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Reports written by

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Dear colleagues, I'm very pleased to be reporting to you again this year with summaries from the EADO Congress, which is being held in-person (at long last!) in Seville. This is the first international oncodermatology conference to be held in-person since the pandemic, and it's really a wonderful feeling.

Updates to our knowledge of cutaneous risks in organ transplant patients, by the "SCOPE" network (Skin Care in Organ-transplant Patients)

The conference started on 21/04 with an update to our knowledge of cutaneous risks in organ transplant patients by the "SCOPE" network (Skin Care in Organ-transplant Patients), a group of European dermatologists founded over 20 years ago to optimise dermatological care for the specific needs of transplant patients.
More information on their website: https://www.scopenetwork.org/

The incidence of squamous cell carcinomas of the skin is still greatly increased among transplanted patients

Although the first kidney transplant was performed in Boston in 1954, the increased risk of skin cancers was first described only in 1973, and remains unresolved to this day. In this context, Alessandra HANDISURYA reminded us that the incidence of squamous cell carcinomas of the skin is still greatly increased among transplanted patients (65 to 100 times greater than in the general population). There are a number of these carcinomas, which are subject to relatively rapid and painful growth, and often in connection with an **HPV (human papillomavirus) co-infection**. Beta-HPV DNA is detectable in 80% of squamous cell carcinomas in transplant patients, vs. 40% of "traditional" squamous cell carcinomas of the skin. HPV allows keratinocytes to survive after genotoxic exposure. In fact, beta-HPV seropositivity at the time of the transplant even tends to predict the later occurrence of squamous cell carcinomas ($p=0.043$). HPV is also responsible for the higher incidence of skin warts, orogenital papillomas/condylomas, and even genital neoplasms in this population.
In the example of a transgenic mouse expressing beta-HPV8 in its epidermis, an increase in skin papillomas and squamous cell carcinomas was observed under UV exposure (Uberoi A. et al., PLOS pathog 2016), particularly in case of immunodepression (Dorfer S. et al., Am J Transplant 2021).

Interestingly, HPV seems to play a facilitating role in triggering the carcinoma, but is not required to maintain its later development. **This raises the question of whether a preventative HPV vaccine should be given to all organ transplant patients, even post-adolescence** (clinical trials in progress).

The role of sun exposure in the occurrence of squamous cell carcinomas in transplant patients

Alexandra Geusau then discussed the role of sun exposure in the occurrence of squamous cell carcinomas in transplant patients, particularly with regard to intentional exposure of the entire body during recreational activities (beach, etc.). The increased risk is particularly notable in light phototypes, especially in patients with certain variants of the *MC1R* gene who have blue or green eyes or actinic keratoses. The Skin Ageing score (with its intrinsic and extrinsic components) can be used to calculate the TSA score (Total Skin Ageing score) to more precisely determine individual risk.

Questioned the definitive theoretical contraindication of kidney transplants in patients with a history of cancer

Nephrologist Bruno Watschinger questioned the definitive theoretical contraindication of kidney transplants in patients with a history of cancer (including skin cancer). He criticised decisions based solely on the SIR (standardised incidence ratio, Benoni et al, Transplant Int 2020). To be sure, many cancer SIRs are higher in kidney transplant patients than in the general population (squamous cell carcinomas of the skin; lips, etc.). But Dr Watschinger argues that in this population, the SIR **should be interpreted in comparison to the population of dialysis patients, since dialysis is still the only alternative to a kidney transplant**. He notes that in dialysis patients, there is a 4x higher risk of kidney cancer, but also a 9x higher risk of Kaposi's sarcoma, a 2x higher risk of melanoma, etc. In practice, there is a 10% risk of all types of cancer combined over 5 years of dialysis, and a mortality risk of 5% per year, notably due to extreme cardiovascular risk, which is much lower in transplant patients (although the latter is of course a selected population). This explains the current tendency to reduce the theoretical contraindication of kidney transplants in patients with a history of cancer in remission. For example, a history of melanoma in situ should no longer be considered a formal contraindication. For invasive melanomas, decisions can be discussed on a case-by-case basis.

PTLDs: post-transplant lymphoproliferative disorders

Deniz Seckin was the 4th speaker of the day. She talked about PTLDs: post-transplant lymphoproliferative disorders (1 to 2% of kidney transplant patients). PTLD is often linked to an EBV infection subsequent to the transplant, and primarily affects men (77%) around the age of 58. Certain PTLDs have a cutaneous presentation, more commonly secondary than primary, but they must be **understood as an entity** that can present in the form of anaplastic large cell lymphoma or mycosis fongoides, and particularly aggressively in the context of a transplant. **The majority of primary skin PTLDs have their origin in T lymphocytes** (69%), while the remaining cases derive from B lymphocytes (31%, associated with EBV in 91%, with a relatively better prognosis). The speaker expressed her disappointment that this entity is often forgotten in classifications of cutaneous lymphomas.

Skin complications in transplant patients "of colour" (phototypes IV to VI)

Catherine A. Harwood discussed the topic of skin complications in transplant patients "of colour" (phototypes IV to VI), who represent 2/3 of transplant candidates in London where her practice is located. Unsurprisingly, carcinomas and melanomas of the skin are much rarer in these populations than in transplant patients with light phototypes. The only case of metastatic melanoma that she has reported for a patient with a dark phototype was actually a case transmitted by the organ donor. However, transplant patients with dark phototypes are still subject to **induced HPV neoplasms, which requires careful clinical attentiveness to the anogenital region** by the dermatologist.

Kaposi's sarcomas particularly affect people with sub-Saharan African origins, due to the high endemic prevalence of HHV8.
Finally, sun avoidance combined with a dark phototype tends to produce **vitamin D deficiencies**, which practitioners should look out for and supplement if needed.

30-year retrospective on dermatology with organ transplant patients

The final speaker in the session on transplant patients, Jan Nico Bouwes Bavinck, presented his **30-year retrospective on dermatology with organ transplant patients** in Leiden. He was involved in demonstrating **the clinical interest of acitretin**, which slowed the appearance of squamous cell carcinomas at a dose of 30mg/day in a double-blind study vs. placebo (JN Bavinck et al., JCO 1995). Today, he recommends **starting at 10mg/day, and limiting the dose to a maximum of 20mg/day**, due to side effects such as dry lips and hair loss. **The clinical value of sirolimus** after excision of a squamous cell carcinoma was described in JCO 2013, but this immunosuppressive treatment is relatively poorly tolerated and its utility is debatable beyond 2 years post-excision.

Prevention is key, as we were reminded by Dr Nageli, with his case of a lung transplant patient suffering from a metastatic squamous cell carcinoma (primary site was the lip, high mutational load), who died due to transplant rejection while taking PD-1 inhibitors (cemiplimab), despite a complete remission of the carcinoma.

Dermoscopy of non-pigmented lesions

The first plenary session of the conference was dedicated to dermoscopy of non-pigmented lesions, presented by Prof. Aimilios Lallas. In contrast to pigmented lesions, dermoscopy of non-pigmented lesions is more commonly used to decide whether or not a biopsy/excision is indicated, rather than to produce a precise diagnosis of the lesion. Although it has been shown that dermoscopy significantly improves dermatologists' ability to diagnose non-pigmented lesions, this diagnosis was still incorrect in 2/3 of cases in a study that appeared in the Blue Journal a few years back.

Prof. Aimilios Lallas described the **two different algorithms to use in cases of non-pigmented lesions**: the first for raised ("nodular") lesions, and the second for flat lesions.

For raised ("nodular") lesions:

First, check for the presence of **"lacunae"** (rounded vascular structures).
If they are present, with no other visible vessels besides the lacunae, this is an angioma – no biopsy necessary.
If they are not present, the second sign to look for is **comma vessels**. The presence of these vessels confirms the diagnosis of a dermal naevus, a lesion that tends to lose its pigmentation with age.
If neither lacunae or comma vessels are present, check for the presence of **white clod linear vessels** at the periphery to make a diagnosis of sebaceous hyperplasia.
If none of the above are present, but **milial brain-like hairpin** vessels are identified, the lesion is seborrhoeic keratosis.
In the absence of all of the signs mentioned above, histology is recommended.

For flat lesions:

If ulceration is present: branched linear vessels point to a superficial basal cell carcinoma. Absence of these vessels should be cause for a biopsy (SCC? BCC? melanoma?).
If no ulceration: glomerular, helical or short linear vessels suggest Bowen's disease, while anything else should be cause for a biopsy (Spitz, lichenoid keratosis, achromic melanoma, …). Shiny white perpendicular lines known as "chrysalis" structures, visible under polarised light, point to a melanoma.

New developments in European recommendations for the treatment of skin carcinomas

Basal cell carcinomas: the effectiveness of cemiplimab in patients with resistance to Hedgehog pathway inhibitors

Ketty Peris presented the most important new development of the year for basal cell carcinomas: the effectiveness of cemiplimab in patients with resistance to Hedgehog pathway inhibitors.
Recall that inoperable basal cell carcinomas (locally advanced or metastatic) can be effectively treated with a Hedgehog pathway inhibitor like sonidegib 200mg/day or vismodegib 150mg/day, with better tolerance likely for sonidegib (to be confirmed by a comparative prospective study). In cases of primary or secondary resistance to these targeted therapies, 350mg cemiplimab intravenously every three weeks has recently been shown to be potentially effective, and is already available in certain European countries (Stratigos AJ et al., Lancet Oncology 2021).

Latest news on squamous cell carcinoma (SCC)

Next, Alex Stratigos presented the latest news on squamous cell carcinoma (SCC).
It appears that in addition to the well-accepted distinction between SCCs at low risk vs. high risk of recurrence, it may be useful to distinguish a new class of **very high-risk SCCs: >4cm in diameter**, thickness >6mm, extends beyond the hypodermis, even to the bone, with in-transit metastasis and/or perineural invasion. For these SCCs, the surgical margins should be wider (10mm minimum), imaging is indispensable (ultrasound), and adjuvant radiotherapy is recommended for any form of perineural invasion or in case of multiple risk factors.
There is still no evidence that sentinel lymph node biopsy is useful here, even though U.S. recommendations suggest it for very high-risk SCCs.
At the inoperable metastatic or locally advanced stage, the preferred treatment is still immunotherapy via PD-1 inhibitors (cemiplimab 350mg/3 weeks or pembrolizumab 200mg/3 weeks), and if that fails, chemotherapy and/ or cetuximab.
Future advancements will likely relate to adjuvant or neoadjuvant immunotherapy for squamous cell carcinomas, with clinical trials currently under way (cemiplimab, pembrolizumab).

The new EADO recommendations for Merkel cell carcinoma

Marie-Léa Gauci then reported on the new EADO recommendations for Merkel cell carcinoma, based on the consensus meeting of 13 July 2021:
The recommended margin is now 1cm (previously 2) to facilitate rapid execution of adjuvant radiotherapy, which must be started within 8 weeks after surgery.
A sentinel lymph node biopsy must be proposed for all Merkel cell carcinomas, regardless of the size, and in case of a positive result, adjuvant lymph node radiotherapy must be carried out.
At the inoperable stage, avelumab is still the preferred treatment in Europe, then chemotherapy, but preferably inclusion in a clinical trial if possible. Radiotherapy is of interest for palliative purposes as well.
Data suggesting efficacy of avelumab in transplant patients is sparse, from clinical cases only, but in cases of blood disorders that cause immunodepression as with SCCs, good responses have been seen.

Updated the 2015 recommendations for DFSP (Darier-Ferrand dermatofibrosarcoma)

Philippe Saïag then updated the 2015 recommendations for DFSP (Darier-Ferrand dermatofibrosarcoma).
Very frequent fusion of COL1A1 and PDGFbeta, CD34+ (breast: col6a3 PDGFdelta)

Treatment should favour excision of the deep fascia, with lateral margins of 1 to 1.3cm in 3D or Mohs surgery (or 3cm if Mohs is not possible), with CD34 marking in IHC on the excised tissue.
Due to very frequent fusion of COL1A1 with PDGFbeta (or COL6A3 with PDGFdelta), imatinib can be effective even at a dose of 400mg/day, which is well-tolerated with the same efficacy as 800mg. It is also sometimes an interesting option in a neoadjuvant role. Response rate 55.2%, complete response 5.2%.
Monitoring should be every six months for 5 years, then annual.

News on Kaposi's sarcoma

Finally, Céleste Lebbé presented news on Kaposi's sarcoma. Beyond the recommendations that she published in 2019 (Lebbé et al., European Journal of Cancer 2019), depending on the various types of Kaposi's sarcomas, she reminded the audience that the best treatment for localised symptomatic forms is still **radiotherapy**. If involvement is too diffuse, the first line of systemic treatment is still chemotherapy: pegylated liposomal doxorubicin and paclitaxel, 50% to 70% response rate.
However, a new treatment has recently been approved in the U.S. for Kaposi's sarcoma: **pomalidomide**, with a 71% response rate. This is the same response rate as the 71% figure described in cases of immunotherapy for **pembrolizumab** (Delyon J et al., Lancet Oncology 2022).

That's all for day one. Until the conference continues tomorrow, let me inform you – since I wasn't aware of this myself – that EADO membership is free. This is isn't mentioned very often, so if you have a strong interest in oncodermatology (which seems likely if you've read this far!): https://www.eado.org/about-eado/join-eado/11.

Dear friends,
To start the second day of the EADO conference, I decided to attend the selected oral presentations about melanoma treatment.

Melanoma diagnosis & treatment

Amit Roshan reported the results of his study of 925 patients, showing the **absence of any significant difference in the 5-year prognosis when injecting of the Tc-99m nanocolloid tracer the day before vs the day of adenectomy of the sentinel lymph node**. This is good news, because his hypothesis was that increasing the time between the injection and the surgery might increase the likelihood of false negatives via migration of the tracer into a lymph node near the actual sentinel. Whether the tracer is injected the day before or the day of surgery, the sentinel lymph node was positive in 1 out of 5 cases.

Terouz Pasha from Cambridge compared the predictive value of this sentinel lymph node technique in melanomas of the head and neck (complex lymphatic network) vs melanomas of the trunk and limbs (simpler lymphatic network).
Of the 1080 patients included in the study, with a median age of 59.8 years, the results show **3 times as many false negatives among the 147 patients with melanomas of the head and neck**. This risk of false reassurance should be kept in mind for this population in particular.

Next, Christina Mangas talked about side effects of immunotherapy, including a success story of treatment with **omalizumab**, a monoclonal antibody targeting IgE, for an immuno-induced bullous pemphigoid which was resistant to corticosteroid therapy and methotrexate.

This targeted treatment could also be useful in cases of hypereosinophilic syndrome resulting from immunotherapy.

Lukas Kraehenbuehl presented his retrospective study on patients who had developed an **autoimmune bullous dermatosis following immunotherapy** between 2005 and 2021 at the Memorial Sloan Kettering Cancer Center.
Among these bullous dermatoses, he distinguishes 4 entities:
- **bullous pemphigoid** with characteristic direct immunofluorescence (DIF) or presence of anti BP180/230 antibodies (n=36)
- **bullous lichen planus** with lichenoid histology but negative DIF and autoantibodies (n=8)
- **pemphigoid lichen planus** with lichenoid histology and DIF or presence of anti BP180/230 antibodies (n=5)
- **overlapping autoimmune bullous dermatosis** with presence of anti BP180/230 and DSG1/DSG3 antibodies (n=7)
His multiplex immunohistochemistry technique identified increased CD8+ immune infiltration in lichenoid dermatoses, near the basement membrane.

Perhaps the most audacious/innovative presentation of the morning: An-Sofie Vander Mijnsbrugge presented **impressive responses in metastatic melanomas to regorafenib, a multi-kinase inhibitor that blocks BRAF V600 as well as wild-type A/B/CRAF**.
Her retrospective study involved 12 patients showing disease progression after multiple treatments, continuously treated with 40-80mg/day of oral regorafenib provided by Bayer at no cost (MA for colorectal cancer, GISTs and hepatocellular carcinoma).
In this population with a poor prognosis, 2 partial responses were observed (NRAS- and BRAF V600-mutant melanoma, in combination with an MEK inhibitor).

Aleksandar Popovic presented his retrospective study of 59 patients with inoperable or metastatic melanomas, which confirms the poor prognosis of high LDH levels in immunotherapy. He mentioned the **characteristic immunosuppressive effect of LDH**, reported by S Daneshmandi et al., Cancers 2019: shLDH-A (i.e. “artificial” inhibition of the expression of lactate dehydrogenase A) improves the efficacy of PD-1 inhibitors in a mouse melanoma model.

Management of actinic keratosis and field cancerization

The second session of the morning was on **new developments in the field of actinic keratoses (AKs)**.

The biggest news this year is the appearance of a **new topical treatment for AKs**:
tirbanibulin ointment 1% (Klysiri), 1 application/day for 5 nights in a row on an area no larger than 25cm2, is now approved for AKs of the scalp and face. According to Thomas Dirschka, it is easy to apply, doesn’t drip, and has few side effects. Its mechanism of action is inhibition of tubulin polymerisation and hence of mitosis, with **72% partial response** (itself defined as a reduction of at least 75% in the targeted AKs, Blauvelt A et al., NEJM 2021).

This new “short-term” treatment is a welcome addition for a pathology in which observance can be difficult to maintain with longer treatments.

However, **5FU still plays as important a role as ever in prevention** of squamous cell carcinomas (MA Weinstock et al., JAMA Dermatol 2018; M Jansen et al., NEJM 2019), ahead of imiquimod and PDT. Although traditionally used at 5%, **a new 4% formulation of 5FU has been available throughout Europe since 2020 and in the United States since 2021**, and is better tolerated while maintaining its efficacy (80% success at 4 weeks). Unfortunately, this new cream (TolakR) is not available in France, though I don’t know why.

Thomas Dirschka emphasised that the **response rates** to AK treatments reported in the literature **should be interpreted in terms of the number of AKs initially targeted** (baseline zone), since one strategy to obtain a better cure rate than the competition is to limit the surface area of the zone to be treated.
He also shared a tip for providing daylight PDT (less painful than traditional PDT) without having to worry about unpredictable weather patterns: artificial-daylight PDT (1 hour of application, 1 hour of indoor lighting).

Nicole Kelleners-Smeets noted that an isolated AK will regress spontaneously in 15 to 63% of cases, but that this percentage drops to 0% in **organ transplant patients**. This is all the more problematic in light of the fact that this population is at very high risk for AKs (250x risk: 35 to 40% of these patients develop one within the 5 years after the transplant) and for squamous cell carcinomas (Carla FERRANDIZ). Verbalising the **"precancerous" nature of AKs helps motivate patients** to prevent/treat them.

As a preventative measure with transplant patients, when it is not possible to ease back on immunosuppressive therapy, Ketty PERIS has a **preference for acitretin 10mg/day** over nicotinamide, which has not yet been proven effective in this context (clinical trials in progress). In the rare cases of **areas of extreme cancerisation** that are resistant to treatment, **oral capecitabine** (500mg x2/day, every other week for 1 to 3 months, then 1000mg x2/day, 2 weeks per cycle of 21 days) may be effective (DM Schauder et al., JAMA Dermatol 2020).

Checkpoint inhibitors in non-melanoma skin cancers
Prof Axel Hauschild

The more mutated a cancer's DNA is, the more responsive it is to immunotherapy with checkpoint inhibitors; this explains the success of PD-1 inhibitors in skin cancers, which typically have a high mutational load, resulting from UV.
For example, **cemiplimab has been shown to be effective in squamous cell carcinoma** (MR Migden et al., NEJM 2018): **47.2% response rate, including 20% complete responses**, with fast and long-lasting effects. **63.8% of responses continue after 3.5 years**. To keep the good news coming, this treatment is **well-tolerated** even in older patients.
It is currently administered **as a curative treatment every 3 weeks at 350mg intravenously**, but it is currently being studied for **subcutaneous use** or every **4 weeks**, and also as an **adjuvant or neoadjuvant therapy**.
A phase II clinical trial is also in progress, combining cemiplimab with RP1 (genetically modified oncolytic HSV-1 virus) as an intratumoural injection.
Outside of clinical trials, the first data available from **immunosuppressed patients show partial response rates as high as 45.5%** (but 0 complete responses, unfortunately).
About 50% of kidney patients reject their transplant under treatment with PD-1 inhibitors. To reduce this risk of transplant rejection, or the risk of an outbreak of an existing auto-immune disease, a phase I trial is currently under way for **intralesional use**. This mode of administering cemiplimab limits systemic toxicity while achieving a 71% rate of complete histological response (10/14 patients).

Interestingly, **first-line immunotherapy even appears to increase the rate of response to cetuximab as a 2nd-line treatment**: 54% responses post PD-1 inhibitors (JA Marin-Acevedo et al., abstract #9562, ASCO 2021) vs 28% responses to first-line cetuximab (E Maubec et al., JCO 2012).

Looking beyond squamous cell carcinomas, cemiplimab will soon be indicated for use as a 2nd-line treatment for inoperable or metastatic basal cell carcinoma, but that was already covered yesterday in detail.

Meanwhile, the PD-L1 inhibitor avelumab produces a **47% response rate in Merkel cell carcinoma as a first-line treatment** in real life. Adjuvant or neoadjuvant immunotherapy is currently being studied for this indication too, with initial results expected in time for the 2022 ESMO conference.

Successful treatment with PD-1 inhibitors has also been described in cases of **pleomorphic dermal sarcomas, which are also highly mutated** (just like atypical fibroxanthomas).

Finally, even in **angiosarcomas**, which have a poor 5-year prognosis (8-18% survival), successful immunotherapy treatments (**ipi 1mg/kg+ nivo**) have recently been reported, particularly in cases of **facial involvement** (phase II trial, MJ Wagner et al., Journal of Immunother Cancer, 2021).

Future therapies in malignant melanoma

Olivier Michielin presented a review of present and future melanoma treatments.
In general, he recommends **prioritising a combination of first-line ipilimumab + nivolumab in cases of metastatic melanoma**. Because an acquired resistance to targeted therapies creates cross-resistance to immunotherapy via modification of the tumour micro-environment (L. HAAS et al., Nature Cancer 2021), there is increasing interest in starting with immunotherapy (DREAMseq, SECOMBIT and other clinical trials) in the presence of BRAF mutations.
A second generation of CTLA-4 inhibitors, a “CytomX probody” (a precursor of ipilimumab), is arriving from BMS to intensify ADCC (antibody-dependent cellular cytotoxicity) specifically at the tumour site, after local proteolytic cleavage.

Also arriving as an **alternative to ipilimumab, which is fairly toxic when combined with nivolumab, is relatlimab, an LAG-3 inhibitor** from BMS, a new immunotherapy treatment which also fights T-cell exhaustion. Relatlimab was discussed particularly extensively at the 2022 ASCO and ESMO conferences. Novartis is developing its own LAG-3 inhibitor in parallel, while Roche has developed a bispecific monoclonal antibody that is both a PD-1 and LAG-3 inhibitor, and has the advantage of activating TILs but not Tregs (LC Deak, SITC meeting 2019). As another way to amplify immunotherapy, **the STING agonist SB11285, designed to stimulate the interferon pathway**, is starting to be tested in systemic administration to human patients, with or without atezolizumab.

As for **targeted therapies, naporafenib** (Novartis LXH254) is an upcoming BRAF and CRAF inhibitor being studied in BRAF- or NRAS-mutant melanomas that are resistant to immunotherapy.

In terms of **angiogenesis inhibition**, which is synergistic with immunotherapy, **lenvatinib** is the most advanced targeted therapy.

For **inhibition of tumour-infiltrating neutrophils**, an **IL-8 inhibitor** (BMS-986253) is currently being tested with nivolumab (M Simonelli, AACR 2022).

For **metastatic choroidal melanoma**, which is considered to show very little mutation, **tebentafusp** has earned a place in first-line systemic treatment (58.5% survival at 1 year, never equalled in this context). Tebentafusp is a bispecific protein that allows for reactivation of the T-cell response against cells expressing gp100 in HLA-A*02:01 positive patients (P Nathan et al., NEJM 2021). Tebentafusp is administered on a weekly basis, initially in a context of limited hospital stays.
Interestingly, receiving tebentafusp delays death even in non-responsive patients.

Difficult to treat malignant melanoma

Cerebral metastasis

Hussein Tawbi discussed the topic of cerebral metastasis.

Recall that while melanoma is the cancer that most commonly metastasises to the brain, clinical trial data on this context are extremely sparse (just 775 patients vs. 7939 patients with no cerebral involvement).
What we do know at this point is that in cases of corticosteroid therapy aimed at reducing neurological symptoms, the efficacy of targeted therapies is not affected, unlike with immunotherapy (CTLA-4 inhibitors or PD-1 inhibitors).
Looking ahead to the near future, a phase II trial combining relatlimab and nivolumab will soon be opening at MD Anderson for patients with cerebral involvement.
Until then, following the example of the SECOMBIT clinical trial, proposing 8 weeks of targeted therapy – long enough to take the corticosteroids – before switching to immunotherapy could be an interesting approach, in Hussein TAWBI's opinion.
Radiotherapy's place in the order of treatments is still a subject of debate; randomised clinical trials are coming soon.

Melanomas with advanced locoregional extension

Alexander Van Akkooi, whose assigned topic was melanomas with advanced locoregional extension, reminded listeners of the potential of the **isolated limb perfusion** (ILP) technique in cases of resistance to immunotherapy and extension limited to a single limb. This technique is often "forgotten" in centres where it is not used.

This concludes my summary of the 2nd day of the EADO conference in Seville. For me, it was a fascinating day – and I hope you thought so too! Thank you for reading this far, and I'll be back tomorrow with more!

Dear friends,
Today is the third and final day of the 2022 EADO conference. I started with the free communications session on genetic or epidemiological research on skin cancers.

Basic research, genetics and epidemiology of skin cancer

Mercè Grau-Pérez presented her study on **disparities in the incidence of melanoma on one of the Canary Islands** (Gran Canaria), with certain districts of the island seeing 2 to 7 times more cases of melanoma than the expected rates for a population of the same age (**the Northeast area in particular, between 2007 and 2018**).
Disparities in access to healthcare may partially explain this, but are not a sufficient reason. A **genetic predisposition** linked to low rates of genetic admixture, or the **well-known pollution of local underground water** sources with radon/sulphates, could be to blame.

Penny Lovat from Newcastle discussed the prognostic value of **combined marking (via immunohistochemistry) of AMBRA1 and loricrin expression in the epidermis overlying non-ulcerated stage I/II melanomas**.
She showed that loss of these proteins is associated with a poor prognosis, independently of the Breslow thickness. The advantage of this marking is that it is simple and inexpensive.
The physiopathology behind this phenomenon is explained in her recent publication: **secretion of TFGb2** by the melanoma reduces the expression of AMBRA1 and loricrin by the adjacent epidermis (I Cosgarea et al., BJD 2022).

Georg Lodde compared the clinical/genetic profile of "**immunotherapy super-responders**" (in a cohort of patients treated for metastatic melanoma, these are the patients who responded at 3 months, i.e. 8% of patients treated) vs. non-responders.
The super-responders were in better overall condition, with less metastasis at the start of treatment. Their primary melanomas were often less ulcerated, and more frequently expressed PD-L1 in over 5% of the cells in their melanomas. Genetically, they often had *NF1* or *TERT* promoter mutations. Their tumours' mutational load was higher than that of non-responders (> 10 mutations/Mb of DNA), which confirms the data published in the literature (L Dousset, F Poizeau et al., JCO PO 2021).
Not surprisingly, these "super-responses" are long-lasting and translate to longer overall survival.

Robert Stassen reported experiences with the use of the **"ClinicoPathological-GEP" predictive test** (Skyline Dx) to help prioritise sentinel lymph node operations at his medical centre during the covid period. This test, which incorporates the **patient's age at the time of the melanoma diagnosis, the Breslow thickness, and the expression profile of 8 genes** (*MLANA, ITGB3, LOXL4, SERPINE2, PLAT, GDF15, TGFBR1, IL8*), has been validated in several independent cohorts (D Bellomo et al, JCO PO 2020).
Feasibility was good, but the process could stand to be faster.
Among tested patients who did have the sentinel lymph node procedure (n=148/176 patients tested), sensitivity was 93.3%, specificity was 42.5%, negative predictive value was 96.4%, and positive predictive value was 28%. Of the 3/148 patients with false negatives, 2 had a micrometastasis in their sentinel lymph node.

Finally, Neel Maria Helvind reported the results of a Danish national cohort study on melanomas. **Stage IIIA melanomas had a better prognosis than IIB and IIC**, and she therefore suggested perhaps reducing monitoring of the former. Stage IIB, IIC and IV melanomas affected older patients, with more comorbidities.

New diagnostic approaches in skin cancer

Giovanni Pellacani, Salvador Gonzalez and Julia Welzel each recommended confocal microscopy +/- optical coherence tomography (OCT) to refine the diagnosis of uncertain carcinomas/melanomas. They presented a few clinical cases in which neither clinical approaches nor dermoscopy produced a clear diagnosis. Note that a "low-cost", smartphone-compatible confocal microscope has recently become available (Curiel-Lewandrowski, C. et al., JAAD 2021, for US$6000 and weighing 1kg).
Julia Welzel mentioned the innovative "OCTOLAB project", which integrates a laser into the OCT device to combine diagnosis and treatment.

Session on supportive/palliative care

Peter Arenberger reminded us that **supportive care should be set up right at the start of the metastatic phase (or even as soon as the cancer is diagnosed)**. This type of care plays a role in maintaining quality of life, but possibly also in longer overall survival. Beyond treatment for pain, supportive care also includes psychological, nutritional and functional support (physical activity), and even spiritual support. Supportive care options are diversifying to include music therapy, meditation and more. In my opinion, every doctor should be made aware of this type of holistic treatment approach.
Palliative treatment does not necessarily mean an end to all anti-cancer treatments. Even after disease progression under immunotherapy, **there may still be an interest in continuing immunotherapy** (retrospective analysis of data from two phase 3 clinical trials, Checkmate 066 and

Checkmate 067, with nivolumab, G. Long et al., JAMA Oncology 2017). Similarly, after pausing targeted therapies for a certain period of time, they are often activated again.
Radiotherapy, cryosurgery, and even local chemotherapy (e.g. intratumoural methotrexate in squamous cell carcinoma, cited by Lidija Kandolf Sekulovic) can help when systemic treatments have failed.

Monika Arenbergerova discussed **side effects specific to Hedgehog inhibitors** (cramps, alopecia, dysgeusia), which can have a significant impact on quality of life. The most effective approach is to propose giving this treatment discontinuously. But she also recommends:
- for cramps, to drink lots of liquids (2 to 2.5L/day), take magnesium supplements, or possibly treat with amlodipine 10mg/day for 8 weeks (this reduces the frequency of cramps but not their intensity, according to M Ally et al., JAMA Dermatology 2015)
- for alopecia, minoxidil 2-5%
In case of failure, possibly attempt immunotherapy with PD-1 inhibitors, then propose the targeted therapy again if needed.

To conclude the session, Zeljko Mijuskovic spoke about **symptomatic treatments**. For **fatigue**, which can be measured with the “fatigue NRS” (numeric rating scale), he recommends mild exercise (walking at 5km/h, stationary bikes, etc.), except of course in cases of cachexia. All psychostimulants are discouraged, with the possible exception of corticosteroids. He does not recommend anything in the category of L-carnitine, coenzyme Q10, ginseng, guarana, etc. However, he does recommend psychosocial care, both for the patient and their family. Mindfulness meditation, yoga and acupuncture can have a positive impact.

That’s all for this final day of the EADO conference! I’d like to thank Géraldine Fleury at Bioderma for trusting in me once again this year for these summaries. This was a very busy conference for me and I didn’t see much of Seville, but I hope that these reports are useful to you – that will be enough of a reward in itself! Until next time!

Reports written by

Dr Oriol YELAMOS

Dermatologist, Spain

Influence of germline genetic variants on dermoscopic features
Dr Susana Puig

MC1R (melanocortin 1 receptor) gene

One of the main genes that influence skin color is MC1R. There are 9 polymorphisms associated with red hair phenotype when inherited in autosomal recessive manner.
MC1R polymorphisms are associated with freckling in childhood. This predicts at least one polymorphism in MC1R.
Dermoscopic features associated with MC1R polymorphisms:
- Freckling in childhood
- Eccentric pigmentation
- Blue nevi
- Visible vessels in dermoscopy

People with MC1R polymorphisms have larger nevi (more if they have the two alleles of MC1R) thus suggesting MC1R is associated with nevogenesis.
Dermoscopic characteristics of melanomas in MC1R carriers:
- They have less dermoscopic features
- Network is poorly visible because the color is rather orange and makes the network less visible
- Dotted vessels
- Perifollicular pigmentation --> in lentiginous melanomas
When you do dermoscopic comparative approach in MC1R carriers, the melanomas do not stand since they look very similar to their nevi --> in these patients the “ugly duckling” rule does not really work and you need to do sequential follow-up monitoring and excise changing lesions.

MITF gene
Mutations in MITF increase the risk of melanoma and renal cancer.
This mutations is present in 3/1000 inhabitants, increasing the risk x10 for melanoma and renal carcinoma.
These carriers have many moles (>300) mostly reticulated nevi, and they can develop fast-growing melanomas (MITF carriers have an odds ratio of 4.48 for nodular melanomas).

BAP1 gene
BAP1 is a tumor suppressor gene that increases the risk for uveal melanoma, mesothelioma, renal cell carcinoma among other cancers.
They also develop melanocytic lesions called BAP1-inactivated melanocytic tumors (informally called bapomas) which are pink and dome-shaped. Histologicalloy, they have two types of melanocytic cells (thus they have a byphasic melanocytic population): one population with normal looking melanocytes, and another with atypical spitzoid melanocytes which lack the expression of BAP1.
Finding one BIMT is not a hallmark of the multiple cancer syndrome mentioned above, but multiple BIMTs are a hallmark with this cancer syndrome.
There are multiple dermoscopic patterns associated with bapomas, among them being more frequent in patients with cancer syndrome:
- Peripheral eccentric globules with central homogenous areas
- Reticulated with pink-tan, raised, homogeneous areas

POT1 gene
Among melanoma-prone families with POT1 germline gene mutations, the melanomas display a Spitzoid morphology (40%) and prominent infiltrating lymphocytes.

Conclusions
1- Our genetic background influences dermoscopy
2- MC1R red hair variants are associated to:
- Presence of blue nevi, higher count of large nevi, larger nevi
- Presence of globules, eccentric pigmentation and vessels in nevi
- More difficult to diagnose melanoma (less dermoscopic criteria and less dermoscopic colours)
- Early melanomas in red hair individuals may show only atypical orange pigment network
- Melanomas in red hair and albino patients may show dotted vessels as main clue for diagnosis
3- Low risk melanoma single nucleotide polymorphisms (SNPs) in several genes (MTAP, PLAZG6, PAX3, IRF4) are associated to dermoscopic features of de novo and worse prognosis melanoma
4- MITF mutations are associated to risk to Develop Fast Growing Melanoma
5- Several dermoscopic patterns are associated to BAP1-related tumours that allow to identify patients at risk of cancer
6- Spitzoid morphology and POT1

Management of toxicities of targeted therapies

Toxicities of targeted therapies
Dr Caroline Robert

There are some questions that need to be considered regarding patient's perception of targeted therapy (TT) adverse events (AE):
- Type of adverse events and organs involved
- Incidence and severity
- Necessity to stop treatment
- Reversibility of adverse events
- Cam be change from one treatment combination to another in case of certain AE happening?

When immunotherapy is used, normally AE are not permanent. However, AE seen in TT sometimes can be severe and irreversible. Fortunately, this doesn't happen often although AE with TT are very frequent.
It is important to note that some AE are class AE (for example ocular toxicity with anti-MEK) and other occur more frequently with given drugs (for example, pyrexia is more more frequent with trametinib, and photosensitivity and gastrointestinal AE are more frequent with encorafenib + binimetinib)

Ocular toxicity with anti-MEK
- Serous retinal detachment (SRD): the most frequent and typically reversible in days or hours sometimes without interrupting the drug. Usually bilateral, it presents with blurry vision and importantly may appear very fast after starting the drug, even hours after initiating MEK inhibitors.
- Retinal vein occlusion: this is an emergency and typically starts with unilateral vision loss without pain. It can be severe, so treatment withdrawal is required.
- Increase of intraocular pressure: does not normally require TT withdrawal, but it needs to be treated.

Cardiovascular AE with TT
- High blood pressure: occurs in 14-29% of cases and can be normally medically managed.
- Decrease of left ventricle ejection fraction: occurs in 6-11.5% of cases. It requires stopping the TT if the ejection fraction <40%
- Increase of QT interval in the ECG due to BRAF inhibitors: It requires stopping the TT if QT >480ms
- Lower limb edema
Since cardiovascular AE are common, it is recommended to perform ECG and echocardiogram after 1 month and every 3 months.

Neurological (NRL) AE
Some NRL AE associated with TT can be permanent!

Muscoloeskeletal AE
Fatigue related to TT is very common and very difficult to treat.

Conclusions
13-18% require treatment discontinuation and 33-53% treatment adjustment.
However, TT AE are rarely permanent, as opposed as immunotherapy toxicities, and can be managed in the majority of cases.

Skin toxcities of TT
Dr Onofre Sanmartin

Papulopustular eruption

Best known side effect of TT, especially EGFR inhibitors, but also mTOR inhibitors and some MEK inhibitors (cobimetinib, trametinib).
It presents as a monomorphous papular and pustular rash to an eczematous rash. It typically is more frequent in the face and then the trunk.
It starts at day 8 day after treatment and in worsens 2-4 weeks.
It correlates with treatment response.
More intense in 1st month, in fair skinned people, and in patients older than 70.
In more severe cases there is superinfection wit S.aureus which is due to direct effect of antiEGFR treatment which favors S.aureus colonization
The treatment includes antibiotics such as tetracyclines: doxycycline or minocycline 100/12h x 8 weeks.

Paronychia and nail changes

It is very common with antiEGFR TT.
It is treated with high potency topical steroids (ie clobetasol), topical antibiotics, or if more severe oral antibiotics and podiatric care.
AntiFGFR such as induce more nail changes.

Calcyphilaxis

FGFR inhibitors induce hyperphosphatemia as side effect in 70% of patients, and this may induce an increase of calcium levels and risk of calcyphilaxis (although it is a rare AE).

Multikinase inhibitors induced rash

Frequent dose-dependent exanthema which occurs the first weeks of treatment.
It does NOT correlate with treatment response as opposed as papulopustular rash.
The types that are more common are dermatitis, followed by maculopapular, followed by lichenoid eruptions.
It can be very pruritic and occasionally painful.
It responds well to treatment and typically does not require stopping the treatment.

Multikinase inhibitors induced hand foot syndrome

Frequent and dose dependent.
It happens because of blockade of PDGFR.
It presents with intense painful hyperkeratosis in pressure areas.

Pigmentary changes

They can occur because of different mechanisms:
- Direct deposit of the drug:
o Yellowinsh discoloration: sunitinib
o Mottled pigmentation: vandetanib
- Impaired melanogenesis
o C-kit blockade: imatinib, sunitinib, pazopanib
- Apoptosis of melanocytes
o CDK 4/6 inhibitors à they induce a vitiligoid hypopigmentation

Gastrointestinal toxicities

Dr Carbonnel

They are more frequent with encorafenib + binimetinib and can present with colitis.
A colonoscopy with biopsies should be performed without delay to confirm the diagnosis and if the diagnosis is confirmed, the drugs should be permanently stopped.

Rare severe AE with TTX

Dr Hassel

TT AE are common and non-severe. However, some of the severe ones are rare but need to be known and include neurological AE, kidney failure, cardiac arrest, uveitis, or systemic inflammatory syndrome.
NRL severe AE include encephalitis and polyneuropathy.
Encephalitis can occur at a relatively fast onset but the good news is that there's a full recovery after you stop the TT.
Polyneuropathy can be reversible if identified soon and the treatment stopped.
Rare ocular AE: uveitis is uncommon (5%) but disabling and tends to recur.
Rare cardiac AE: cardiac arrest and rhabdomyolisis.
Systemic inflammatory response syndrome (SIRS): typically induced by BRAF inhibitors after checkpoint inhibitors. It starts days after the initiation of the treatment (8-21 days) and presents with malaise, fever, chills, nausea, vomiting, diarrhea, hypotension, tachycardia, somnolence. The blood test shows kidney failure and elevation of liver enzymes. It's treated with high dose steroids and one may consider anti-IL6 such as tocilizumab.

Prognostic and predictive markers in melanoma

Clinical Prognostic factors for melanoma

Dr Nagore

There are several clinical factors which correlate with melanoma prognosis and include age, gender, tumor site, and number of nevi.
Age is related with positive sentinel lymph node biosy and ticker tumors and higher mitotic rates. With increasing age, disease survival decreases.
Number of nevi: patients with more nevi have better survival and this could be related to telomere length. It seems that patients with more nevi have longer telomere, which correlate with better survival.
Sex: it seems that females have better prognosis factors (Breslow thickness, mitoses...). However, there are conflicting results on whether this means a worse survival. It seems that it is also related to age, so if young the immune response is better in younger females so the prognosis is better in young females, but no differences are found between males and females when older. This may be due to hormonal differences, vitamin D metabolism, environmental factors, stress, among others.
Body site: acral and head and neck melanomas have a worse probably because of lymphatic drainage.

Imaging and artificial intelligence

Dr Jean Jacques Grob

Artificial intelligence (AI) could be helpful to integrate the information that we use to stratify our patients: imaging studies (CT, PET, MRI) LDH, GEP, clinical data...
Potential advantages of using imaging results as biomarkers is that allows to measure kinetics of metastatic cancers. Kinetics are important in decision making (for example tumor boards) but doctors don't measure kinetics, but we use it ("wow, the tumor grows fast so we have to give this patient a different drug").
The problem is that to get kinetic information you need successive images (ie CT, PET…), and this is time consuming of radiologists' time, since they may need to measure all the metastases and they don't do it. This can be overcome by using AI since machines can measure and compare multiple parameters present in imaging studies, not only the size of the tumor: metabolic activity, texture of the tumor… Then we could study kinetics in order to predict treatment response (radiomics). In fact. this

could be better than RECIST criteria that humans generate and use since you can study all the metastases at once. Also, studying all the visible tumor has the advantage of studying metastases with different biology. This has advantages compared to performing biologic studies (histology, molecular biology) on a single piece of biopsy (if you take a sample of one metastasis is this representative of all the metastases? Probably not).
Therefore, it is important to develop AI algorithms to be applied to imaging studies to better understand the tumor kinetics and predict treatment response.

Liquid biopsy
Dr Dawson
We all have circulating DNA from healthy cells, but when tumors occur we have also levels of circulating tumor DNA (ctDNA). Still, the levels of ctDNA are still low compared to DNA from healthy cells.
ctDNA can also help see treatment response by quantifying the levels of ctDNA.
One can also use this to see different tumor clones occurring by identifying different ctDNA -> ctDNA analysis can capture genomic heterogeneity in cancer.
ctDNA can be used to identify early progression before can be detected by imaging.
Also ctDNA can help identify minimal residual disease.

Tissue based markers
Dr Schadendorf
High levels of PD-L1 show better responses to immunotherapy compared to patients with low levels of PD-L1. However, we still using immunotherapy in all patients since we know that even if these levels are low, the response rates are better than conventional chemotherapy.
CD8+ lymphocyte infiltration, interferon are other tissue-based marker which have shown similar results. The issue here is the same, better responses but overall immunotherapy works better for all patients than chemotherapy.
Treatment resistance to immunotherapy is related to mutations in the JAK STAT signaling pathway since they prevent antigen detection.
Probably the future are the gene-expression profiling (GEP) tests which evaluate a number of genes which are up or down-regulated. Currently three brands are available: Castle Biosciences, MelaGenix, and Merlin/Skyline Dx. However, the data using these genes comes from retrospective studies and prospective studies are necessary.

Adjuvant therapy of malignant melanoma. Candidates, risks and benefits

Long term benefit of adjuvant therapy in stage III patients
Dr Claus Garbe

<u>Pembrolizumab</u>
There is a large benefit in RFS with pembrolizumab having a hazard ratio (HR) of 0.56 (so the risk has decreased by around 40%). This benefit is more pronounced if higher levels of PD-L1 are found but there's still benefit if PD-L1 is not high. Also, this benefit of pembrolizumab is higher in patients with BRAF mutation. Also, it occurs in all III stages (IIIA, IIIB and IIIC).

<u>Nivolumab and ipilimumab</u>
In the CHECKMATE 238 nivolumab was evaluated with ipilimumab, having a HR 0.79. There was not a difference of ipi vs nivo when looking at overall survival in this trial.

Targeted therapy
In the COMBI-AD trial compared dabrafenib + trametinib vs complacebo and showed a HR 0.51 (so it works for 50% of patients), with the highest benefit being achieved at 1st year and is maintained for 5 years.

Conclusions
Experience with ipilimumab shows that the survival benefit lasts at least 10 years.
PD1 inhibition and BRAF/MEK inhibition lead to a comparable survival benefit.
Patients with BRAF mutation have a greater benefit with PD1 therapy than BRAF wild type.

Adjuvant treatment in stage II melanoma patients

Dr Hoeller

Why is it important to use adjuvant therapy in some stage II melanomas? Because stages IIB and IIC may have a worse prognosis than IIIA, and is similar to IIIB patients. So, in order to study this we have 4 clinical trials:
- Keynote 716 (pembro vs placebo): this is the only one that has some preliminary results since the other trials are still running.
- NivoMela (nivolumab using a gene expression profiling [GEP] platform)
- Checkmate 76K (nivolumab vs placebo)
- Columbus-AD (encorafenib + binimetinib vs placebo)

Keynote 716 results: it seems that it works better in lower T stages (T3b patients do better compared to T4b) so it could be related to the PD1 expression in these patients.
If we look at the number needed to treat, we need to treat 12 patients to prevent 1 recurrence in stage IIB and IIC patients.
Is this treatment risky? The side effects are the same seen in patients in stages III with adjuvant therapy: 20% will require hormonal treatment, mostly thyroid treatment which can be managed but will last forever. If we look at the number needed to harm, the severe AE are low (12) but hypophysitis is high (40) and very high for type I diabetes (250). So, we need to think carefully when using these drugs in stage II patients and needs to be discussed with the patients regarding AE.
So, it seems that the results in stage II are promising, AE are similar to other stages, but we don't have long-term data, we don't have biormarkers to predict responders, and we don't have data with targeted therapies.

What future place for sentinel node biopsy (SLNB) and new biomarkers to select the right indications of adjuvant therapy?

Dr Grob

Anatomical biomarkers (tumor depth, SLNB status…) of current AJCC 8th are not good biomarkers because they show morphology and not biology. For example, if we look at the tumor thickness, low Breslow indexes may mean a low aggressive tumor but also the early diagnosis of an aggressive tumor. Conversely, a thick tumor may mean either a highly aggressive tumor or a late diagnosis of a low aggressive melanoma. This is the same with SLNB: a negative SLNB means either a non-aggressive tumor which has not yet been able to metastasize, or an early diagnosis of highly aggressive tumor before it spreads to the lymph nodes. Conversely, a positive SLNB may mean a highly aggressive tumor, or a late diagnosis of a low aggressive tumor which ultimately has extended to the nodes. So, is it time to stop using SLNB? Maybe yes since these tests do not reflect the biology of the tumors.
However, if we stopped doing SLNB, there would be some repercussions in our patients, especially in intermediate tumors. However, we know that patients in stages IIB and IIC also have bad prognosis, similar to IIIB, and that is why clinical trials using immunotherapy have been done and show good results. So maybe the impact of not doing SLNB in these patients would not be that big. However, we can't stop doing SLNB since immunotherapy isn't still approved in Europe for stage II and targeted

therapies have not shown results yet in stage II. Also, stage IIIA has a relatively good prognosis so adjuvant therapy doesn't make a lot of sense here. So yes, it's time to stop using SLNB but we need to develop other prognostication tools.
In this sense, we have new gene expression profiling (GEP) tests which may be better to provide good prognostic information, but validating their results is not easy since the information needs to be tested together with AJCC data, must be validated prospectively, must be validated in multiple samples different from the ones that were used to generate it, and must be validated on relevant endpoints.
What would be a good new prognostic biomarker?
- In patients considered high risk T by AJCC
o The objective is to spot the patients who are actually not at high risk and are submitted to potentially toxic adjuvant therapy for nothing
- In patients considered low risk T by AJCC
o The objective is to spot the biologically aggressive cases, wrongly excluded from adjuvant therapy by a negative SLNB or no indication of SLNB.
However, due to the poor performance of the current AJCC even biomarkers with low or uncertain performance can be interesting to identify patients justifying an adjuvant treatment.
What about predictive biomarkers for efficacy of adjuvant therapy? There are no good biomarkers, except JAK3 loss of function, which is highly predictive of PD1 resistance but is very unusual (so, this biomarker has low impact).
We also need toxicity prediction markers; given the risk of melanoma itself, only biomarkers predictive of **severe toxicity** like acute cardiomyopathy, or **permanent toxicity** are relevant. However, we have no current candidates for these biomarkers.
To conclude, when deciding whether to use adjuvant treatment we have to predict the individual benefit (individual risk for progression, ability to respond to a given adjuvant treatment, absence of high individual risk of severe or permanent toxicity), SLNB does not provide these data and should be abandoned over time, biomarkers available are not really useful to determine treatment response or toxicity, and novel biomarkers and prognostication tools require further prospective validation.

What is the best timing of treatment in melanoma: Neoajuvant, adjuvant or only if disease progression?

Dr Paul Nathan

Adjuvant therapy is the standard of care for many cancers, so why melanoma should be different? What is different in melanoma? We have data that drugs are curative in the metastatic setting, so also we could think about treating them when they progress. So, which is the proportion of patients that get cured with adjuvant therapy and how many they get cured in the metastatic stage? 1/3 of patients will be cured in the adjuvant setting and 1/3 in the metastatic setting. The issue here is that not all patients who relapse will be able to receive treatment with curative intent because of distribution of disease (multi-organ, disease burden, LDH, brain mets…), co-morbidities precluding immunotherapy, co-morbidities precluding combination immunotherapy. So, patients receiving systemic treatment in the advanced setting are significantly selected.
Also, tumor biology always gets worse with time, never better (increased heterogeneity, increased resistance, lowered immunity) so the response may be worse if treated later. Nevertheless, adjuvant treatment would be greatly improved by enhanced identification of high risk patients: biomarkers, GEP…
What happens with neoadjuvant treatment? Historically was used to facilitate surgery, but now is proposed to improve overall outcomes. It all started with the Opacin trial (Blank et al.) which in a small trial with 20 patients the outcomes were better when performing neoadjuvant treatment vs adjuvant treatment. But we need more data from larger studies, although the results are promising.
To sum up, adjuvant treatment remains the standard of care but we need to improve the patient selection and adapt treatment duration. Regarding neoadjuvant treatment, it is not the standard of

care yet, it requires results from practice changing phase III, and patients with macroscopic resectable disease should be considered for neoadjuvant clinical trials.

Controversies in melanoma management

Stage III malignant melanoma: surgery first?

Yes: Dr Farricha

Performing surgery may be useful in some subsets of patients such as patients with macrometastases. However, with neoadjuvant treatments surgery may change and may be more related to improve quality of patient related outcomes.

No: Dr Van Akkoi

The advantage of Neo-Adjuvant Systemic Therapy (NAST) is that when you give treatment before surgery, when you perform surgery you can know if there has been response or not, and this also has a prognostic relevance: if pathological response is observed (either complete or partial) the survival rates are better than in patients without pathological response. This results in better outcomes with neoadjuvant compared with adjuvant treatment.

Follow-up examinations. Does it matter?

Dr Ulrike Leiter-Stöppke

The aims of melanoma follow-up are:

1. Early detection of recurrences.

a. Since now we have efficacious drugs in melanoma, do we need to continue following the patients very closely the way we are doing now, or we can “relax”. More imaging improve survival in the age of effective drugs? Probably no, but patients will not like the idea of being followed less if having melanoma.

2. For how long patients should be followed?

a. Typically it is recommended to follow these patients for 10 years in high risk patients since only 5% of recurrences occur after 10 years.

b. However, lifelong skin examination should be performed due to increased secondary melanomas.

3. Which examinations should we perform? How often should we perform follow-up examinations?

a. Typically CT scans, brain MRI, nodal ultrasound, and blood tests are recommended every 3 to 6 months depending on the tumor stage. However, not all centers can perform these tests and maybe it be good to focus on clinical symptoms and if they progress we can give them the highly effective treatments we have nowadays.

4. Should we promote self surveillance?

a. Yes, and actually some attempts from the MEL-SELF trial in Australia are showing that empowering the patient and creating a fast track way of communication between the patient and the dermatologist (for example an app) is a very good way to increase early detection of tumor progression.

Systemic triplet therapy - a new approach?

Dr Alexander Eggermont

The results of the triplet therapy (BRAF/MEK inhibitor + immunotherapy) trials are contradictory:

- IMSPIRE (vemurafenib + cobimetinib + atezolizumab): positive trial
- COMBI-I (dabrafenib + trametinib + spartalizumab): negative trial

So, although the rational of triple therapy seems good, still data is not convincing and we may need additional studies. Probably the future is triplet therapy not with BRAF/MEK + antiPD1, but with ipi + nivo + antiLAG3, maybe even in the neoadjuvant setting.

Neoadjuvant therapy in malignant melanoma
Dr Christian Blank

One of the beauties of neoadjuvant treatment is that after you remove the tumor, if there's complete response or partial response (pathological response) this correlates with better prognosis. So, it's important to study the potential biomarkers in responders and non-responders.
Why does neoadjuvant work? Because in neoadjuvant immunotherapy what happens is that the treatment response is stronger since there's a more active T cell population surrounding the tumor that may be reduced if the tumor is removed before giving immunotherapy. This allows for ways to personalize the treatment by using biomarkers. These biomarkers can used to predict treatment response or toxicity.
Treatment response biomarkers which predict better pathological responses with neoadjuvant immunotherapy are high IFN and high tumor burden. Hence, patients with low IFN may require more intensive treatment since we know that they will get around 30% response rates vs 90% in patients with high IFN.
Therefore, multiple combination treatments are being studied in patients with baseline low IFN prior to neoadjuvant treamtn, such as adding to the antiPD1 treatments with HDAC inhibitors, ipilimumab, IL2 or antiLAG3 treatments. However, results of these combinations are pending although seem promising.

Surgical management of non-melanoma skin cancer

Value of imaging techniques to define and control excision margins in NMSC surgery
Dr Josep Malvehy

There are now multiple in vivo imaging machines that are improving the management of tumor margin delineation: reflectance confocal microscopy (RCM), line field confocal optical coherence tomography (LC-OCT), combination of RCM and OCT. Also, we should not forget that dermoscopy can be helpful (for example the presence of multiple aggregated yellow globules indicate invasion in basal cell carcinoma). And there are multiple new technologies coming (Raman, multiphoton microscopy…)
Also, now there's improvement in ex vivo confocal microscopy, since the new machines are much faster and using computer algorithms can create an artificial hematoxylin-eosin image which is helping clinicians and pathologists use these machines. So, a lot of exciting new technologies in tumor delineation.

Mohs's micrographic surgery in high-risk SCC
Dr Onofre Sanmartin

Standard surgery margin recommended in SCC is 1 cm in lateral margins (this comes from the Zittelli's studies). However, they don't talk about how deep you have to go to excise SCC, especially in high risk SCC.
There are no randomized trials comparing standard surgery vs Mohs for SCC. But many cases show that the results are better with Mohs, with around 3% recurrence rates with Mohs (and one has to bear in mind that the cases treated with Mohs tend to have more risk factors). This is because the entire margins are studied with Mohs. In addition, Mohs is cost-effective.

How is Mohs done in SCC? Either using frozen sections (conventional Mohs) or permanent sections (slow Mohs). When to use frozen sections or permanent sections? Slow Mohs is better to identify perineural invasion (also one can perform immunohistochemical stains), also when removing large tumors is better permanent sections since if doing frozen sections it will be a lot of work and also they tend to have a lot of fat which is very hard to process in frozen sections.
Also, now ex vivo confocal microscopy is having a potential role since it allows further permanent sections since the sample is evaluated fresh.

NMSC surgery of the face - My favourite techniques
Dr Cristina Magnoni

How to reconstruct a surgical defect depends on multiple factors: the size of the defect, the location of the defect, but also related to the surgery: the surgeon's experience and the surgeons' preferences.
Dr Magnoni's favorite flaps are the frontonasal flap for tip of the nose defect, and tarsoconjuctival advancement flap for lower eyelid defects.

Surgical challenges in NMSC located on the scalp
Dr Roland Kaufmann

When doing surgery on the scalp there are several challenges
Challenge 1: where is the tumor? Sometimes there is a lot of crusting and the tumor is underneath, so it's important to clean the area well since
Challenge 2: the battle with the hairs? They always complicate the surgery.
Challenge 3: sometimes the challenge is the patient's comobordities, not only the tumor itself.
Challenge 4: Tumor-related challenges: neglected tumors, multiple lesions, giant lesions
Challenge 5: some tumors are more challenging such as pleomorphic dermal sarcoma which tend to recur a lot à in these cases
Challenge 6: difficult to mobilize tumors à in these cases sometimes you have to undermine under the galea or the skin will not mobilize and you won't close the defect. Or sometimes simply take a graft from the internal side of the arm which has a lot of skin.
Challenge 7: scalp and bone exposure which sometimes require using skin substitutes such as integra.

Special techniques in NMSC defect repair of the ears
Dr Ricardo Viera

The ear has different areas which require different surgical techniques.
In the central part of the ear, secondary intention healing works very well, although it may be a bit annoying for the patient since it requires some wound healing care. An alternative is performing a revolving door flap.
What happens with defects on the helical rim? Wedge excision is the most common in full thickness repairs, although it can produce a notching of the rim if the defect is big. Alternatives are advancement flaps such as double advancement flaps. For larger defects, the Antia-Buch flap can be used.
And defects of postauricular defects one can use advancement flaps, bilobed flaps… It's not a big issue since it will be behind the ear.

SLNB – is there a role in SCC?
Dr Antonio Tejera-Vaquerizo

In the current guidelines there is not consensus on whether to perform SLNB or not. However, lymphatic dissemination is more frequent with SCC than melanoma. But studies have not been performed and we don't know why: maybe aggressive SCC patients are older?
We now know that in tumors <2cm in diameter, SLNB is almost always negative.

When comparing survival in patients in whom SLNB was performed or not, there were no differences in the two groups.
However, although no recommendations exist on whether to perform SLNB, it seems that it may be beneficial to perform in immunocompromised patients.

Challenging cases in dermoscopy

Challenging facial lesions
Dr Aimilios Lallas

Some lesions on the face can be very similar clinically but dermoscopy really helps:
- Pigmented actinic keratosis (PAK): erythema (strawberry pattern), white and wide follicles, rosettes, scale
- Solar lentigo: sharp demarcation, pigmented network (Network on the face is a clue for solar lentigo, NOT for melanocytic lesions).
- Seborrheic keratosis: comedo-like openings, milia-like cysts

These features have been integrated in a new algorithm called the inverted approach (in print in JAAD by Lallas et al.). In this algorithm instead of looking for melanoma features one starts by the opposite, on starts by looking at the features of PAK, lentigo or seborrheic keratosis and if none of these features are present one should think it's a malignant lesion (melanoma, SCC…).
Vessels and white structureless areas are indicative of SCC.

Challenging non pigmented lesions
Dr Harald Kittler

It is crucial to include the clinical information when assessing non-pigmented lesions.
When assessing white flat lesions it could be basal cell carcinoma (BCC) or sebaceous hyperplasia, and both can present with white-yellow clods. In BCC yellow clods can be seen both in polarized and non-polarized light and are called multiple aggregated yellow clods (MAY clods). MAY clods indicate invasive BCC since histologically they correspond to calcification (which is a well-known indicator of high risk BCC). However, in sebaceous hyperplasia the clods are aggregated at the periphery, one next to another, surrounding a central follicular plug.
There is a subtype of flesh-colored nevi that are called BAP1-deficient tumors (BIMT or bapomas) which are associated with a cancer syndrome which associated uveal melanoma, mesothelioma, among other cancers. These bapomas have multiple dermoscopic patterns which range from a pink homogeneous pattern to a globular pattern with irregular globules at the periphery. This cancer syndrome can be suspected when multiple bapomas are encountered, but a single lesion may NOT be associated with this cancer syndrome.

Challenging nodular lesions
Dr Zoe Apalla

Nodular lesions can be very challenging and if malignancy is suspected excision may be warranted, even if the final lesion is benign.
BCC on the lower extremities can be challenging and can mimic a lot of lesions.
Blue-black rule is useful for heavily pigmented lesions: when we see a nodular lesion and the blue-black color is >10% it is likely to be nodular melanoma, except for some angiomas or seborrheic keratosis.
When assessing lesions pyogenic granuloma-like lesions, one may be careful since they can also be amelanotic melanoma or Kaposi sarcoma. Regarding Kaposi sarcoma, classically it was described to have the rainbow pattern, especially in nodular lesions. In flat Kaposi sarcoma, it is more common to

have rosettes. In addition, the rainbow pattern can be seen in many other conditions such as BCC, melanoma, Merkel cell carcinoma, stasis dermatitis…
Merkel cell has a classical dermoscopic pattern which shows milky red areas and poorly focused linear irregular vessels, although this is not the most common one. A similar pattern with a more orange color can also be identified in granulomatous diseases (ie sarcoidosis) and in cutaneous lymphomas and pseudolymphomas. This orange color correlates with dense cell infiltrates rather than granulomas.

Challenging pediatric lesions
Dr Giuseppe Argenziano
Melanomas before puberty are extremely rare, but they exist. Which is the everyday problem? The parents that are extremely worried about their children's moles. In fact, if we look at the number needed to excise to find a melanoma, in adults it's maximum 30 whereas in children is almost 600! So you need to excise almost 600 benign lesions to find a melanoma in children.

Melanoma guidelines update

Melanoma diagnostics: focus and key questions of the update
Dr Josep Malvehy
Dr Malvehy discussed the last EADO melanoma guidelines on diagnostics (Garbe et al. Eur J Cancer. 2020 Feb;126:141-158.)
One of the important points raised is that the diagnosis of melanoma needs to be confirmed histologically, which is something that may seem trivial but it's not since in some settings this is not done.
Regarding artificial intelligence (AI) it is important to highlight that apps using AI need prospective validation.
Regarding staging, although it's not perfect we need to follow AJCC 8th edition TNM staging.
Regarding gene expression profiling (GEP) and liquid biopsy, they are very promising but at the present moment, we don't have good evidence since the information comes from retrospective studies.
Regarding follow-up, typically it is recommended to perform an intensive 10-year follow-up in more aggressive melanomas.

Melanoma therapy: focus and key questions of the update
Dr Claus Garbe
Dr Garbe reviewed the EADO melanoma guidelines on treatment (Garbe et al Eur J Cancer. 2020 Feb;126:159-177)
Regarding surgical margins, in the new guidelines the margin should be added to the initial excision margin: for example, if you excised the initial lesion with a 3mm margin, the wide local excision margin should be added to these 3mm. Hence, we are becoming less aggressive.
Regarding SLNB, it is said now that it should be offered, not performed, in patient with a Breslow index >0.8 mm.
Regarding adjuvant therapy, in the guidelines it is highly recommended in patients IIIA to IIID, starting with antiPD1 irrespective of the BRAF status. For fully resected stage IV melanoma, patients can be treated with nivolumab. However, in stage IIIA, the use of adjuvant therapy should be carefully discussed since the benefit in IIIA is uncertain, since in all the trials patients in stage IIIA were not included (also, IIIA patients have a better prognosis than IIB and IIC patients).

In stage IV patients, antiPD1 should be offered with or without anti-CTLA4. In particular scenarios (high tumor burder, high LDH, symptomatic brain metastases, poor performance status…) and with positive BRAF V600 mutation, antiBRAF/MEK drugs should be offered first. Chemotherapy can be considered in patients with good performance status only when there's resistance to immunotherapy or to targeted therapies.
For brain metastases, it is recommended stereotactic surgery + combined immunotherapy, while whole brain radiotherapy can no longer be recommended for brain metastases since it does not prolong survival. Alternatively, immunotherapy or targeted therapies may be used in symptomatic brain metastases.
In mucosal melanomas, combined immunotherapy should be offered.

Mucosal Melanoma Guidelines update (anorectal, urogenital and H&N)
Dr Paul Lorigan

Mucosal melanomas represent 1.3% of melanomas in Western populations. The most common sites is head and neck (55%), followed by anorectal (23%). These melanomas tend to do worse.
Dr Lorigan reviewed the UL guidelines on mucosal melanomas (Smith et al. Eur J Cancer).
There are multiple issues with these patients: they require a wide range of specialist teams, they typically are excluded from clinical trials…
There are some recommendations different in these melanomas: punch or incisional biopsies are recommended in order to render the diagnosis. The biopsy should be reviewed by a melanoma pathologist, and a CT or PET-CT should be done before radical excision.
Regarding the anorectal and vulvovaginal melanomas, surgery should be done with a narrow margin (1mm) but achieving complete resection (R0). SLNB needs to be done only if we are going to give them adjuvant treatment, and no lymphadenectomy is needed.
For head and neck, it is also similar, but it's relevant to performing an imaging exploration before surgery.
What about adjuvant therapy in mucosal melanomas? In Checkmate 238 there were 39 patients with mucosal melanomas but there's only some response with ipilimumab. However, the benefit of adjuvant therapy remains unknown.

Dermoscopy of pigmented lesions
Dr Iris Zalaudek

Nowadays, there is a slight tendency of improving melanoma survival. This is due to the onset of immunotherapy or targeted therapy, but also due to the improved use of dermoscopy. This happens because dermoscopy allows us to diagnose melanoma earlier than the clinical ABCDE rule.

Also, dermoscopy is very relevant before undergoing melanoma surgery. It is mandatory to perform a full body exam using dermoscopy before performing surgery since patients can have other melanomas, basal cell carcinomas… and the skin used to graft the patient may harbour some of these lesions.
Also, some dermoscopic features may have prognostic implications. For example, black blotches may mean epidermal consumption which may mean an early stage of ulceration.
What about follow-up? We now have evidence that the diagnosis of melanoma is improved if the detection is performed by a dermatologist, especially if using digital dermoscopy follow-up. In some subsets of melanomas such as lentigo maligna melanoma, scalp melanoma or acral melanoma, it is also important to palpate the initial scar since these melanomas have a high tendency to recur. If there's a hard area or a minimal pigmentation, it is advised to biopsy.

What about skin reactions to immunotherapy or targeted therapies? We know that vitiligo represents a sign of good response with immunotherapy. Interestingly, it seems that the presence of regression signs in nevi seen under dermoscopy, or the presence of halo-nevi, this may precede the onset of vitiligo related to immunotherapy, thus forecasting a good response to immunotherapy.

Sex bias in skin cancer
Dr Amaya Virós

There is a huge bias related to sex in multiple diseases, from infectious diseases, immune disorders, cancers, among others. In most cancers, except breast and prostate cancers that are gender-related, there are more cancers in males and more mortality in males.
In males, their cancers have more mutations hinting that there are multiple genes that are upregulated in males.
When we look in melanoma, there is an increased mortality in males. So, females have a better prognosis especially when they are young. Similar results occur in cutaneous squamous cell carcinoma (SCC), with men doing worse with more metastatic SCC compared to females.
One hypothesis is that men have more sun exposure and have more skin to be affected by skin cancer (they are balder than females). Another well-established reason is that they seek for medical advice later than women. However, there are other factors that may be relevant here.
The team of Dr Virós performed experiments in mice and induced skin cancers in both male and female mice. They saw what has also been seen in humans, that males develop more aggressive SCC than females. They thought it may be due to differences in DNA gene repair. So, they did whole exome sequencing (WES) on this population and there were no differences in DNA gene repair. So, the differences may be in the mutation landscape? No, there were no differences. Then later they looked at the immune landscape and they saw that females have a better immune response with a better T lymphocyte response. To check if this hypothesis was correct, they decreased the mice immunity with prednisolone and then they saw that the prognosis of the tumors developed were the same between males and females. So, immunosuppression reverts the female “privilege” against cancer. Why is this happening? It could be because females have high expression of CDKN2A which blocks the proliferation of cells. Hence, if CDKN2A is mutated, the cancer grows faster.
And what happens with humans? In single-cell human culture experiments they could replicate these results found in animals.
To sum up, there is a huge sex bias in skin cancers, females upregulate cancer immune-fighting pathways + CD3 and CD8 T cells, and immunosuppression affects both sexes but affects females more profoundly.

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