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DERMA TODAY

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Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "Derma Today" which contains latest and interesting news in the field of Dermatology.

This issue contains:

Should you require any article or, medical information, please feel free to contact us medicalservices@microlabs.in

Looking forward to your valuable feedback.

Best Regards,

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First-line treatment for unresectable advanced *BRAF*$_{V600}$ mutation positive melanoma: Atezolizumab, vemurafenib, and cobimetinib

Introduction

Immune checkpoint inhibitors and BRAF and MEK inhibitors in adults with BRAFV600 mutation-positive metastatic melanomas have greatly increased clinical results. Although high objective response levels equate BRAF and MEK inhibitors, most responses are short-lived. Immune checkpoint inhibitors have longer lasting responses with comparatively lower reaction levels.

Because of these complementary clinical characteristics, the combination of the two approaches is appealing. A hybrid strategy is backed by preclinical and translational evidence demonstrating the immunological impact of BRAF and MEK inhibitors such as the infiltration of CD4 and CD8 T cells into tumours, the upregulation of melanoma antigens and the production of MHC class I and main Class II histocompatibility complex on tumor cells, and a cytokine transfer to the tumor milieu. With such combinations early phase studies showed promising antimelanoma activity and manageable safety. The atezolizumab programmed cell death ligand 1 (PD-L1) inhibitor is approved for selected patients with urothelial, lung, and breast cancer as a monotherapy or combination and has shown activity in advanced melanoma as a monotherapy. Patients with BRAFV600 mutation-positive advanced or metastatic melanoma are approved for combination therapy with the BRAF inhibitor, vemurafenib, and MEK inhibitor, cobimetinib.

A phase 1b study in patients with BRAFV600 mutationpositive advanced melanoma showed that initiating vemurafenib and cobimetinib 4 weeks before atezolizumab and reducing vemurafenib dosing from 960 mg twice-daily to 720 mg twice-daily after 3 weeks was tolerable and efficacious.

In addition, the initial targeted therapy period was associated with beneficial changes in the immune microenvironment of the tumor. Therefore, this randomized, controlled, phase 3 study was carried out which incorporated this dosing schedule to compare the above molecules in patients with advanced or metastatic mutation-positive BRAFV600 mutation melanoma in previously untreated.

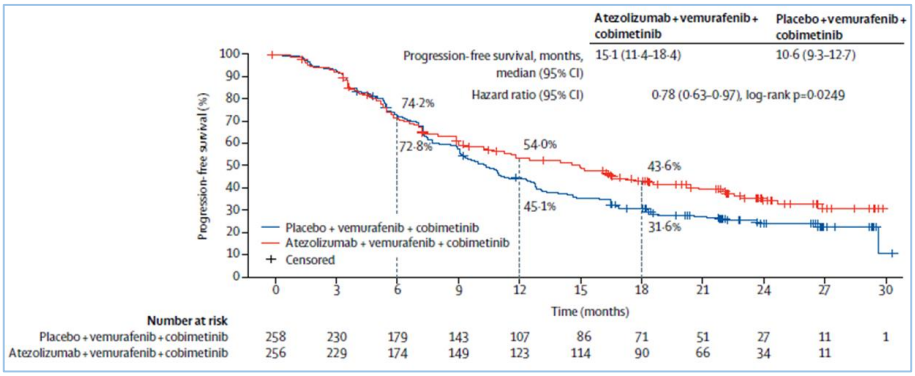
Methods

This was a randomised, double-blind, placebo-controlled phase 3 study done at 112 institutes in 20 countries. Patients with unresectable stage IIIc–IV, BRAFV600 mutation-positive melanoma were randomly assigned 1:1 to 28-day cycles of atezolizumab, vemurafenib, and cobimetinib (atezolizumab group) or atezolizumab placebo, vemurafenib, and cobimetinib (control group). In cycle 1, all patients received vemurafenib and cobimetinib only; atezolizumab placebo was added from cycle 2 onward. Randomisation was stratified by lactate dehydrogenase concentration and geographical region. Blinding for atezolizumab was achieved by means of an identical intravenous placebo, and blinding for

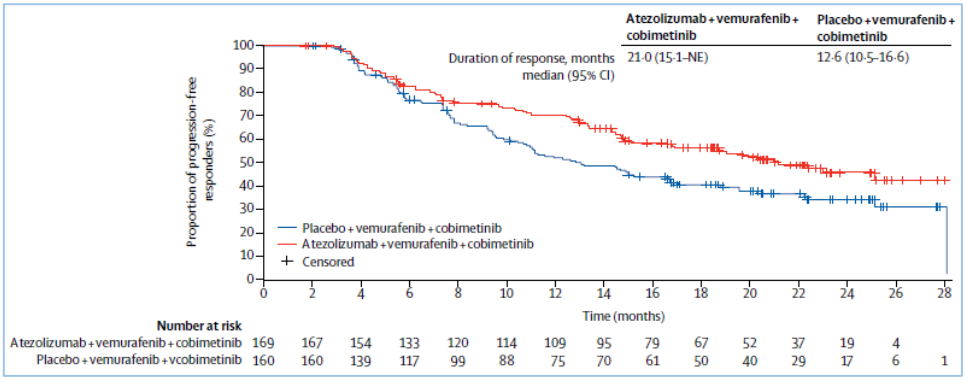
vemurafenib was achieved by means of a placebo tablet. The primary outcome was investigator-assessed progression-free survival.

Results

Between Jan 13, 2017, and April 26, 2018, 777 patients were screened and 514 were enrolled and randomly assigned to the atezolizumab group (n=256) or control group (n=258). At a median follow-up of 18·9 months (IQR 10·4–23·8), progression-free survival as assessed by the study investigator was significantly prolonged with atezolizumab versus control (15·1 vs 10·6 months; hazard ratio [HR] 0·78; 95% CI 0·63–0·97; p=0·025). Common treatment-related adverse events (>30%) in the atezolizumab and control groups were blood creatinine phosphokinase increased (51·3% vs 44·8%), diarrhoea (42·2% vs 46·6%), rash (40·9%, both groups), arthralgia (39·1% vs 28·1%), pyrexia (38·7% vs 26·0%), alanine aminotransferase increased (33·9% vs 22·8%), and lipase increased (32·2% vs 27·4%); 13% of patients in the atezolizumab group and 16% in the control group stopped all treatment because of adverse events.



Progression-free survival in the intention-to-treat population as assessed by the study investigators



Kaplan-Meier estimate of duration of response in the intention-to-treat population

Conclusion

This research found that attaching the PD-L1 inhibitor atezolizumab to BRAF's pathway-targeted agents vemurafenib and cobimetinib is a safe and efficient treatment choice for BRAFV600 mutation-positive metastatic melanoma patients.

Source: Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;395(10240):1835-1844.

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Pediatric Skin Procedures and the risk of General Anesthesia

Introduction

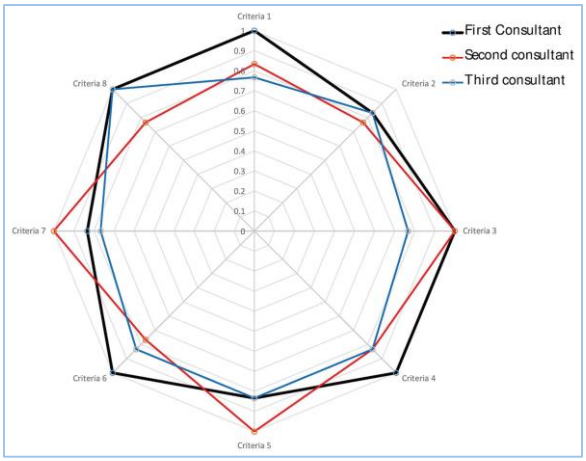
Surgical skin procedures are usually performed as an outpatient service, with some trivial complications accompanying it. A retrospective multicenter review of pediatric patients found no serious complications. The usage of general anesthesia lately has risen in pediatric skin procedures. It is challenging to mollify a conscious infant even with local anesthesia during an invasive procedure. Sometimes, doctors choose to treat small children with general anesthesia to reduce the discomfort and neurological distress associated with local anesthesia and also to maximize the final effect. Randomized control trials assessing general anesthesia in pediatric invasive skin procedures are sparse compared with local anesthesia or any other approach. To assess the safety of general anesthesia in the pediatric population undergoing dermatological procedures, we conducted this retrospective cohort study.

Methods

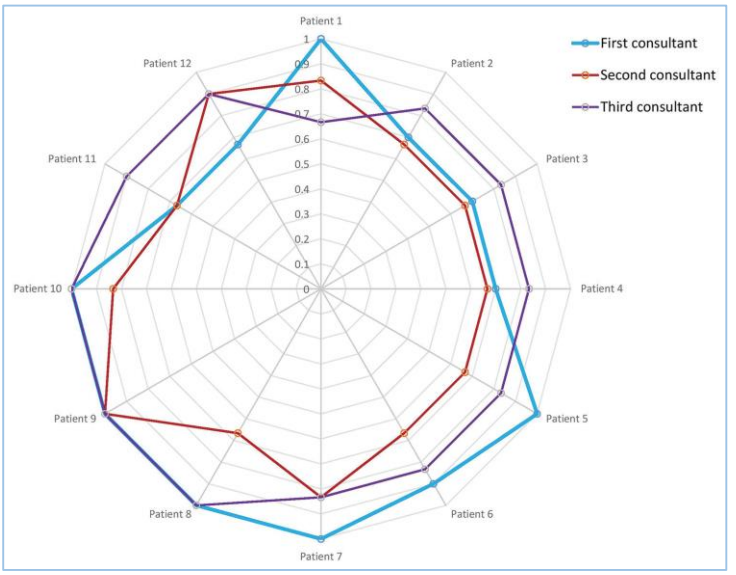
A retrospective cohort study of a patient chart review from the period (September 1, 2017, to September 2019). All patients admitted for pediatric skin procedures during this period have participated in our study. We reviewed selected charts to document any unexpected admissions, adverse events, or complications. Surgical outcomes and anesthesia complications were reviewed by three anesthesiologists.

Results

A total of 211 procedures were reported for 211 patients with 19 diagnoses. No adverse events related to anesthesia were recognized, apart from minor complications noticed in 12 patients. Kappa value ranges between 0.78 and 1.00 (95% confidence interval, 0.46809–1.00).



It shows percent agreement among raters for the eight prespecified criteria used for the evaluation of the 12 patients



It shows percent agreement among raters for the 12 patients evaluated by the consultants in terms of complication criteria

Conclusion

In conclusion, with appropriate staff, suitable surgical procedure, patient selection, and modern technology, dermatologists and pediatricians can perform the necessary procedures safely under general anesthesia with the supervision of pediatric-trained anesthesiologists.

Source: Alhabeeb BM, Alhazmi AM, Alobaid OA, et al. Risk of general anesthesia in pediatric skin procedures: A retrospective cohort study. J Dermatol Dermatol Surg 2020; 24:41-6.

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High-Grade Myelodysplastic Syndrome and Cutaneous Langerhans Cell Histiocytosis Suggested by Next-Generation Sequencing

A rare dendritic cell disease with complex cutaneous activity is Langerhans cell histiocytosis (LCH). New research indicates the root of LCH cells is from the precursor of amyeloids. We report a case of clonally related cutaneous LCH preceded by myelodysplastic syndrome, in which the next-generation sequencing suggested a common clonal origin of these 2 disorders.

Case study

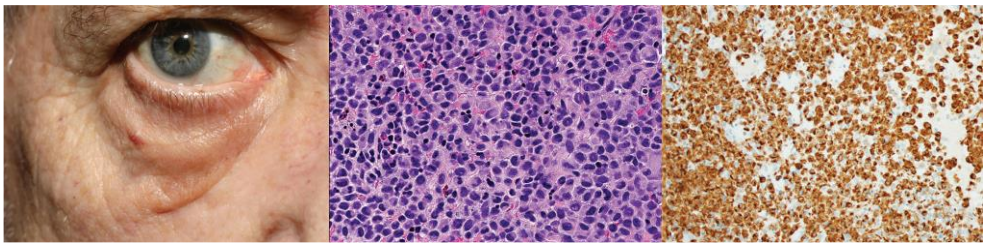
A 60-year-old man suffered an asymptomatic, new-onset eruptive lesion of the face. His medical background was noteworthy in the environment of persistent high-grade myelodysplastic syndrome and refractory anemia with severe blasts for producing acutemyeloid leukemia (AML). A smooth, red, dome-shaped papule under the right lower eyelid was revealed by physical examination. A shave biopsy specimen showed a diffuse atypical dermal infiltration of monocytoid-appearing cells mixed with rare eosinophils, consistently positive for CD207 / langerin and negative formyeloperoxidase, all diagnosed with cutaneous LCH. The status of the BRAF-V600E variant was identified by immunohistochemical studies and confirmed by analysis of the polymerase chain reaction. Prior biopsy of the bone marrow revealed hypercellular bone marrow of

Atypical erythropoiesis and 10 % to 15% myeloblasts, indicative of developing AML. Molecular research using next-generation sequencing in the bone marrow aspirate targeted detailed gene profiles, and paraffin-embedded skin biopsy specimens identified similar pathogenic variants in the genes ASXL1, IDH2, and STAG2. Targeted treatment for progression of myelodysplastic syndrome with enasidenib, an IDH2 inhibitor, resulted in stable cutaneous LCH with no new lesions.

DISCUSSION

Adult LCH is rare and may present with variable cutaneous involvement at one location or involve multiple end-organs. AML and LCH co-occurrence is well documented; the LCH can be accompanied by or occur synchronously with AML. Since gene expression profiling has established the initial LCH cell as a dendritic myeloid precursor,1 it is possible that LCH and myeloid malignant neoplasms may have a shared clonal origin. The transdifferentiation hypothesis was used to identify tumors that are clonally linked and express 2 phenotypically distinct hematopoietic lineages. This was previously identified through molecular research between LCH and subsequent B-cell or T-cell lineage lymphoma or leukemia, with a polymerase chain reaction demonstrating similar rearrangements of the B-cell and/or T-cell receptor genes. Prior to this, a clonal relationship between myeloid malignant tumors and cutaneous LCH was reported based on a shared immunohistochemical profile between these two diseases. In this case, the use of next-generation sequencing was uniquely demonstrated by identifying common variants of the genes IDH2, ASXL1, and STAG2. The molecular

mechanism of transdifferentiation is hypothesized as the acquisition of the unique BRAF-V600E variant, identified in cutaneous LCHcells but absent inmyeloblasts, which induces constitutive activation of downstream mitogen-activated protein kinase and extracellular signal-regulated kinase. To our knowledge, the STAG2 variant has never been reported in LCH before; however, it has been shown to activate mitogen activated protein kinase signaling in melanoma cells that are resistant to BRAF inihibitors and is proposed as another molecular pathway that contributes to the conversion of myeloblasts into cutaneous LCH cells



A, Red papule under the right lower eyelid. B, Atypical diffuse dermal monocytoid-appearing infiltrate admixed with eosinophils (hematoxylin-eosin; original magnification ×40). C, Immunohistochemical studies reveal strong positivity for langerin

Although skin involvement may be the only clinical presentation in LCH, systemic involvement must be excluded; often affecting the hypothalamic-pituitary region, lungs, and bones in adults. This disorder occurs occasionally with leukemia or lymphoma which may develop after the initial diagnosis of cutaneous LCH. Vemurafenib treatment should be seen in BRAF-associated LCH patients with severe skin exposure or other significant clinical complications. In summary, this case report supports the hypothesis that LCH and AML cells that derive from a specific clonal myeloid precursor and that transdifferentiation of the tumor lineage can clarify the connection between cutaneous LCH and myeloid blood cancers in these settings.

Source: Khurana S, Sluzevich JC, He R, et al. Association Between High-Grade Myelodysplastic Syndrome and Cutaneous Langerhans Cell Histiocytosis Suggested by Next-Generation Sequencing [published online ahead of print, 2020 May 6]. JAMA Dermatol. 2020;10.1001/jamadermatol.2020.0544.