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LETTERS TO THE EDITOR

Adjuvant interferon therapy and rheumatoid arthritis – a contraindication?

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To the Editor

Incidence of melanoma has strongly increased since the last decades [1,2]. For stages I and II (AJCC classification) adjuvant application of low dose interferon alpha (IFNα) has shown improvement of progression-free survival (PFS) and in addition a trend towards improvement of overall survival (OS) [3–5]. For stage III with regional lymph node metastasis, treatment with high doses of IFNα (Kirkwood scheme: 4 weeks IFNα-2b 20 Mio IU/m^2 BSA i.v. 5 ×/week followed by 48 weeks 10 Mio IU/m^2 BSA s.c. 3 ×/week) has proven to provide significant OS prolongation in one study [6]. The presence of active autoimmune diseases such as rheumatoid arthritis (RA) has been considered to be an absolute contraindication to use of IFNα therapy [7]. However, since there is a growing number of newly diagnosed cases with melanoma, there will also be an increasing amount of patients with coincident presence of autoimmune diseases such as RA. According to current practice most of these patients will be denied treatment with IFN in spite of its definite advantages in adjuvant treatment of melanoma and in spite of the high incurability of melanoma once it has metastasized systemically. Here, we present a case of a patient with metastatic stage III melanoma who also had RA, but who we treated with adjuvant IFN.

A 53-year-old woman presented to our dermato-oncological outpatient clinic with the history of malignant melanoma of the left lower leg 4 years ago (Breslow depth 0.85 mm, no ulceration). The patient now had a node in the left groin. Ultrasound examination detected an enlarged and highly suspicious lymph node, prompting surgical exstirpation. Histology revealed lymph node metastasis with massive infiltration by melanoma cells. Staging procedures (CT of the chest, abdomen and pelvis, MRI of the head) revealed no further metastases, and total lymph node dissection of the left inguinal and iliacal region detected no further (lymph node) metastasis. Hence the patient was staged as having stage IIIB metastastic melanoma in which high dose adjuvant IFN therapy was clearly indicated. However, the patient had also been suffering from seropositive RA for 6 years, which was currently controlled with sulfasalazine 2 × 1 g and prednisolone 7.5 mg per day. Yet, we wanted to consider treatment with IFN due to its proven effects in stage III melanoma.

After consultation with our local rheumatologists who diagnosed a moderately active RA and after informed consent of our patient we started high dose IFNα treatment according to the Kirkwood scheme under intensified clinical and laboratory controls. The patient‘s antirheumatic medication was not changed. Therapy was well tolerated except for the known side effects (fatigue, loss of appetite, loss of weight etc.). The patient did not develop deterioration of joint symptoms. Arthritic complaints even weakened during therapy. Unfortunately, 5 months after beginning of treatment the patient developed brain and disseminated cutaneous metastasis. IFN was discontinued while the brain metastases were irradiated, followed by systemic chemotherapy. The patient died 8 months after onset of disseminated metastasis.

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To the best of our knowledge, this is the first report of adjuvant IFN therapy in metastatic melanoma in a patient who was also suffering from RA. In literature, there is only one single case of IFN therapy in a patient with known RA who had chronic hepatitis C. His RA was well controlled with etanercept [8]. We presume that the low number of reports on IFN in conjunction with RA is due to the fact that many physicians do not administer IFN in patients with RA. On the other hand, in literature there are only 19 reports on the onset of RA under therapy with IFN [9–12]. In a larger study about side effects of IFN treatment in hepatitis C, the rate of newly diagnosed RA after IFN start was 0.3% (2 of 677 patients) [10] while the prevalence of RA in the general population is 8/1000 [13]. This is in marked contrast to the frequent appearance of autoimmune thyroid antibodies under IFN treatment (26% according to the study by Gogas and coworkers [14]) and the high rate of clinical onset of autoimmune thyroid disease (15% according to the study by Satzger and coworkers [15]).

Thus, the risk of treatment with IFN to exacerbate pre-existing RA or to induce RA is comparatively low. Also, neither potential exacerbation of pre-existing RA nor possible induction of RA by IFN is a life-threatening event. As systemically metastasized melanoma has a bad prognosis while adjuvant therapy with IFN has a significant effect in melanoma we suggest to consider the cautious use of IFN therapy in melanoma, and possibly also in other indicated cases with chronic hepatitis C or CML. In the apparently unlikely event that RA is induced or exacerbated by IFN there is a good chance to control the disease by antirheumatic substances, although inhibitors of TNF are banned for use in patients with malignancies. In this context it is noteworthy that in melanoma the induction of exacerbation of RA under adjuvant IFN therapy may present a positive sign because the appearance of autoantibodies or clinical manifestations of autoimmunity during treatment with IFNα has been shown to be of significant improvement in PFS and OS [14,15].

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