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EDITORIAL

The critical recommendation for the treatment of melanoma patients: Primum nil nocere

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Re: S. Retsas: Systemic treatment of melanoma: Quo vadis oncologist?

It is hard to accept that taking care of patients with melanoma has not followed the success expressway in oncology we are quite euphorically rushing forward on at present.

Looking back on 40 years of clinical and basic research there are advances which have added practical value to our efforts in prevention, diagnosis and treatment of this disease and also stimulated tumour research in general. But much of this development is characterized by early optimism and sobering corrections later on. So far none of the many options of systemic treatment with active or passive immunotherapy, cytostatic agents and / or biological response modifiers have improved the cure rates to any relevant degree.

Defining inherent and acquired risk factors and educating the public had a significant effect on early diagnosis, but did not reduce the continuously rising incidence. Up to now Governments, Health Authorities and scientific societies struggle to inform the public, warning parents in particular with little children how to enjoy sun without ill consequences, but the impact is negligible except for some short-lived improvements.

We have learned a lot about how to deal with the primary and regionally extended tumour and save the patient from useless mutilations and we are able to define the individual prognoses with depressing accuracy. But we have not altered the overall fate of the majority of our patients.

Without being able to translate research from bench to bedside leading to noticeable progress we have realized that melanoma is an early migrating, heterogeneous and highly resistant tumour that deceives our immune system. Research has mainly focussed on the immunomodulation of host and tumour. But success celebrated in mice and exceptional patients so far could not be translated to our every-day patient. Most if not all of the positive results of adjuvant and palliative treatments showing an increase in remission rate, disease-free intervals or overall survival initially, did not stand the test of time. Some led to borderline improvements only, or even had to be revoked after results of properly conducted, prospectively controlled and randomized trials became available. It is interesting to observe how many favourable studies in accordance with the biostatistic "law of the first cases" presented as preliminary results at renowned conferences "got lost", were abandoned, and couldn't be verified or reproduced.

Aside from the interferons, dacarbazine (DTIC) is such an example. Considered as "standard" since the early 1970s DTIC yields some meagre 7% remissions rather than the 20% plus published from selected populations previously. DTIC therefore may be considered as a "reference drug" but by no means as a "standard of treatment" for disseminated melanoma.

Cancer medicine has learned that enthusiastic reports and consciously articulated, unicentric empirism lead to erroneous therapeutical recommendations. The number of false "standard treatments" such as major surgery with wide margins initially, prophylactic lymphadenec-0tomy, adjuvant chemo- and/or immunotherapy with low or intermediate dose interferon alpha, BCG, levamisole, corynebacterium parvum etc is legion in oncology in general and particularly in melanoma.

Advances in oncology have been made in small increments, new classes of drugs or their combinations been developed, also active against metastatic melanoma, clearly with a superior therapeutic ratio than DTIC. Single agent chemotherapy with DTIC has been surpassed by new agents belonging to various classes of drugs such as the nitrosoureas, vinca alkaloids, platinum analogues, taxanes and some biomodulators.

Patients should be carefully selected by expert oncologists and appropriate treatment should be recommended, and individualized for their particular

needs. Chemotherapy with DTIC as a single agent for patients with disseminated melanoma can now be considered obsolete.

When appropriate, especially in the presence of large tumour volumes, combinations of two or more drugs with established antitumour activity should be considered as first choice, provided relative and absolute contra-indications have been ruled out.

If symptomatic tumour progression has been documented after adequate treatment with first line combinations, second or even third line chemotherapy may be suggested for highly motivated patients provided the toxicity and the chances of response or disease stabilisation have been fully explained.

Progress in the routine care of disseminated melanoma is hampered by national health policies based largely on pharmaco-economic constraints and the inertia of the authorities. Ill- conceived policies may deny individual patients a chance of palliation from distressing manifestations peculiar to melanoma, and at times, even of meaningful prolongation of life.

Government hospitals or Health Insurance Companies have the obligation to provide evidence-based, potentially helpful treatments, provided they are supervised by expert oncologists and endorsed by multidisciplinary boards such as now established everywhere and proof of a Centre of excellence in oncology. "Off-label" cannot mean leaving a patient alone when evidence-based medicine has proved efficacy of a particular treatment option. Evidence-based effective drugs are those appropriately investigated and referenced in standard textbooks or in peer –reviewed literature. When the potential of such treatments has been exhausted, patients should be encouraged to participate in clinical trials of novel and promising new drugs.

In this issue of J BUON a much needed critical overview is presented, thanks to S. Retsas, a veteran student of melanoma, addressing the medical community and the Health Authorities.

To overcome the autistic-undisciplined thinking in medicine, as wisely defined by E. Bleuler in 1919, remains the dominant task of the true scientist.

References

1. Kleeberg UR, Tilgen W. Palliative und supportive Therapie bei Melanompatienten – das Primat des nihil nocere. Onkologe 1996; 2: 465-472.
2. Kleeberg UR. Wishful thinking, unicentric empiricism and the everyday world of the medical melanomologist. Melanoma Res 1997; 7: S143-S149.

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