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Overview of Malignant Melanoma and Treatment Approaches

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Abstract: **Melanoma is a serious form of skin cancer it is a disease in which malignant (cancer) cells form melanocytes (cells that color the skin). This review was aimed to overview the malignant melanoma from different perspectives, we intended to discuss the bases and etiology behind melanoma forming, but the main aim was to evaluate the treatment options of malignant melanoma. An electronic database (PubMed/Midline, and Embase) were comprehensively searched for relevant articles there were published in English language and containing human subjects only up to December 2016. we used a following term as Mesh term to find related trails to our study; "malignant melanoma" Or 'skin cancer" Or" metastatic melanoma" combined with "management" Or "treatment approaches", Moreover we searched the references of each identified study for more related articles to support our evidence on treatment approaches of malignant melanoma. Treatment of melanoma malignancy remains an obstacle. Identifying the mutations in the various paths that cancer malignancy patients have obtained would enable the ongoing advancement of more efficacious treatments that aim to prevent drug resistance and cancer recurrence. The convergence of immunology with other disciplines of biomedical research would lead to additional improvement in the advancement of more recent and more efficacious restorative approaches to manage this debilitating and fatal disease While surgical treatment and radiation therapy might play a role in the palliation of signs from local tumor growth, systemic treatment is the essential of treatment for metastatic cancer malignancy.**

Keywords: **malignant (cancer) cells, Treatment Approaches.**

1. INTRODUCTION

Melanoma is a serious form of skin cancer it is a disease in which malignant (cancer) cells form melanocytes (**Figure1**) (cells that color the skin) [(1)]. Melanoma is the 6th most common cancer in the United States, and the variety of melanoma cases diagnosed every year is increasing quicker than for any other cancer [(2)]. Over the past decades the occurrence of deadly melanoma tends to be increasing [(2,3)]. Inning accordance with the data supplied by the WHO about 132,000 cancer malignancy skin cancers are being identified each year internationally [(3)]. Cancer malignancy has been reported as the seventh and fifth most typical cancer type in the United States in females and men, respectively, leaving out basal cell and squamous-cell skin cancer as well as in situ cancer other than urinary bladder cancer [(4)]. As it is estimated by the National Cancer Institute about 73,870 brand-new cases of melanoma (42,670 in males and 31,200 in women) will be detected in 2015 in the United States and the variety of deaths from the disease will reach 9940 [(4)]. The occurrence of cancer malignancy in addition varies by ethnic group. It represents 1 (per 100,000) in black people, 4 in Hispanics, and 25 in non-Hispanic whites every year [(4,5)].

Ultraviolet Radiation (UV) direct exposure has been linked as a major cause in the etiology of malignant melanoma [6]. However, acral lentiginous cancer malignancy (ALM) and mucosal cancer malignancy, which are more typical in Asia, are usually not a result of direct exposure to ultraviolet irradiation. The etiology is yet to be identified. In an epidemiologic study of ALM from Australia, an increased risk was connected with permeating injury of the feet or hands (relative risk [RR], 5.0) and with heavy direct exposure to agrichemicals (RR, 3.6) [7].

Surgery is the conclusive treatment for early-stage melanoma. Wide regional excision with sentinel lymph node biopsy and/or elective lymph node dissection (LND) is considered the essential of treatment for patients with main melanoma. In patients with solitary or acutely symptomatic brain metastases, surgical management might ease signs and provide local control of disease [8].

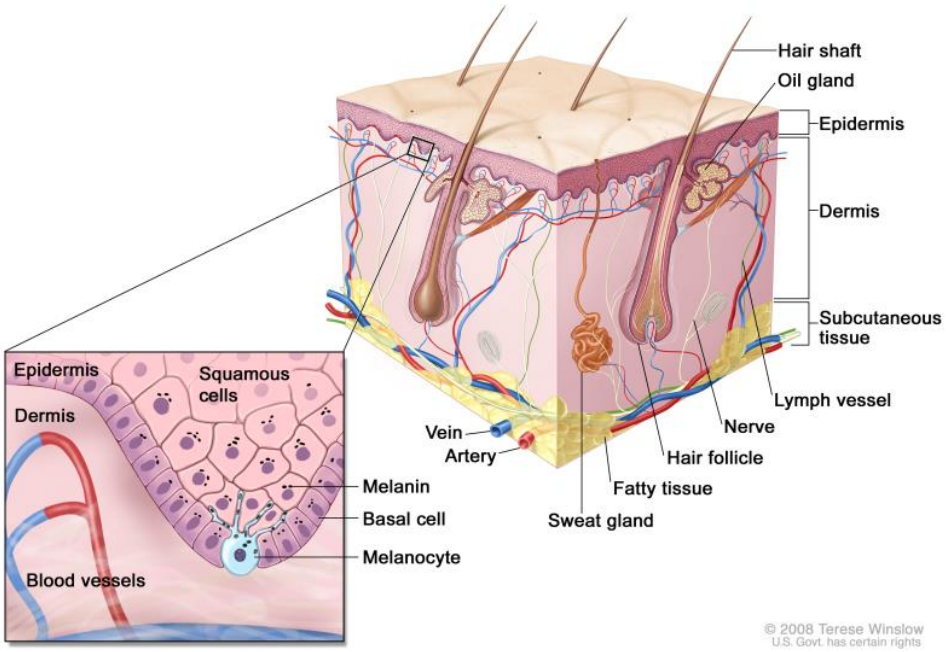

Figure1: Anatomy of the skin, showing the epidermis, dermis, and subcutaneous tissue. Melanocytes are in the layer of basal cells at the deepest part of the epidermis. [6]

AIM of study:

This review was aimed to overview the malignant melanoma from different perspectives, we intended to discuss the bases and etiology behind melanoma forming, but the main aim was to evaluate the treatment options of malignant melanoma.

2. METHODS

An electronic database (PubMed/Midline, and Embase) were comprehensively searched for relevant articles there were published in English language and containing human subjects only up to December 2016. we used a following term as Mesh term to find related trails to our study; "malignant melanoma" Or 'skin cancer" Or" metastatic melanoma" combined with "management" Or "treatment approaches", Moreover we searched the references of each identified study for more related articles to support our evidence on treatment approaches of malignant melanoma.

3. RESULTS & DISCUSSION

- **Classification and Staging of Malignant melanoma (MM):**

There are four significant kinds of cancer malignancy including (i) shallow spreading, (ii) nodular, (iii) lentigo maligna and (iv) acral lentiginous cancer malignancies. Of these, the shallow spreading type remains the most common and represent about 70% of melanomas followed by nodular kind that represents about 15 - 30% of melanoma cases. The lentigo maligna and acral lentiginous kinds represent less than 10% of melanoma cases [9,10]. In terms of staging, four systems are followed consisting of (i) the Clark scale (**Figure 2**), (ii) the Breslow scale, (iii) TNM staging and (iv) Number phases. The Clark scale examines the depth of sore in terms of it impacting different skin layers. The Breslow

scale evaluates regarding how thick the cancer malignancy is in the skin. The TNM (Tumor, Node, Metastases) staging is based on density of the sore and assessment of its infect lymph nodes and various tissues in the body and is also used for medical staging per the American Joint Committee on Cancer (AJCC). The number staging system (Stage 0 to Stage 4) couples details on depth of the sore and the TNM staging. For instance, Stage 0 suggests that the sore is restricted to epidermis (in situ) without spread to much deeper layers such as dermis whereas Stage 4, the other extreme, indicates infect lymph nodes and metastases to remote parts of the body such as brain, liver or lung [9,11].

Clark Level	Histological tumour characteristics
Level 1	Confined to the epidermis; "*in situ*" melanoma
Level 2	Invasion of the papillary dermis
Level 3	Filling of the papillary dermis but not extending to the reticular dermis
Level 4	Invasion of the reticular dermis
Level 5	Invasion of the deep, subcutaneous tissue

Figure1: Clark scale for melanoma [9]

- **Diagnosis of MM:**

Diagnosis of cancer malignancy can be accomplished through clinician evaluation of the skin lesion with the unaided eye. Clinicians often examine lesions based upon the "ABCDE rule" that is implied to indicate A: asymmetry, B: irregular border, C: color variations, D: diameter > 6 mm, and E: raised surface [9,12,13]. Nevertheless, medical diagnosis with the unaided eye is not always precise as seen in the approximately 80% precise diagnosis rate demonstrated among skin specialists, and around 30% rate for non-dermatological professionals [12]. Detection procedures have actually ended up being more technical with time in order to enhance efficacy and restrict the number of false negative cases that would allow undiscovered melanoma to establish to unsafe phases. Making use of a skin surface area microscopic lense or a dermoscope enables enhanced visualization of the sore [14,15]. Advancement of sophisticated digital systems have enabled the development of an automated cancer malignancy medical diagnosis system called MEDS, which integrates several category algorithms and uses them to evaluate various measurements and characteristics of the patient sore to produce effective diagnoses [12]. Research study in cancer malignancy diagnostics has likewise concentrated on spotting melanoma-specific biological markers that may help predict the course of the disease. Assaying the blood of melanoma patients who had actually been considered cancer complimentary for melanoma cells and other mRNA markers helps anticipate the possibility that the patient will experience remission of metastatic melanoma [16].

- **Role of Ultraviolet Radiation (UV) as an etiology of Malignant melanoma:**

Epidemiological studies have actually done much to clarify the possible causes of deadly melanoma. Research studies have actually shown that a major risk factor for melanoma advancement is exposure to Ultraviolet (UV) radiation direct exposure. Several blistering sunburn during childhood or adolescence more than doubles the risk for melanoma in later life [17]. This recommends that UV exposure plays an essential function in melanoma tumorigenesis. Additional experiments have actually revealed that UV radiation often leads to DNA mutations, such as the formation of pyrimidine dimers or deamination of cytosine into thymidine [18,19]. Cutaneous cancer malignancy samples demonstrate a high base anomaly rate that goes beyond that of nearly every other type of solid cancer, which might be attributed to the effectiveness of UV mutagenic impacts [20,21]. Individuals who have history of familial melanoma, which contributes to 8--12% of cancer malignancy cases, show a high level of sensitivity to UV radiation [22,23]. These people are more likely to develop melanoma earlier in age and to develop several melanoma sores [24].

- **Treatment of Malignant melanoma:**

One potential advance [25] that showed a great deal of pledge in the preclinical, and now in the clinical setting, is the targeting of the BRAF kinase in cancer malignancy. Vemurafenib and dabrafenib are BRAF kinase inhibitors available in

the United States. Trametinib, a mitogen-activated extracellular signal managed kinase (MEK) inhibitor, is likewise FDA-approved.

BRAF Inhibitors:

A. Vemurafenib:

The discovery of the anomalies worrying BRAF enabled us to present the inhibitors of the mutant BRAF kinases. The representative that must be considered a substantial advancement is certainly vemurafenib, an extremely particular inhibitor of the BRAF kinase that harbours the mutation V600. Numerous efforts to prevent the BRAF kinases had been performed before the discovery of vemurafenib, especially using sorafenib, the nonspecific BRAF inhibitors, but they all ended up being a failure eventually due to the insufficient scientific activity or the barely acceptable unfavorable effects of the drug. The scientific trials of vemurafenib began in 2008 but shortly after, in 2011, it was authorized by the FDA to deal with unresectable or late-stage melanoma [(25)]. Prior to vemurafenib was introduced, dacarbazine was the drug of choice for metastatic cancer malignancy, in spite of its low medical activity and poor action rates ranging from 11 to 25% and typical survival time of 4, 5 to 6 months [(26)]. The study that contributed most to the development of vemurafenib as the treatment for patients with metastatic melanoma was BRIM. In phase I (BRIM-1) patients with innovative tumors, the majority of whom had metastatic cancer malignancy with BRAF V600E mutation (89%), went through treatment with vemurafenib. The trial included two stages where patients were grouped into the dose-escalation mate and the dose-expansion associate. Being given the dose up to 720 mg two times daily, the patients did not develop dose-limiting toxicities. However, unfavorable effects such as arthralgia, queasiness, tiredness, rash, and photosensitivity were observed quite frequently. Among the patients in the dose-escalation group about 69% (11 from 16 who harbored V600E anomaly) experienced a response, whereas in the dose-expansion group 26 from 32 patients with cancer malignancy with V600E anomaly fulfilled the requirements for ORR (overall reaction rate) on the dose of 960 mg two times daily. The PFS (progression-free survival) in dose-escalation accomplice reached more than 7 months while the average survival had to do with 13.8 months [(25)].

B. Dabrafenib:

Another BRAF inhibitor utilized for treatment of melanoma is dabrafenib. In the United States it was approved by the FDA in 2013 as a single-agent treatment for unresectable or metastatic melanoma with BRAF V600E mutation [(28,29)]. Dabrafenib is thought about as a next generation agent and has a mechanism of action just like that of vemurafenib. A phase III (BREAK-3) trial compared dabrafenib and dacarbazine in $BRAF^{V600E}$-positive unresectable or metastatic (stage III or IV) formerly neglected melanomas. Dabrafenib was provided at 150 mg BID orally and dacarbazine at 1000 mg/m2 IV every three weeks. The trial enrolled 250 patients and the outcomes prosecuted dabrafenib to have appropriate safety profile and showed improvement in PFS over dacarbazine. The FDA authorized dabrafenib in 2013 for $BRAF^{V600}$-positive unresectable or metastatic cancer malignancies and the suggested dose is 150 mg BID orally. Dabrafenib is contraindicated in cancer malignancy harboring wild type BRAF. The most typical negative effects consist of hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erhthrodysesthesia syndrome. The major negative events consist of the development of new primary squamous cell cancer, cancer malignancies, and keratoacanthomas, febrile drug responses, hyperglycemia, and uveitis, iritis [(30,31)].

MEK inhibitors:

A. Trametinib:

Trametinib, an extremely selective MEK1/2 inhibitor, was authorized by the FDA on May 29, 2013, as a first-line treatment for patients with unresectable or metastatic melanoma with V600E/K anomaly. The approval was based upon stage III multinational, randomized trial METRIC [(31,32)]. The research study measured the efficacy of trametinib in comparison to chemotherapy. The main endpoint of the research study was PFS in patients with BRAF V600E-mutant melanoma with no prior brain metastases. Secondary endpoints consisted of ORR, OS, and security profile of the drug. In general, 322 patients with BRAF V600 E/K anomaly were randomized into trametinib arm and chemotherapy (dacarbazine or paclitaxel) arm in a 2: 1 manner. A total number of 273 patients were BRAF V600E positive without any history of brain metastases. The research study showed obvious enhancement in PFS in the group of trametinib when compared with the chemotherapy group (4.8 months versus 1.4 months, resp.). The validated ORR was 24% for trametinib and 7% for chemotherapy. Risk ratio (HR) for interim OS was 0.53 (95% CI, 0.30-- 0.94,) in favor of trametinib group. The patients were permitted to cross over from chemotherapy group to trametinib group after

verification of the disease progression (PD). The most commonly observed negative events during the treatment consisted of rash, diarrhea, edema, high blood pressure, and fatigue. The events typical of MEK inhibitors that could be seen were chorioretinopathy (<1%) and the decrease of ejection portion (7%). On the basis of the METRIC research study, treatment with trametinib is related to longer PFS when compared to chemotherapy (dacarbazine or paclitaxel) in patients with BRAF V600 E/K mutant cancer malignancy [33].

B. Selumetinib:

Selumetinib, a highly selective MEK 1/2 inhibitor, has actually been checked in order to evaluate its effectiveness and security profile in many research studies connected with various kinds of tumors. The combinations of selumetinib and various chemotherapeutic representatives including irinotecan, doxorubicin, docetaxel, and temozolomide showed the enhanced activity against tumor cells in malignancies such as BRAF-mutant melanoma, non-small-cell lung cancer, pancreatic cancer, or hepatocellular carcinoma [34,35,36,37]. The research study comparing selumetinib and temozolomide was carried out on patients with innovative mucosal or uveal cancer malignancy, despite the status of BRAF mutations. In general, 200 patients were enrolled in phase II of the study. They were randomized into selumetinib group, where they were administered the medicament in dosage 100 mg two times day-to-day and temozolomide group, where they were offered temozolomide 200 mg/m2 daily for 5 days every 28 days [38]. The crossover from temozolomide to selumetinib was allowed case of disease development. The outcomes of the study showed the equivalent progression-free survival in both groups of 78 and 80 days for selumetinib and temozolomide, respectively (HR 1.07; 80% CI: 0.86 - 1.32). Additionally, there was no significant distinction in PFS between 2 subgroups of BRAF- and/or NRAS-mutants. Partial reactions were observed in 5.8% in selumetinib and 9.4% in temozolomide group. As for patients with BRAF anomalies, unbiased reactions did not differ noticeably in between selumetinib and temozolomide arms (11.1% and 10.7%, resp.) [38]. Another phase II randomized trial was conducted to compare the results of treatment with mixes of dacarbazine plus selumetinib and dacarbazine plus placebo. In general, 91 formerly without treatment patients with innovative cancer malignancy were registered. The crossover from one group to another in case of disease development was not enabled throughout the research study. Median OS was 13.9 months in the selumetinib plus dacarbazine group and 10.5 months in the placebo plus dacarbazine group (HR 0.93; 80% CI: 0.67 - 1.28;). When compared to placebo and dacarbazine, the results of the study showed there was no enhancement in survival after the addition of selumetinib to dacarbazine. In spite of the information mentioned above, PFS was significantly longer in selumetinib plus dacarbazine group than in placebo plus dacarbazine group (5.6 months (80% CI: 4.9 - 5.9) versus 3.0 months (2.8 - 4.6), resp.) [39].

Another study reported the outcomes also of a phase III trial that compared vemurafenib and cobimetinib combination with vemurafenib and placebo group. Much like trametinib, cobimetinib is a MEK inhibitor. It was noted that the mix of vemurafenib and cobimetinib enhanced substantially the PFS in metastatic cancer malignancy harboring BRAFV600 anomaly [40]. Based upon these research studies, it is therefore, logical to think that the mix of BRAF and MEK inhibitors would appear to be superior to monotherapy moving forward (**Figure 3**) [41].

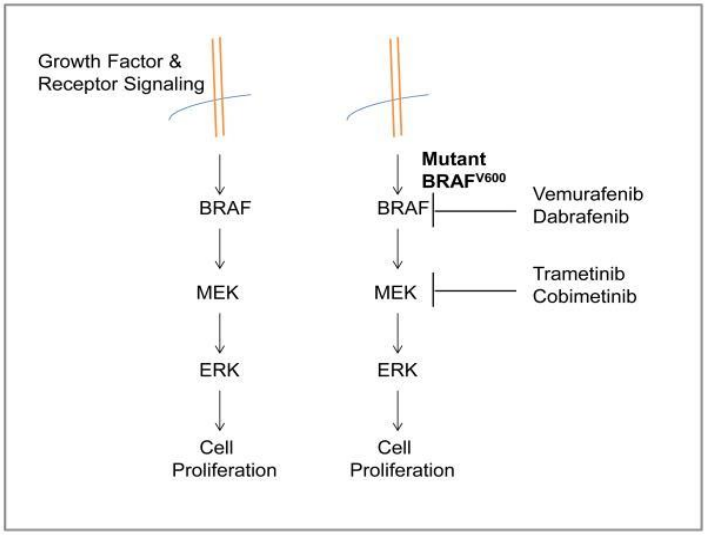

Figure 3: BRAF activation signaling events. Vemurafenib and dabrafenib inhibit BRAF^{V600} mutant form, whereas trametinib and cobimetinib inhibit MEK [41]

➢ **Surgical procedures in the management Malignant melanoma:**

Wide Margin Resection:

The dogma of large excision of ≥ 5 cm lost its rationale when Breslow showed that prognosis correlated with density of the main cancer malignancy. The idea of the need of a 5 cm margin was challenged and assessed in a variety of phase-III-trials. 3 trials were carried out in patients with thin melanomas < 2 mm. In the French Trial [42] (319 patients) and the Scandinavian Trial [43] (769 patients) patients were randomized to go through an excision with margins of 2 vs. 5 cm, while in the WHO-Melanoma Program Trial [44,45] (623 patients) margins were 1 cm vs. 3 cm. The Intergroup Trial in the USA [46,47] (486 patients) compared different margins (2 vs. 4 cm) in the management of thicker melanomas (1- 4 mm melanomas). (**Table 1**) shows that trials had really comparable results: regional recurrence rates, diseasefree survival (DFS) and general survival (OS) were essentially identical in the narrow excision and the large excision arm in all 4 trials. The conclusion from these trials is that a 1 cm margin suffices for melanomas < 2 mm which a margin of 2 cm is adequate for cancer malignancies 1- 4 mm. A nonrandomized research study based upon 278 cases [48] demonstrated a lack of impact of wider than 2 cm excision margins on the regional reoccurrence rate, DFS and OS in patients with cancer malignancies thicker than 2 mm. Taken together it shows that a 2 cm margin can be thought about adequate for all melanomas thicker than 2 mm. This means that essentially all melanomas at any site can be dealt with by excision and main closure.

Table 1: Surgical margins and outcome in primary melanoma [44-48]

Study (Ref)	Margin	# Pts	NE LR	WE LR	NE OS	WE OS	AT YRS
Melanomas < 2 mm							
WHO-10 [44,45]	1 vs. 3	623	2.5%	1.0%	87%	87%	10 yrs
French Trial [42]	2 vs. 5	319	-	-	93%	90%	4 yrs
Scandinavian [43]	2 vs. 5	769	0.8%	1.0%	90%	93%	5 yrs
Melanomas 1–4 mm							
Intergroup Trial [46]	2 vs. 4	486	0.8%	1.7%	80%	82%	6 yrs
Update [47]	2 vs. 4	470	2.1%	2.6%	ns	ns	8 yrs
Melanomas > 2 mm							
Nonrandomized Study [48]	< 2 vs. 3–5	278	8%	16%	58%	50%	5 yrs

Ref = reference; Pts = patients; NE = narrow excision; WE = wide excision;
LR = local recurrence; OS = overall survival; yrs =years.

Elective lymph node dissection:

Elective lymph node dissection (ELND) has been practiced commonly based upon the hypothesis that micrometastases from the main cancer malignancy share sequentially from the main tumor to local lymph nodes then to far-off sites. As in breast cancer lymphatic and haematogenic spread occur typically concurrently and it is for that reason unlikely that removal of lymph nodes including micrometastases changes the prognosis as most often prevalent micrometastatic disease exists. Retrospective research studies using historical controls (choice predisposition, phase migration) normally demonstrated a survival advantage in patients dealt with by ELND however 3 big studies making up some 10,000 patients, that did not compare outcomes between different period and lacked these pit falls failed to reveal an overall benefit for ELND (49,50) Thusfar 4 randomized phase-III-trials have actually been carried out. These trials have actually cannot show a substantial effect of ELND on general survival. In the first 2 trials, the big WHO-1 Trial [51,52] and in the much smaller Mayo Clinic's Trial [53,54] no benefit was observed for ELND. Patients with microscopically included lymph nodes in the ELND arm did not fare much better than the patients who underwent a delayed lymph node dissection for scientifically positive nodes. The overall outcome of the USA Intergroup trial in patients with intermediate primaries of 1-4 mm density was likewise unfavorable [55].

4. CONCLUSION

Treatment of melanoma malignancy remains an obstacle. Identifying the mutations in the various paths that cancer malignancy patients have obtained would enable the ongoing advancement of more efficacious treatments that aim to prevent drug resistance and cancer recurrence. The convergence of immunology with other disciplines of biomedical research would lead to additional improvement in the advancement of more recent and more efficacious restorative approaches to manage this debilitating and fatal disease While surgical treatment and radiation therapy might play a role in the palliation of signs from local tumor growth, systemic treatment is the essential of treatment for metastatic cancer malignancy. elective lymph node dissections and prophylactive separated limb perfusions, bring no survival advantage in comparison to restricting the surgery of the primary melanoma to an excision with a fairly narrow margin of maximally 2 cm and main closure. The prognosis of patients with main melanomas depends upon the presence or absence of systemic micrometastatic disease. This cannot be altered by extended locoregional surgical procedures.

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