Journal of BUON **12:** 29-32, 2007
© 2007 *Zerbinis Medical Publications. Printed in Greece*

SPECIAL ARTICLE

Systemic treatment of melanoma: quo vadis oncologist?

S. Retsas

Oncology Centre, Cromwell Hospital, London, United Kingdom

Key words: chemotherapy, dacarbazine, interferon, melanoma, sentinel node, survival

At a time of exciting, if not spectacular, therapeutic developments in some other common and uncommon cancers, melanoma remains depressingly pendulous.

Is melanoma so different in its responsiveness to treatment from, say, lung or colon cancer for which combination chemotherapy is now the norm? [1,2].

Perhaps not! There are several reasons for the sorry state of affairs that we find ourselves and our patients with metastatic melanoma today. Principally, this is a tumour refractory to treatment. But flawed treatment strategies may have played a greater role in the dearth of progress to date.

The incomprehensible, almost compulsive adherence to the "reference drug" for melanoma, dacarbazine (DTIC), a cytotoxic in evidence for over 30 years but with an unimpressive efficacy record and response rates, as repeatedly documented recently of the order of 7-8%, is one of the obvious causes of this therapeutic stagnation [3,4].

Oncologists constrained by national or private insurance policies are unable or unwilling to divert from this "reference drug" and find their hands tied up when attempting to individualise treatments with alternative drugs to the specific needs of their patients.

Individualisation of treatment starts at the bedside, not with the genome.

Received 05-02-2007; Accepted 19-02-2007

Author and address for correspondence:

Spyros Retsas, MD, FRCP
Oncology Centre
Cromwell Hospital
London SW5 0TU
United Kingdom
Tel/Fax: +44 20 7460 5622
E-mail: sretsas@msn.com

In this respect another 10 or so drugs with documented, albeit modest, activity against metastatic melanoma [5] but in some cases with superior therapeutic ratio to dacarbazine, are ignored. Vinca alkaloids, nitrosoureas, platinum derivatives, taxanes and their potential combinations - routinely now used in other cancers-remain largely unexploited. Instead, the emphasis for over 30 years has centred with almost desperate perseverance on the immunomodulation of the tumour [6].

No cancer is curable or meaningfully controlled with single-agent treatment. Melanoma is no exception [7]. Yet, melanoma has been indicted to the "gold standard" of dacarbazine as a single agent. If you read the abstracts of clinical trials with the label "randomised" you may guess the reason.

I estimate that to study combinations of dacarbazine with each and any of these other active drugs or to compare their activity with each other would require something like 10^{10} prospective randomised studies to prove that some individual drugs or combinations are superior to dacarbazine alone!

With this practical impossibility, demanded nevertheless by contemporary evidential requirements, the skills of experienced oncologists who could be optimising existing resources with imaginative drug combinations suited to particular circumstances - combinations that may radically improve the outcome of individuals, but not necessarily of cohorts - are consumed in meaningless or ill-conceived randomised trials of predictable outcomes. Dacarbazine is invariably the "reference drug" featuring as the comparator in these trials.

Perhaps another impediment to therapeutic progress in this cancer has been the focus in the last decade on interferon-a as another "approved standard" for the adjuvant treatment of high-risk melanoma [8]. A recent

search through Medline for "melanoma" with limits for "Randomised Control Trial" revealed 549 entries of which 126 refer to "Interferon".

Thousands of patients have endured this potent molecule at considerable inconvenience and financial cost for no convincing evidence of improved overall survival but perhaps for a clinically inconsequential extension of freedom from relapse [9].

And yet the melanoma-medical community and influential research organisations have persisted for over 10 years with variations of the same theme and even more randomised trials of interferon in the pursuit of the elusive cure.

It is tempting to argue that the adjuvant interferon story in melanoma may have delayed therapeutic advancement in this disease by at least 10 years. There is now concern that other molecules with an appealing biological profile in the laboratory but of doubtful clinical significance are lining up to take its place.

Consider now the latest surgical "revolution" in melanoma; that of the sentinel node biopsy entrenching into the routine management of the disease [10, 11].

Clinically apparent metastatic involvement of regional lymph nodes is a common occurrence in cutaneous melanoma and heralds, in the majority of patients, dissemination of the tumour usually within 2 years from this clinical manifestation. The risk of such regional lymph node metastases increases as the grade of the primary lesion worsens. Thicker, ulcerated, bleeding primary lesions with a high mitotic count are likely to be early offenders [12,13].

In order to improve outcomes it became fashionable to perform immediate (elective or prophylactic) lymphadenectomies at the time of initial diagnosis of the primary tumour in the hope that resection of regional lymph nodes harbouring microscopic metastases would add protection. However, this approach, studied in randomised trials, showed no improvement in overall survival versus delayed lymphadenectomy, performed at the time when regional lymph node metastases became clinically apparent. Instead, it exposed patients to complications resulting from the procedure; notably intractable - in a substantial percentage of patients-lymphoedema and potentially to an increased risk of in transit metastases [14,15].

Lymphatic mapping and sentinel node biopsy was developed as a minimally invasive surgical alternative to elective lymph node dissection in order to identify patients with occult nodal metastases who might benefit from total lymphadenectomy [14].

This approach is conceptually no different to the objectives of prophylactic lymphadenectomy; namely, the resection of microscopically involved lymph nodes at a stage before regional lymph node metastases become clinically apparent [16].

The hypothesis of this approach is based on the assumption that the metastatic cells detected microscopically at the time of prophylactic lymphadenectomies are the same, if left behind that proliferate and give rise to the clinically palpable state of regionally metastatic lymph nodes and further, to dissemination.

Biopsy of the sentinel node positive for microscopic metastases is followed by a completion (total) lymphadenectomy of the involved regional lymph node basin.

One would have anticipated intuitively that this approach could not be expected to make a difference in survival for the simple reason that such occult metastases-detectable by routine microscopy, by immunocytochemistry and now possibly with Polymerase Chain Reaction (PCR)-would have occurred and would have been resected in the earlier randomised studies of elective lymph node dissections, which however showed no difference in survival.

But intuition had to be put to the test with yet another "gold standard" of contemporary clinical science; the randomised prospective trial.

However, the randomised study which sought to resolve this issue, did not confirm an overall survival advantage for patients who underwent a sentinel node biopsy versus those who were randomised to observation and who underwent a lymphadenectomy at the time of development of clinically palpable metastatic lymph nodes [14].

What has now become a fashionable practice, established before the publication of the results of this randomised trial, is likely to continue in the foreseeable future despite the fact, broadly acknowledged, that the sentinel node biopsy does not confer added protection to the patient [15-18].

What does this mean for the patient with melanoma? A staging surgical procedure which will not improve the chances of survival but which, like the staging splenectomies for Hodgkin's lymphoma in the old days, may well be performed to the patient's detriment. Add now the possibility of treating these patients with adjuvant interferon for microscopically detectable metastases [19], and the patient ends up in a state of "double jeopardy"; two unwarranted interventions, of no demonstrable survival benefit [20-23].

It seems that melanoma is becoming the paradigm of how progress is stifled in the treatment of cancer [24].

The time has come to extricate the management

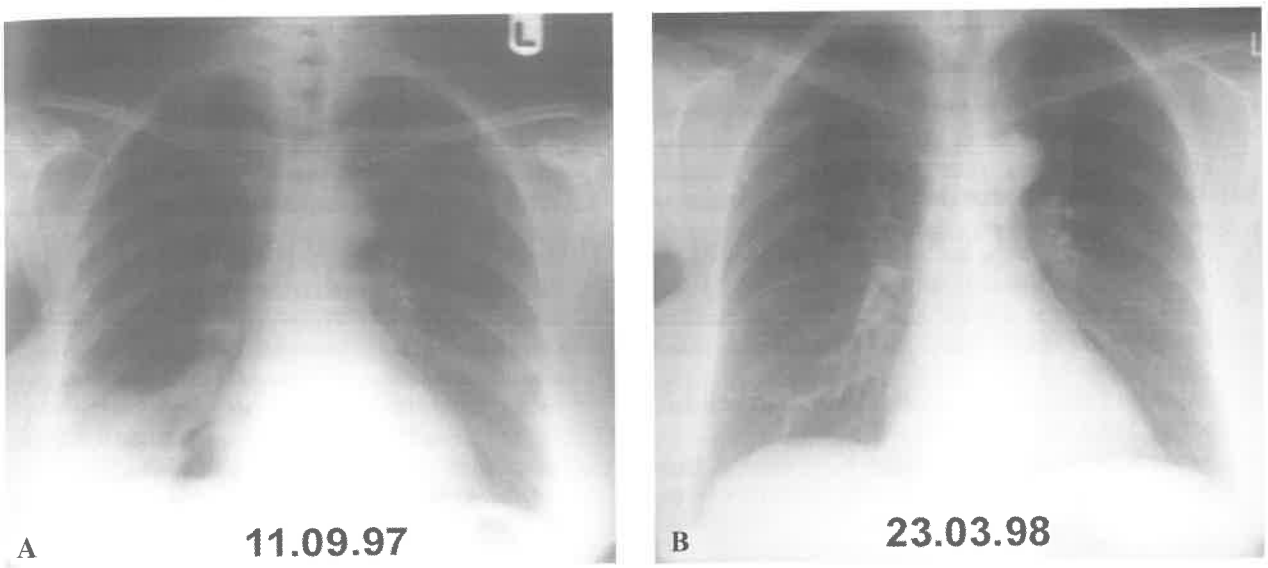


Figure 1. A 56-year-old woman presented with cough and haemoptysis following two melanoma locoregional metastases on the right arm for which twice she declined adjuvant treatment. Biopsy of the pulmonary mass confirmed metastatic melanoma (A). She received a 2-year course of treatment with the DJV3 combination (vinblastine, carboplatin, vindesine, alternating every 3 weeks with dacarbazine and vincristine) [25] which resulted in complete resolution of pulmonary metastases (B). She remains in apparent clinical remission to date.

of melanoma from "reference drugs" and "standard treatments" that have not stood the test of time. Treatment of the patient with metastatic melanoma with single-agent dacarbazine outside a specialist unit is likely to be wasteful in resources and inconsequential to the course of the disease.

In contrast, appropriate and individualised combination chemotherapy administered in a specialist establishment, may result in a drastically positive outcome for carefully selected patients, at times, similar to the result of the example - by no means unique [25-27] - shown in Figure 1.

Newer and better treatments are urgently needed for melanoma as they are for every other cancer. This, however, does not mean that in the process, patients should endure procedures or treatments emanating from "evidence-based medicine" that show no evidence of benefit nor that they should be denied the optimal use of existing resources, until genuinely better treatments become available.

References

1. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. N Engl J Med 2004; 350: 379-392.
2. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med 2005; 352: 476-487.
3. Avril MF, Aamdal S, Grob JJ et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol 2004; 22: 1118-1125.
4. Eggermont AM. Reaching first base in the treatment of metastatic melanoma. J Clin Oncol 2006; 24: 4673-4674.
5. Balch CM, Atkins MB, Sober AJ. Cutaneous Melanoma. In: DeVita VJ, Hellman S, Rosenberg S (Eds): Cancer: Principles & Practice of Oncology (7th edn). Philadelphia: Lippincott Williams & Wilkins; 2005, pp 1754-1809.
6. Danson S, Lorigan P. Melanoma vaccines-they should work. Ann Oncol 2006; 17: 539-541.
7. Eigentler TK, Caroli UM, Radny P, Garbe C. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. Lancet Oncol 2003; 4: 748-759.
8. Retsas S. Adjuvant therapy of malignant melanoma: is there a choice? Crit Rev Oncol Hematol 2001; 40: 187-193.
9. Spitler LE. Adjuvant therapy of melanoma. Oncology (Williston Park) 2002; 16(1 Suppl 1): 40-48.
10. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. Lancet 2005; 365: 687-701.
11. Retsas S. Cutaneous melanoma. Lancet 2005; 365: 2003-2004.
12. Balch CM, Buzaid AC, Soong SJ et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 2001; 19: 3635-3648.
13. Retsas S, Henry K, Mohammed MQ, McRae K. Prognostic factors of cutaneous melanoma and a new staging system proposed by the American Joint Committee on Cancer (AJCC): validation in a cohort of 1284 patients. Eur J Cancer 2002; 38: 511-516.
14. Morton DL, Thompson JF, Cochran AJ et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 2006; 355: 1307-1317.
15. Thomas M. Sentinel node biopsy in melanoma: a house of

cards? Melanoma Res 2007; 17: A6-A7.
16. Retsas S. Sentinel lymph node biopsy. N Engl J Med 1999; 340: 318-319.
17. Medalie NS, Ackerman AB. Sentinel lymph node biopsy has no benefit for patients with primary cutaneous melanoma metastatic to a lymph node: an assertion based on comprehensive, critical analysis: part II. Am J Dermatopathol 2003; 25: 473-484.
18. Medalie NS, Ackerman AB. Sentinel lymph node biopsy has no benefit for patients with primary cutaneous melanoma metastatic to a lymph node: an assertion based on comprehensive, critical analysis: part I. Am J Dermatopathol 2003; 25: 399-417.
19. Balch CM, Cascinelli N. Sentinel-node biopsy in melanoma. N Engl J Med 2006; 355: 1370-1371.
20. Verma S, Quirt I, McCready D, Bak K, Charette M, Iscoe N. Systematic review of systemic adjuvant therapy for patients at high risk for recurrent melanoma. Cancer 2006; 106: 1431-1442.
21. Grichnik JM. Sentinel-node biopsy in melanoma. N Engl J Med 2007; 356: 418-419.
22. Retsas S. Sentinel-node biopsy in melanoma. N Engl J Med 2007; 356: 419-421.
23. Kanzler MH, Levitt L, Lin A. Sentinel-node biopsy in melanoma. N Engl J Med 2007; 356: 419-421.
24. Wu J. Could evidence-based medicine be a danger to progress? Lancet 2005; 366: 122.
25. Retsas S, Bayliss MA, Sheikh N, Chong SL, Bafaloukos D. Chemotherapy of malignant melanoma; The European Experience. La Revue de Medecine Interne 1990; Tome XI (Supplement au Numero 2): 51-58.
26. Retsas S, Quigley M, Pectasides D, McRae K, Henry K. Clinical and histologic involvement of regional lymph nodes in malignant melanoma. Adjuvant vindesine improves survival. Cancer 1994; 73: 2119-2130.
27. Retsas S. Scientific evidence and expert clinical opinion for the investigation and management of stage III malignant melanoma - medical intervention. In: Mackie RM, Murray D, Rosin RD, Hancock B, Miles A (Eds): The Effective Management of Malignant Melanoma. UK Key Advances In Clinical Practice Series 2001, Aesculapius Medical Press, London, 2001, pp 65-82.