Chemotherapy in Metastatic Melanoma – Still Useful or Out of Date?

Selma Ugurel

Klinik für Dermatologie und Venerologie, Universitätsklinikum Graz, Austria

Treatment of metastatic melanoma is currently undergoing a fulminant change in standards and decision-making. Until now, chemotherapy with dacarbazine (DTIC) served as the therapeutic standard, without any proof of a real benefit in survival. Anyhow, polychemotherapy regimens never showed a superior survival when compared with DTIC monotherapy in prospectively randomized trials [1]. Very recently, for the first time in more than two decades of clinical trials in metastatic melanoma, two agents, the immunotherapeutic ipilimumab [2] and the kinase inhibitor vemurafinib [3], demonstrated a significant prolongation of patient survival, and registration for both substances is imminent. In particular vemurafinib, which blocks the Ras-Raf-Mek-Erk phosphokinase pathway in tumors carrying the BRAF V600E mutation, achieved response rates and a prolonged overall survival never seen before in metastatic melanoma.

However, it soon became clear that the proportion of responding patients as well as the duration of response to these therapeutics is limited, and resistance mechanisms arise sooner or later during treatment. Moreover, the currently available targeted agents are suitable for only about 50% of metastatic melanoma patients due to the frequencies of the corresponding gene mutations. For this reason, it would be short-sighted to jump to the conclusion that the ‘old-fashioned’ treatment strategies are completely outdated and of limited future use in metastatic melanoma. Especially chemotherapy can produce long-term remissions of chemosensitive tumors as shown in the report of Metzner and coworkers in this issue of ONKOLOGIE [4]. Here, the authors describe a series of 23 patients with advanced metastatic melanoma treated with mono- or polychemotherapy followed by tamoxifen maintenance, with 6 (26%) of these patients showing median long-term remissions of 8.6 years. The chemotherapy regimens used contained DTIC, BCNU, cisplatin and carboplatin, alone or in combinations. The favorable treatment outcomes observed by the authors are likely attributed

to chemotherapy rather than to tamoxifen, because the latter has already been demonstrated to show no benefit when applied in addition to chemotherapy compared to chemotherapy alone [5]. However, a positive effect of tamoxifen on the maintenance of a chemotherapy response cannot be excluded and has never been tested in a prospectively randomized study. The observations of Metzner et al. [4] indicate that chemotherapy is still a promising treatment option in metastatic melanoma, and should be considered all lines of therapy after testing for gene mutations selective for currently available kinase inhibitors. In patients whose tumors harbor no specific gene mutations, chemotherapy could serve as first-line therapy. In patients tested positive for a genetic aberration allowing treatment with targeted agents, chemotherapy could be used as second- or third-line therapy following resistance against the kinase inhibitors used in first line.

The major obstacle for chemo- and immunotherapy of metastatic melanoma that has to be overcome is the current lack of reliable biomarkers helping to identify patients who are likely to benefit from either therapy. In this regard, the ongoing phase III trial ChemoSensMM of the Dermatologic Cooperative Group (DeCOG, ADO) in Germany and Austria investigates a methodology of ex-vivo sensitivity profiling [6] to allow an individualized, sensitivity-driven polychemotherapy versus DTIC in metastatic melanoma. It should be further noticed, that this methodology can also be used to test targeted therapeutics. If this trial achieves a positive result, chemotherapy will persist as one of the major mainstays in the treatment of metastatic melanoma.

Disclosure Statement

The author declares no conflict of interest.

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