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REVIEW

Treatment beyond progression and locoregional approaches in selected patients with *BRAF*-mutated metastatic melanoma

Francesco Serra[1], Carlotta Faverio[1], Angioletta Lasagna[1], Stefania Barruscotti[2], Tommaso Dominioni[3], Marco Benazzo[4], Paolo Pedrazzoli[1], Silvia Chiellino[1]

[1]Medical Oncology Unit, IRCCS Policlinico San Matteo, Pavia, Italy; [2]Dermatology Unit, IRCCS Policlinico San Matteo, Pavia, Italy; [3]General Surgery Unit, IRCCS Policlinico San Matteo, Pavia, Italy; [4]Otolaryngology Unit, IRCCS Policlinico San Matteo, Pavia, Italy

Abstract

The clinical management of *BRAF*-mutated metastatic melanoma had an important turning point after the introduction of the targeted therapy. Despite the efficacy and good tolerability of this treatment, the development of resistance mechanisms causes disease progression. The aim of this review is to investigate the role of treatment beyond progression and locoregional approaches in *BRAF*-mutated metastatic melanoma and provide oncologists dealing with this malignancy a useful road map on when and why to choose this strategy.

The article is structured in the form of a narrative review reporting the most significant studies on the subject. Most of the available articles are represented by retrospective studies and case reports, leading to limitations in the final interpretations. Nevertheless, a correct analysis of the selected studies allows the drawing of some conclusions. In well-selected cases, treatment beyond progression could play an important role in the treatment sequence of patients with *BRAF*-mutated advanced melanoma and would seem to produce good disease control rates and positive survival outcomes. A careful evaluation of the radiological examinations and laboratory tests, based on the clinical conditions, allows the identification of which patients can benefit from this strategy. Such patients are those who, at the time of progression, have favourable features such as a lower performance status according to Eastern Cooperative Oncology Group (ECOG-PS), normal lactate dehydrogenase levels and lower disease burden. The clinical benefit is also consolidated by the addition of locoregional approaches. Locoregional approaches can include electrochemotherapy, radiotherapy or surgery, and their use provides local disease control and a better quality of life for patients.

Keywords: *BRAF*-mutated metastatic melanoma, locoregional approaches, targeted therapy, treatment beyond progression.

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Introduction

The most updated epidemiological data on melanoma, standardized for the general population, for both sexes and for all ages, indicate an average incidence of 3.4/100,000 and a mortality of 0.56/100,000. However, if we narrow down our research by age, we find that melanoma is the 14th most frequent cancer in those under 30 years of age. The data lead us to consider that melanoma affects an important slice of patients at a young age.[1]

The aetiology of melanoma is multifactorial, and the most important factor is certainly exposure to UV rays. For diagnostic purposes, excisional biopsy represents the essential standard; whereas, for staging, national and international guidelines recommend differentiating the examinations based on the disease stage, favouring first-level examinations for initial stages and second-level ones for advanced stages.[2–4]

Melanoma occurs in a limited form in about 60% of cases whilst in the remaining cases it presents as an advanced disease with an understandable reduction in survival outcomes.[5] Metastatic melanoma is a poorly chemosensitive disease; therefore, oncological research has had to study over the years treatment alternatives that are efficacious and tolerable. The advent of targeted therapy and immunotherapy revolutionized the landscape of clinical management of metastatic melanoma.

Targeted therapy has its rationale in the mutations of the *BRAF* gene; these mutations affect about half of the melanomas and, amongst them, the most common is the V600E type. *BRAF* status is recognized as a negative prognostic factor and positive predictor of targeted therapy.[6,7] The first drugs developed were pure *BRAF* inhibitors such as vemurafenib and dabrafenib.[8,9] Nevertheless, the appearance of severe adverse reactions and secondary tumours, like cutaneous squamous cell carcinomas and keratoacanthomas, led oncological research to deepen the biological basis in the activity of these drugs, understanding the need to block the MAPK pathway at different points. Thus, MEK inhibitors, such as trametinib and cobimetinib, were born in the context of combination therapies.[10–12]

The drug combination of BRAF and MEK inhibitors, in addition to reducing adverse effects, also improves survival outcomes. In the COMBI-d trial, researchers specifically compared the efficacy of the association of dabrafenib + trametinib *versus* dabrafenib in monotherapy and achieved a progression-free survival (PFS) of 11 and 8.8 months, respectively, and an overall survival (OS) of 25 and 18.7 months, respectively.[11] In a similar study, the COMBI-v trial, the combination of dabrafenib plus trametinib was compared with vemurafenib alone, with the results also in favour of the combination arm with an OS rate of 72% and 65%, a PFS of 11.4 and 7.3 months, and an overall response rate of 64% and 51%, respectively.[13]

In addition to the already mentioned drug associations (dabrafenib plus trametinib and vemurafenib plus cobimetinib), the recent combination of encorafenib plus binimetinib is also available.[14] Currently, the targeted therapy involves the use of the pharmacological association.[15] Currently, the concept of targeted therapy in melanoma treatment involves the combined use of a BRAF inhibitor plus a MEK inhibitor.

Immunotherapy, on the other hand, involves the stimulation of the immune system against cancer. This process occurs by acting on the immune checkpoints – receptor interactions between immune cells, cancer cells and microenvironment cells that normally lead to a negative regulation of the immune response. To reverse this type of signal, oncological research developed different immune-checkpoint inhibitors – drugs capable of stimulating the immune response. The main classes are anti-CTLA4 (ipilimumab), anti-PD1 (nivolumab and pembrolizumab) and anti-PD-L1 (atezolizumab) drugs. In advanced melanoma, the first two classes are used.[16]

Although the efficacy and good tolerability of these treatments, the development of resistance mechanisms causes the disease progression.

Treatment beyond progression

Treatment beyond progression (TBP) is an expression that in oncology indicates the continuation, without any stop time, of the ongoing therapy despite disease progression. Later, we report the most significant issues on the TBP strategy applied to *BRAF*-mutated metastatic melanoma.

The article is structured in the form of a narrative review, where we report the most significant studies on the subject along with a brief explanation of their selection. A search in the PubMed database using the search terms 'treatment beyond progression' and '*BRAF*-mutated metastatic melanoma' and limiting the search to the last 10 years, we obtained 21 articles of which we chose five, considering the others to be eliminated due to repetition of the data, with small samples or off topic.

The first article selected is the reference study on the chosen topic; Chan et al. published a retrospective analysis of 114 patients with *BRAF*-mutated advanced melanoma treated with dabrafenib and vemurafenib.[17] Disease progression was observed in 95 patients and, of these, 37 prolonged the ongoing therapy (*BRAF* inhibitors with or without *MEK* inhibitors) whilst 58 patients started a new treatment line or supportive care. Survival outcomes were better in the group of patients who experienced TBP compared to the other group (PFS 6.9 *versus* 3.8 months [$p<0.001$] and OS 11.6 *versus* 2.0 months [$p<0.001$]). The study also highlighted some positive prognostic factors: low disease burden according to RECIST criteria, low LDH levels and the presence of brain metastases; in the multivariate analysis, the low disease burden was the only factor that showed a statistical significance.[17]

The second selected issue examines in detail the resistance mechanisms to targeted therapy; Spagnolo et al. reviewed the main resistance pathways dividing them into three types: primary or intrinsic, secondary or acquired, and finally adaptive resistance mechanisms. Intrinsic mechanisms include the RAC1 mutations, loss of PTEN, dysregulation of the CDK4 pathway, loss of NF1, COT expression, alteration in RTK signalling and HOXD8 mutations. Secondary resistance mechanisms are the upregulation of RTKs, NRAS mutations, alternative splicing of V600E *BRAF* mutation, *MEK* mutations and elevated CRAF levels. Finally, the adaptive mechanisms include the alteration of the PI3K–PTEN–AKT pathway, upregulation of FOXD3 and the upregulation of mitochondrial synthesis and oxidative metabolism. The analysis of these processes documented how complex the interaction network amongst them is and how difficult it is to transfer this knowledge to clinical practice. Nevertheless, the authors invite to consider TBP as a therapeutic option; in oligometastatic patients, in fact, the main mechanism of malignant proliferation could still be represented by the MAPK pathway and, consequently, they could still benefit from targeted therapy. Oligoprogression due to new mutations on the same pathway blocked by the ongoing treatment is not a valid reason to immediately change the therapy because, in this way, the major brake on the pathway is removed and disease progression can become much more pronounced.[18]

The third selected article is a monumental work on the progression patterns during targeted therapy. Hassel et al. published a retrospective study in which 180 patients with *BRAF*-mutated metastatic melanoma progressed during

targeted therapy with dabrafenib or vemurafenib and, of these, 47 patients applied the TBP strategy.[19] Authors identified three main patterns of progression: pattern I (general types of metastases: 20.6% of patients developed new lesions only, 28.3% progressed in existing lesions only and 50.6% progressed in both new and existing lesions); pattern II (general sites of metastases: 20.0% of patients showed involvement of the central nervous system [CNS] only, 50.6% progressed in other sites but not in the CNS and 29.4% progressed in both the CNS and other sites); and pattern III (general behaviour of metastases: 10.6% of patients progressed in lesions that had completely disappeared and 76.7% had controlled lesions, despite progression). These patterns showed a better survival in patients who progressed in limited sites, even if with CNS involvement, suggesting the continuation of targeted therapy; however, TBP did not impact OS in this study.[19]

The fourth study selected is an interesting Italian experience about combination regimens; Queirolo et al. evaluated the association of vemurafenib and fotemustine, after disease progression with vemurafenib.[20] Despite the small study size, the results obtained are encouraging because 19 (61.3%) patients achieved disease control (14 patients on stable disease, 4 on partial response and finally 1 on complete response).

The fifth article chosen is a Dutch study that deals with the continuation timing of TBP. In their work, Scholtens et al. analysed 70 patients with *BRAF*-mutated advanced melanoma treated with vemurafenib and in disease progression.[21] These patients were divided equally into two groups: 35 continued on vemurafenib beyond progression whilst the other 35 changed therapy. Median PFS was 5.6 months in the TBP group and 4.0 months in the other group whilst median OS was 12.8 *versus* 6.3 months, respectively. The results of this study confirm, in line with other issues, that patients who benefit most from TBP have a low Eastern Cooperative Oncology Group (ECOG-PS) score, a low disease burden and normal LDH levels. However, the authors of this work also noted that, in the setting of TBP, if treatment with vemurafenib was stopped and then resumed at a later time, the survival of patients tended to decrease.[21]

Locoregional approaches

In oligometastatic patients with *BRAF*-mutated melanoma, locoregional approaches (LRA) should be considered in therapeutic management. The most common sites of metastases in melanoma patients are skin and lymph nodes, lung, brain, liver and bone.[22] In this section, we report the articles available in the medical literature recommending the use of LRA together with targeted TBP.

In patients who progress with secondary lesions on the skin, subcutaneous tissues and nearby lymph nodes, an LRA that can be used is electrochemotherapy with bleomycin. Dolinsek et al. tested the efficacy of electrochemotherapy with bleomycin on melanoma cell lines in combination with vemurafenib in vitro; their results demonstrated good synergy between the targeted therapy and the locoregional approach.[23] From these preliminary considerations, a series of issues emerged in the literature, mostly in the form of case reports, in order to define the efficacy of the combined treatments. Valpione et al. reported their clinical experience of a patient with *BRAF*-mutated metastatic melanoma treated with dabrafenib who had disease progression in soft tissue.[24] Their treatment strategy involved electrochemotherapy on the secondary lesion and continuation of targeted therapy, thus obtaining a good quality of life for patients and disease control of over 17 months.

In the other metastatic sites, the most common LRAs are radiotherapy and, when possible, surgical resections. Brain metastases from melanoma represent a much-debated topic for the purpose of the best treatment strategy. Tawbi et al. published a study that led to the consideration of several elements: brain metastases represent a clinical problem[25]; in well-defined lesions, especially if symptomatic, the radiotherapy or stereotactic approach is certainly recommended to provide local disease control; and targeted therapy, even when used beyond progression, produces a high response rate that lasts a short time compared to extracranial disease.

Bong et al. proposed that pulmonary metastasectomy in advanced melanoma can be performed in selected patients; in patients with a well-defined lesion, surgically accessible and in the presence of good respiratory function, lung resection can represent an LRA integrated into systemic therapy.[26]

Discussion

Despite the introduction of targeted therapy and immunotherapy, metastatic melanoma remains an oncological disease that remains difficult to treat. The poor chemosensitivity and the few treatment options available require oncologists to make the most of therapies also resorting to specific strategies such as TBP and LRAs.[27]

In our work, we focused on the population with *BRAF*-mutated metastatic melanoma. These patients can benefit from both targeted therapy and immunotherapy but, currently, there are no comparative studies nor any studies on the best treatment sequence; nevertheless, the available evidence clearly suggests that targeted therapy produces significant benefits in objective response and rapidity of response and, therefore, targeted therapy represents the first treatment line in *BRAF*-mutated advanced melanoma. This consideration is reflected in clinical practice.[28]

The steps to be taken when the disease progresses represent a major challenge, and our review tries to provide clear help to better plan the treatment sequence – the careful selection of patients is key.

If the patient should have negative prognostic factors, such as a high ECOG-PS score, high LDH levels and a high disease burden, it is understandable that the most suitable choice is

to change the treatment line or candidate the patient to best supportive care.[29]

However, if the patient, on the contrary, should present a favourable feature, such as a low ECOG-PS score, normal LDH levels and a low disease burden, then TBP may be a treatment option that can produce positive results both on disease control rates and on survival outcomes. The clinical benefit is also consolidated by the addition of locoregional approaches. LRA can be of varied nature, electrochemotherapy, radiotherapy or surgery, and their use provides local disease control and a better quality of life for patients.

The main limitations in the writing of this work concern the nature of sources – the limited number of studies, retrospective or anecdotal; therefore, the conclusions they bring must be supported by the subsequent level of evidence, that of controlled and randomized clinical trials.

Conclusion

To overcome the relatively limited duration of efficacy of targeted therapy, new strategies are being studied to combine targeted therapy and immunotherapy.[30] The SECOMBIT study is a phase II trial evaluating the sequential use of targeted therapy and immunotherapy in three treatment arms that allow both to be used in a different order.[31] The use of combination therapies could become the future in the management of *BRAF*-mutated metastatic melanoma.

Nevertheless, as we have seen, there are rather strong biological bases to validate the use of TBP strategies and this consideration suggests the need to also deepen on this subject in prospective trials. Additionally, even as cancer research progresses forward with new applications, TBP and LRA remain useful treatment options to offer to selected patients.

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Correspondence: Francesco Serra, Medical Oncology Unit – IRCCS Policlinico San Matteo, 19 Viale Golgi – 27100 Pavia, Italy.
Email: francesco.serra03@universitadipavia.it

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References

1. WHO – International Agency for Research on Cancer. Global Cancer Observatory 2020. https://gco.iarc.fr/. Accessed July 16, 2021.
2. Melanoma: Risk factors and Prevention – Cancer.net Editorial Board 2020. https://www.cancer.net/cancer-types/melanoma/risk-factors-and-prevention. Accessed July 16, 2021.
3. AIOM – Italian Association for Medical Oncology – Guidelines on Melanoma 2020. https://www.aiom.it/wp-content/uploads/2020/10/2020_LG_AIOM_Melanoma.pdf. Accessed July 16, 2021.

4. NCCN – National Comprehensive Cancer Network – Guidelines on Melanoma 2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed July 16, 2021.
5. Sandru A, Voinea S, Panaitescu E, Blidaru A. Survival rates of patients with metastatic malignant melanoma. *J Med Life*. 2014;7(4):572–576.
6. Ascierto PA, Kirkwood JM, Grob JJ, et al. The role of BRAF V600 mutation in melanoma. *J Transl Med*. 2012;10:85. http://doi.org/10.1186/1479-5876-10-85
7. Ny L, Hernberg M, Nyakas M, et al. BRAF mutational status as a prognostic marker for survival in malignant melanoma: a systematic review and meta-analysis. *Acta Oncol*. 2020;59(7):833–844. http://doi.org/10.1080/0284186X.2020.1747636
8. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med*. 2012;366(8):707–714. https://doi.org/10.1056/NEJMoa1112302
9. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358–365. https://doi.org/10.1016/S0140-6736(12)60868-X
10. Gençler B, Gönül M. Cutaneous side effects of BRAF inhibitors in advanced melanoma: review of the literature. *Dermatol Res Pract*. 2016;2016:5361569. https://doi.org/10.1155/2016/5361569
11. Long GV, Flaherty KT, Stroyakovskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. *Ann Oncol*. 2017;28(7):1631–1639. https://doi.org/10.1093/annonc/mdx176
12. Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. 2014;371(20):1867–1876. https://doi.org/10.1056/NEJMoa1408868
13. Grob JJ, Amonkar MM, Karaszewska B, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. *Lancet Oncol*. 2015;16(13):1389–1398. https://doi.org/10.1016/S1470-2045(15)00087-X
14. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603–615. https://doi.org/10.1016/S1470-2045(18)30142-6
15. Evans MS, Madhunapantula SV, Robertson GP, Drabick JJ. Current and future trials of targeted therapies in cutaneous melanoma. *Adv Exp Med Biol*. 2013;779:223–255. http://doi.org/10.1007/978-1-4614-6176-0_10
16. Sullivan, Atkins MB, Kirkwood JM, et al. An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: version 2.0. *J Immunother Cancer*. 2018;6(1):44. http://doi.org/10.1186/s40425-018-0362-6
17. Chan MM, Haydu LE, Menzies AM, et al. The nature and management of metastatic melanoma after progression on BRAF inhibitors: effects of extended BRAF inhibition. *Cancer*. 2014;120(20):3142–3153. https://doi.org/10.1002/cncr.28851
18. Spagnolo F, Ghiorzo P, Queirolo P. Overcoming resistance to BRAF inhibition in BRAF-mutated metastatic melanoma. *Oncotarget*. 2014;5(21):10206–10221. https://doi.org/10.18632/oncotarget.2602
19. Hassel JC, Buder-Bakhaya K, Bender C, et al. Progression patterns under BRAF inhibitor treatment and treatment beyond progression in patients with metastatic melanoma. *Cancer Med*. 2018;7(1):95–104. https://doi.org/10.1002/cam4.1267
20. Queirolo P, Spagnolo F, Picasso V, et al. Combined vemurafenib and fotemustine in patients with BRAF V600 melanoma progressing on vemurafenib. *Oncotarget*. 2018;9(15):12408–12417. https://doi.org/10.18632/oncotarget.10589
21. Scholtens A, Geukes Foppen MH, Blank CU, van Thienen JV, van Tinteren H, Haanen JB. Vemurafenib for BRAF V600 mutated advanced melanoma: results of treatment beyond progression. *Eur J Cancer*. 2015;51(5):642–652. https://doi.org/10.1016/j.ejca.2015.01.009
22. Tas F. Metastatic behavior in melanoma: timing, pattern, survival, and influencing factors. *J Oncol*. 2012;2012:647684. https://doi.org/10.1155/2012/647684
23. Dolinsek T, Prosen L, Cemazar M, Potocnik T, Sersa G. Electrochemotherapy with bleomycin is effective in BRAF mutated melanoma cells and interacts with BRAF inhibitors. *Radiol Oncol*. 2016;50(3):274–279. https://doi.org/10.1515/raon-2016-0042
24. Valpione S, Campana LG, Pigozzo J, Chiarion-Sileni V. Consolidation electrochemotherapy with bleomycin in metastatic melanoma during treatment with dabrafenib. *Radiol Oncol*. 2015;49(1):71–74. https://doi.org/10.2478/raon-2014-0035
25. Tawbi HA, Boutros C, Kok D, Robert C, McArthur G. New era in the management of melanoma brain metastases. *Am Soc Clin Oncol Educ Book*. 2018;38:741–750. https://doi.org/10.1200/EDBK_200819
26. Bong CY, Smithers BM, Chua TC. Pulmonary metastasectomy in the era of targeted therapy and immunotherapy. *J Thorac Dis*. 2020. https://doi.org/10.21037/jtd.2020.03.120
27. Domingues B, Lopes JM, Soares P, Pópulo H. Melanoma treatment in review. *Immunotargets Ther*. 2018;7:35–49. https://doi.org/10.2147/ITT.S134842

28. Tanda ET, Vanni I, Boutros A, et al. Current state of target treatment in BRAF mutated melanoma. *Front Mol Biosci*. 2020;7:154. https://doi.org/10.3389/fmolb.2020.00154
29. Kreft S, Gesierich A, Eigentler T, et al. Efficacy of PD-1–based immunotherapy after radiologic progression on targeted therapy in stage IV melanoma. *Eur J Cancer*. 2019;116:207–215. https://doi.org/10.1016/j.ejca.2019.05.015
30. Long G, Lebbe C, Atkinson V, et al. The anti–PD-1 antibody spartalizumab (S) in combination with dabrafenib (D) and trametinib (T) in previously untreated patients (pts) with advanced BRAF V600–mutant melanoma: updated efficacy and safety from parts 1 and 2 of COMBI-i. *J Clin Oncol*. 2019;15:9531. https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.9531
31. Ascierto PA, Mandala M, Ferrucci PF, et al. First report of efficacy and safety from the phase II study SECOMBIT (SEquential COMBo Immuno and Targeted therapy study). *Ann Oncol*. 2020;31:S1173–S1174. https://doi.org/10.1016/j.annonc.2020.08.2275