REVIEW ARTICLE

Effect of Age on Melanoma Risk, Prognosis and Treatment Response

Simone RIBERO[1], Luigia S. STUCCI[2], Elena MARRA[1], Riccardo MARCONCINI[3], Francesco SPAGNOLO[4], Laura ORGIANO[5], Virginia PICASSO[4], Paola QUEIROLO[4], Guiseppe PALMIERI[6], Pietro QUAGLINO[1#] and Veronique BATAILLE[6#]; for the Italian Melanoma Intergroup (IMI)

[1]Department of Medical Sciences, Section of Dermatology, University of Turin, Turin, [2]Medical Oncology Unit, Department of Biomedical Sciences and Clinical Oncology, University of Bari, Bari, [3]Unit of Medical Oncology 2, Azienda Ospedaliera-Universitaria Pisana; Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, [4]Department of Medical Oncology, IRCCS AOU San Martino – Istituto Nazionale per la Ricerca sul Cancro, Genova, [5]AOU Cagliari, Department of Medical Oncology, University of Cagliari, Cagliari, [6]Unit of Cancer Genetics, Institute of Biomolecular Chemistry (ICB), National Research Council (CNR), Sassari, Italy, and [7]Department of Twin Research and Genetic Epidemiology, King's College London, London, UK

[#]These authors share senior authorship.

As for all types of cancer, the incidence of melanoma increases with age. However, naevus counts (the principal risk factor for melanoma) decrease with age; hence the relationship between ageing and melanoma is complex. Subjects who maintain a high naevus count after the age of 50 years are more likely to be affected by melanoma, as their lesions do not senesce. Longer telomere length, which is strongly related to age, is linked to high naevus counts/melanoma risk; thus melanoma biology is influenced by factors that slow down ageing. Age is also an important prognostic factor in melanoma. Increasing age leads to worse survival in stages I, II and III. Sentinel lymph node (SLN) status, which is a strong predictor of melanoma survival, is also affected by age, as SLN positivity decreases with age. However, the prognostic value of SLN on survival increases with age, so, again, these relationships are complex. In patients with stage IV melanoma, age impacts on survival because it affects responses to treatment. This review examines the effects of age on melanoma risk, prognostic factors and responses to treatment.

Key words: age; ageing; sentinel lymph node; prognosis; therapy.

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Corr: Simone Ribero, Department of Medical Sciences, Section of Dermatology, University of Turin, IT-10126 Turin, Italy. E-mail: simone.ribero@unito.it

The articles forming the basis of this review were collected by searching MEDLINE, Scopus and the Cochrane Library from 1 January 1980 to 1 June 2017, using the following keywords: "naevi", "naevus count", "melanoma", "ageing", "age", "senescence", "follow-up", "survival", "prognosis" and "treatment". The most significant publications were included in the study and discussed. Article titles and abstracts were used for initial screening, followed by a review of the full text. Only original manuscripts in English language were included. Searches were supplemented by scanning the bibliographies of included articles for further relevant articles.

SIGNIFICANCE

Melanoma incidence and mortality like all cancers increase with age. However, the association between age and both melanoma risk and prognostic factors is complex. Naevi undergo a significant senescence with age and yet melanoma incidence increases with age.

Sentinel node biopsy is an important prognostic factor in melanoma, yet sentinel node positivity is higher in younger age groups despite their better prognosis. Telomere biology and delayed ageing are tightly linked to melanoma susceptibility. BRAF positivity is also associated with age and naevus counts. Age should be taken into account when interpreting sentinel node biopsy results but also when planning immunotherapy and targeted therapy treatments.

AGEING

Ageing represents the accumulation of changes in human beings over time, encompassing physical, psychological, and social changes. Ageing is among the greatest known risk factors for most human diseases (1) and is one of the most important risk factors for cancer. After many replications our cells have an increased chance of somatic mutations, which may lead to uncontrolled growth. Due to an inherent end-replication process, chromosomes are exposed to a potential loss of genetic material and telomeres act as a buffer against loss of chromatin. Telomeres are repeated TTAGGG sequences at the end of linear chromosomes, which guard against this loss of genetic material during cellular replication. Repeated cell cycles eventually lead to a critically shortened telomere length, which signals cellular senescence to trigger apoptosis. This arrested proliferation is thought to protect against malignant transformation, and a failure in this protective mechanism can result in genomic instability and carcinogenesis. Telomere length therefore shortens with age (2). The rate of biological ageing in humans varies greatly and this can be estimated, in part, by assessing telomere shrinkage with age. Longer telomeres have been linked with higher naevus counts and melanoma risk, and genes that influence telomere length have been linked with melanoma risk via genome-wide association

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studies (GWAS). In the clinical setting, it is apparent that melanoma patients often appear younger than their chronological age and it is likely that identifying the gap between chronological age and biological age will shed some light on melanoma risk, but may also explain differences regarding responses to treatment.

Ageing, naevi and melanoma risk

Number of naevi is a reliable phenotypic marker of ageing. Naevi typically involute after the fourth decade of life in Caucasian populations and are rare in elderly people. This process is likely to be, in part, genetically driven. However, the rate at which naevi disappear with age varies greatly, with some individuals still having large numbers of naevi in late middle-age. This suggests that reduced senescence in the melanocytic system may be a good predictor of melanoma risk. Oncogene (*BRAF* and *RAS*) and tumour suppressor (p16, p14arf, p53, PTEN, Rb) driven cell senescence is important in melanocytes. PTEN depletion and the pI3K pathway are also thought to be important in inhibiting *BRAF*-induced senescence in naevi (3). Longer telomere length is another important genetic marker of reduced senescence, as both naevi count and melanoma are associated with longer telomeres (4). This suggests that individuals with a large of number of naevi may have reduced senescence and increased longevity (5–7). In 2011, melanoma case control studies replicated these findings in melanoma (8, 9). More recently, germline amplifications of the TERT promoter have been reported in rare melanoma families and this has been replicated at the somatic level in many melanoma tumours (10, 11). *POT1*, another gene controlling telomere length has also been linked with melanoma (12). Several single-nucleotide polymorphisms (SNPs) affect telomere length, and many of these SNPs have been associated with melanoma risk, supporting the role of ageing in melanoma. Longevity may therefore be a trade-off for increased melanoma risk, as many patients with melanoma survive their disease, highlighting the fine balance between ageing and cancer (13).

Age and stage I and II melanoma

It is well established that the mortality rate from melanoma increases with age (14). Although this might be attributed to thicker and ulcerated melanomas in older patients, age has been noted to be an independent adverse prognostic indicator of overall survival (OS) (15, 16). Number of naevi is considered a good marker of ageing. While naevus count is a robust risk factor for melanoma, high naevus count, in turn, is associated with improved survival (17). Melanoma cases with a high naevus count showed a reduction of 57% in melanoma-specific mortality (hazard ratio (HR) = 0.43, 95% CI 0.21–0.89). The improved survival in melanoma cases with high naevus counts suggests that the genetic determinants of naevi number may be associated with biological differences in melanoma tumours. Breslow thickness increases with age as well as ulceration rate, possibly due to late diagnosis in older patients. However, it is possible that, with age, a less efficient immune system leads to more aggressive tumours.

Age and sentinel lymph node status

Since the introduction of sentinel lymph node (SLN) biopsy in melanoma by Morton et al. (18) in the early 1990s, the early identification of regional node metastases has been considered the most important prognostic factor for patients with melanoma. Originally, SLN was not offered to patients over 75 years of age, as it was considered that the morbidity was too great in these age groups, especially in the light of a lack of therapeutic benefit. With increasing life expectancy and with experience showing the ability of SLN biopsy to stratify patients in different risk categories (thus permitting the enrolment in trials on adjuvant treatments), many centres are now offering SLN biopsy in elderly patients. SLN has been reported to be a safe procedure in older age (19) and morbidity is quite limited (20).

SLN status has been described as a prognostic feature, but its role in predicting survival changes significantly according to the age of the patient. Many studies have previously reported the paradox of decreased SLN positivity with age, whilst there is increased mortality in elderly subjects for the same Breslow thickness (21, 22). Despite this, no clear biologic explanation has been given for this observation so far. Although age is known to be an important predictor of outcome in melanoma, it has not been included in the current staging system for melanoma, which was most recently revised by the American Joint Committee on Cancer (AJCC). The reason why SLN may be more likely to be positive in younger patients may be because melanocytes are less senescent and more likely to travel to the sentinel node. However, whilst settled in the sentinel node, it is likely that a younger immune system will be more effective at containing the tumour there (23–25). Conversely, in older patients, melanocytes may be less likely to reach the sentinel node, but, when they do, they may not be successfully controlled by the immune system locally.

How to plan a follow-up adapted to age

The main aim of follow-ups in patients with melanoma is the earliest detection of recurrent disease, the diagnosis of secondary skin cancers and their prevention, through the adoption of healthy lifestyles. Currently there is no scientific evidence that follow-ups improve clinical outcomes for patients with melanoma. In patients with early-stage tumours, the optimal duration of follow-up has not been standardized. Relapse of disease occurs

most commonly in the first 5 years after diagnosis, mostly within the first 2 years. Most of these are detected by the patient and not by their physician. The risk of developing a second melanoma in a subject is approximately 4–8%, so follow-ups at least offer some screening for these subsequent tumours.

Individual follow-ups are acceptable according to the presence of several risk factors, such as age, family history of melanoma and other cancers, the presence of multiple dysplastic naevi and skin type. It is also important to educate patients about skin self-examination and the main lymph node drainage areas. This is particularly important, since early surgical treatment of individual metastases, especially if they are found in lymph nodes, lung, spleen or subcutaneous tissue, has a very favourable effect on both quality of life and life expectancy.

Among studies that have evaluated the best timing of follow-up, the study of the Australian group compared 2 different follow-up schedules: the first included a skin check every 6 months for 5 years and then a yearly check for a further 5 years in patients with stage I; for patients with stage II, a check every 3 months to 5 years and then yearly for an additional 5 years. The second proposed schedule was an annual check for 10 years in patients with stage I, a check every 6 months for 2 years and then annually for a further 8 years in patients with stage IIA, and every 4 months for 2 years, every 6 months the third year and then annually for a further 7 years in patients with stage IIB–IIC. The more intensive follow-up made it possible to detect 44 recurrences and 10 new primary melanomas 2 months earlier compared with the less intensive follow-up (26). More recently, a paper by Tas & Erturk (27) showed that nearly one-third of 332 patients enrolled, all of them initially diagnosed with non-metastatic melanoma, developed recurrence during the disease course and/or follow-up. They were divided into 3 groups according to the pattern of disease spread: (*i*) locoregional relapse alone (including regional lymph node metastases, distant skin, subcutaneous, and satellite/in-transit metastases); (*ii*) mixed relapse (locoregional relapse and distant metastases); and (*iii*) distant metastases alone. The median time of recurrences was 16.5 months: locoregional relapse alone was most frequently associated with earlier stage melanomas, whilst distant metastases alone were mostly observed with stage III and axial melanoma, or in patients with higher serum lactate dehydrogenase concentration. Nearly two-thirds of the relapse occurred within the first 2 years from diagnosis. Even though no association was found between the time of recurrence and the site of relapse sites, a significant survival advantage was observed in locoregional relapse alone compared with other relapse patterns ($p < 0.0001$). This is why follow-ups can make a difference when patients can be detected at the time of loco-regional relapse.

Age and stage IV melanoma

Impact of age on immunotherapies. Immune checkpoint inhibitors (antiCTLA4, antiPD1) have radically changed the prognosis of melanoma patients, leading to an increasing number of patients with long-term survival for stage 3 and 4. These drugs remove the inhibitory immunomodulatory signals from the tumour, enhancing T-lymphocyte activity against melanoma cells. There are age-associated impairments of the immune system, called the "immunosenescence" phenomenon (28, 29), which could affect the efficacy and/or toxicity of the immune checkpoint blockade. In fact, with ageing, the expression patterns of T-cell co-stimulatory or co-inhibitory proteins change considerably: the expression of inhibitory receptors, such as PD-1 or LAG-3, is enhanced, associated with a decrease in co-stimulatory molecules. Therefore, data on the impact of age on the efficacy and safety of these drugs are challenging. The first therapeutic agent approved by the FDA for metastatic melanoma was ipilimumab, a fully humanized monoclonal antibody directed against CTLA-4. In the phase 3 pivotal trial, 676 patients were randomized 3.1:1 to receive ipilimumab 3 mg/kg, ipilimumab plus gp100 peptide vaccine, or gp100 vaccine alone. Among these 676 patients on this trial, 196 (29%) were aged over 65 years. Analyses of OS in these subgroups showed, however, that the effects of ipilimumab were independent of age. For the whole cohort, the median OS was 10.0 months among patients receiving ipilimumab plus gp100, compared with 6.4 months among patients receiving gp100 alone (HR for death 0.68; $p < 0.001$). The median OS with ipilimumab alone was 10.1 months (HR for death in the comparison with gp100 alone 0.66; $p = 0.003$). In the elderly population, a 31% reduction in the risk of death was noted with ipilimumab plus gp100, compared with gp100 alone (HR 0.69 (0.47–1.01)), and a 39% reduction in risk of death was seen with ipilimumab alone compared with gp100 alone (HR 0.61 (0.38–0.99)).

The use of ipilimumab in older patients in a clinical setting is described in a retrospective trial conducted in Italy (30). This study assessed the efficacy and safety of ipilimumab at its approved dose of 3 mg/kg in elderly patients within an expanded access programme. Data were collected from 193 patients over 70 years of age who treated with ipilimumab 3 mg/kg. Twenty-seven patients were aged over 80 years. There was no difference in median OS between ≥70 years (8.9 months (95% CI 7.2–10.6)) and <70 years (7.0 months (95% CI 6.1–7.9)); $p = 0.17$. The immune-related disease control rate (irDCR) was 38%, with 2% of irCR (complete response), 13% with irPR (partial response) and 23% with irSD (stable disease). The median duration of irDC was 11.5 months (95% CI 9.3–13.7).

Major data on the use of CTLA4 or anti PD1 in an elderly population were available from a review by

Friedman and colleagues, reviewing all patients aged 80 years and older at the Memorial Sloan Kettering Cancer Center treated with immune checkpoint blockade (anti-CTLA4 or anti-PD1) for stage 3 or 4 unresected melanoma between January 2008 and December 2015. All patients had at least one infusion visit and one follow-up visit, and 12 patients in the ipilimumab group received subsequent anti-PD-1 therapy and were included in the toxicity analyses for both agents. Patients aged 80 years and older treated with ipilimumab had durable survival at a rate similar to that of the overall population. An immunrelated adverse events (irAE) occurred in 88% of the 74 patients in the ipilimumab group, and 30% experienced a grade 3 or 4 irAE. The most common high-grade irAEs in this group were diarrhoea, transaminitis and rashes. Of the 25 patients receiving pembrolizumab or nivolumab, 84% experienced an irAE, and 16% experienced a grade 3 event. The most common adverse events in this group were pruritus, rash, fatigue, and musculoskeletal complaints, and one case each of grade 3 of elevated lipase, diarrhoea, anaemia, and nausea occurred. Of the 8 patients who received combination ipilimumab/nivolumab, 88% experienced any irAE and 63% experienced a high-grade 3 or 4 irAE. The most common high-grade irAEs in this group were elevated lipase, diarrhoea and transaminitis, occurring in 38%, 25% and 25% of patients, respectively. No deaths occurred in any of the groups (31).

Data from the Italian expanded access programme for ipilimumab reported that patients over 70 years of age presented irAE with a similar frequency to that of the overall population (26). Also, the anti-PD-1, nivolumab seems to have the same toxicity profile in an elderly population as in younger population.

A more recent retrospective analysis compared irAEs in melanoma patients <65 years of age with those in patients >65 years of age treated with nivolumab (26). This study showed no statistically significant differences in incidence of irAEs, and the irAE profile was similar in the 2 groups. Thus, despite speculation about the specificities of older adult immunity, the current safety data appears to be similar to the population at large.

Impact of age on targeted therapy

There is an inverse relationship between *BRAF* mutation prevalence and age (32). Menzies and colleagues conducted investigated *BRAF* mutation status by age-decade: *BRAF*-mutant metastatic melanoma was associated with significantly younger age at diagnosis of first distant metastasis compared with *BRAF* wild-type melanoma (mean, 53.9 vs. 62.7 years) (32). All patients younger than 30 years had *BRAF*-mutant metastatic melanoma, compared with only 25% of patients older than 70 years. An association between age and *BRAF*-mutant genotype was also observed, with the frequency of non-V600E genotypes (including V600K) increasing with older age: less than 20% of *BRAF*-mutant patients under 50 years of age were non-V600E, compared with more than 40% of patients over 70 years of age (32).

The identification of an age-specific prevalence does not obviate the need for *BRAF* mutation testing in patients with metastatic melanoma, but this information may assist clinical judgment, planning and pre-test counselling.

In terms of side-effects of targeted therapy, elderly patients are well represented in targeted therapy clinical trials for metastatic melanoma (33–37). However, elderly patients may be more likely to have severe adverse events. In the safety study of vemurafenib, more than 3,000 patients received at least one dose of vemurafenib and 257 patients were over 75 years of age (38). Severe adverse events (grades 3 and 4) and adverse events leading to discontinuation were reported more frequently in patients aged 75 years and older than in those younger than 75 years (38). The adverse events were predominantly cutaneous squamous cell carcinomas, keratoacanthomas and QTc prolongation. Skin side-effects are a possible consequence of a greater susceptibility to non-melanoma skin cancers due to long-term sun damage in elderly subjects and coexistent cardiac comorbidity in case of QTc prolongation. No significant differences were noted, however, in terms of PFS (5.6 months in patients under 75 years vs. 5.5 months in ≥ 75 years) and OS (12.5 vs. 9.8 months) (38).

Recently, 3 randomized phase III trials demonstrated the superiority of combined BRAF and MEK inhibition over treatment with single-agent BRAF inhibitors, and BRAF plus MEK-targeted drugs are the new standard of care for BRAF-mutant advanced melanoma (39). Despite the lack of specifically designed trials, subgroup analyses of existing phase 3 trials suggest that the use of BRAF/MEK inhibitors seem to be as effective in elderly patients as in younger ones. In an exploratory analysis of clinical characteristics that may predict response to vemurafenib and cobimetinib (Co-BRIM trial), older age was not identified as a negative predictor for response: on the contrary, more complete responses were noted in patients aged >65 years compared with younger patients (28% vs. 13%) (40).

In everyday clinical practice, current data suggest that BRAF/MEK inhibitors can be safely and effectively used in elderly patients and prescribing information recommends no special dose adjustment for BRAF and MEK inhibitors in this subgroup of patients.

Impact of age on chemotherapy and radiotherapy

Therapeutic options for melanoma patients, both young and old, were limited until the most recent 5–7 years, during which period innovative drugs, including targeted agents and immune drugs, became available (41). Over recent years, older patients with metastatic melanoma,

who were previously not eligible for treatment because of concerns about toxicity and existing comorbidities, have been able to receive a variety of active immune and targeted therapies. Several chemotherapies have reported limited activity in advanced melanoma, including dacarbazine, nitrosoureas, temozolomide, carboplatin and taxanes (42). The response rates to chemotherapy are similar in younger and older patients, both in terms of progression-free survival and OS. However, in old age, more deaths were observed due to comorbidity (43). The use of polychemotherapy in elderly patients is contra-indicated because of toxicity and comorbidities. Deterioration in renal and hepatic function, as well as cardiomyopathy, requires dose adjustment. Thus, organ toxicities must not be overlooked in elderly patients (44, 45). Despite the different kinetic profiles of chemotherapy, their efficacy is not age dependent. These concerns, however, are becoming uncommon, as chemotherapy has now been abandoned in most melanoma centres.

Although melanoma was historically considered a radio-resistant tumour, radiation therapy remains a useful treatment option for patients with melanoma in some settings (46). It can provide effective palliation for patients who develop unresectable, locally recurrent, or symptomatic metastatic disease, such as bone pain, epidural spinal cord compression, or central nervous system symptoms. Radiotherapy, as well as chemotherapy, can impact on the bone marrow reservoir in older patients. Elderly subjects can develop myelosuppression, particularly if the patient is in a state of malnutrition. The use of colony-stimulating factors, such as G-CSF and recombinant erythropoietin, for the treatment of febrile neutropaenia and anaemia, respectively, may be required more often in elderly patients. Moreover, age-related T-cell down-regulation and immunosenescence may explain the increased susceptibility to infections with ageing. Therefore, despite similar efficacy of chemotherapy and radiotherapy in elderly patients, the evaluation of benefits with clinical outcome, adverse effects and impact on quality of life must be evaluated carefully.

CONCLUSION

Age has an impact on melanoma risk factors as well as prognosis, SLN positivity and *BRAF* mutations. Age is also important when offering treatment options. Although immunotherapies and targeted therapies give similar responses in elderly patients, as well as comparable toxicity, albeit more non-melanoma skin cancers with targeted therapies, the impact of melanoma drugs in terms of frequent visits to hospital for regular infusions and imaging as well as toxicity needs to be assessed carefully, especially for elderly patients who have very little social support.

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