excess of toxicity is intriguing because patients with metastatic thyroid cancer, a frequently slow growing disease, are expected to have better performance status and better renal and liver functions. The authors reported that 72% of patients could not tolerate the initial planned dosage of 400 mg twice daily and that 56% had dose reductions, suggesting that toxicity may be linked to sorafenib overexposure. Consistently more than 70% of patients suffered from hand-foot syndrome, an adverse reaction that has been associated with high sorafenib plasma concentrations [4].

A key for understanding these results may lie in lean body mass. Patients with thyroid cancer receive long-term thyroxine suppressive therapy, which leads to hyperthyroidism, a major cause of muscle (lean body mass) loss [5]. This muscle loss, named sarcopenia, has been associated with a higher incidence of severe and early dose-limiting toxicities in RCC and hepatocellular carcinoma (HCC) patients treated with sorafenib or sunitinib [6, 7]. In HCC patients, sarcopenia has been associated with higher sorafenib exposure [6]. The unexpected excess of toxicity observed in thyroid cancer patients [1, 2] may therefore be linked to a high prevalence of sarcopenia in this population, resulting in frequent overexposure to sorafenib. Finally, if dose reduction is needed, sorafenib pharmacokinetics prefers a 200 mg twice daily regimen rather than 400 mg once daily [8, 9].

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