Biomarkers and Therapeutic Targets for Melanoma

Subjects: Surgery

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Malignant melanoma is one of the most common cancers in the world. In the disease's early stages, treatment involves surgery, in advanced stages however, treatment options were once scarce. There has been a paradigm shift in advanced melanoma treatment with the introduction of immunotherapy and targeted therapies. Understanding the molecular pathways and their pathologic counterparts helped identifying specific biomarkers that lead to the development of specific targeted therapies.

Keywords: malignant melanoma ; immunotherapy ; adjuvant therapy ; targeted therapy

1. Introduction

Malignant melanoma is one of the most common cancers in the world, ranking fifth for the highest number of estimated new cases in 2022 according to Cancer Statistics Cases [1]. In the disease's early stages, treatment involves surgery; in advanced stages, however, treatment options were once scarce. There has been a paradigm shift in advanced melanoma treatment with the introduction of immunotherapy and targeted therapies. This began in 2011 when the U.S. Food and Drug Administration (FDA) approved the first drug, Ipilimumab, that proved to decrease mortality rates [2]. Since then, the FDA has approved eight more drugs for the treatment of melanoma that have resulted in improved overall survival rates [3].

Many patients, however, develop either primary or even secondary resistance to current systemic treatment options. Resistance is due to multiple complex mechanisms driven by a set of rewiring processes that involve cancer metabolism, epigenetics, gene expression and interactions in the tumour microenvironment.

There are several molecular pathways that, when unregulated, may become pathological and influence the onset, proliferation and invasion of melanoma.

The five main pathways are:

- The Mitogen-activated Protein Kinase (MAPK) pathway, where serine/threonine-protein kinase BRAF (BRAF) is involved [4];
- The phosphatidylinositol-3-kinases (PI3K)-AKT pathway [5];
- The gene suppressor Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) and tumour suppressors pathway [6];
- The microphthalmia-associated transcription factor (MITF) pathway [7];
- The nuclear factor-kappa B (NFκB) pathway [8].

Understanding these molecular pathways and their pathologic counterparts helps identify specific biomarkers that lead to the development of specific targeted therapies.

2. Novel Therapeutic Strategies in the Field of Melanoma

2.1. Gender-Adapted Therapy

Female patents have a survival advantage in the case of melanoma, regardless of other tumour characteristics such as Breslow thickness or ulceration [9]. This leads to the assumption that the genomic differences between males and females may be potentially exploited as a therapeutic target. Differences in melanoma mutation burden associated with gender have already been found [10]. Further gender differences could be related to innate factors such as hormone levels,

hormone receptor expression, immune system function and cell apoptosis susceptibility [11]. The connection between immune response and mutation burden explains the superiority of females over males regarding survival outcomes. The more that is revealed about the exact gender-related differences in melanoma, the more treatment may be accurately adapted.

2.2. Molecular Targeting Strategies

Six hundred and thirty-five biomarkers are associated with malignant melanoma [12]. There are numerous clinical trials aimed at discovering treatments for specific melanoma mutations. Two novel treatments showing promising results with respect to efficacy are:

Targeted therapy for c-KIT-mutated melanoma: The c-KIT gene mutation has been observed in gastrointestinal stromal tumours. Imatinib blocks the receptor tyrosine kinase activity of c-KIT and is a first-line therapy for gastrointestinal stromal tumours (GIST) [13]. Inhibitors of c-KIT, including Nilotinib, Dasatinib and Imatinib, have all been assessed in clinical trials and have delivered disappointing results with minimal activity in c-KIT-mutant melanoma patients. Further studies are required, as the long-term efficacy of c-KIT inhibitors in melanoma patients is uncertain, as well as its efficacy compared to other immunotherapies [14][15][16]. Immunotherapy in combination with c-KIT inhibitors provides hope for future therapeutic responses in mutant melanoma.

MEK inhibitors for NF1-mutation melanoma: Although NF1-mutant melanoma patients do not usually express NRAS or BRAF mutations, inhibition of the BRAF, MEK and mTOR pathways may be therapeutic since the NF1 mutation increases RAS/MAPK pathway signalling [17]. The greatest evidence of this achieved so far is related to treatment with MEK inhibitors for NF1-mutant melanoma [18][19]. Although therapeutic response to MEK inhibitors is impressive, a long period of treatment is necessary to achieve this response [20]. Immunotherapy and targeted therapy are both found to be effective for the treatment of NF1-mutant melanoma; however, further studies are required to determine the best treatment protocol with minimal side effects.

The field of targeted therapy is continuously evolving, with existing agents being investigated for new combinations and indications. Immunotherapy is also making continuous progress, and new standards of treatment are determined frequently.

Immunotherapy as a neoadjuvant therapy: Currently there are no standardized neo-adjuvant treatment regimens; however, there are several trials showing good pathological response rates, ranging from 50–80%, including OpACIN-neo studies and the PRADO trial, which are both phase II studies. These trials have confirmed the safety and high pathologic response rate (approximately 60%) of neoadjuvant Ipilimumab and Nivolumab. Patients with resectable BRAF-mutant stage III melanoma who received concurrent treatment with Dabrafenib+Trametinib+Pembrolizumab triple combination therapy in a new phase II trial had a high pathological response rate (80%) and a pathological complete response of 50% [21].

Adjuvant therapy: Anti-PD-1 monotherapy is an adjuvant treatment option for stage III melanoma and stage IV resectable patients. Standardized treatment options include adjuvant nivolumab treatment, which has shown significantly longer relapse-free survival (RFS) than adjuvant Ipilimumab in patients with resected stage IIIB, IIIC and IV resectable melanoma. In the KEYNOTE-054 study [22] assessing patients with stage IIIA, B or C melanoma, adjuvant Pembrolizumab had an improved RFS compared to the placebo. The COMBI-AD [23] trial of adjuvant BRAF/MEK-inhibitor therapy and dabrafenib and trametinib also exhibited improved RFS and overall survival (OS) compared to the placebo. In a new trial, KEYNOTE-716 [24], patients with stage IIB or IIC melanoma received pembrolizumab and, compared to the placebo, treated patients showed reduced risk of recurrence and improved distant metastatic-free survival. Although not yet a standardized treatment, this regimen has recently received FDA approval.

Immunotherapy is discussed as a neoadjuvant and adjuvant therapy in the current standards of treatment in melanoma, while surgery is still an essential part of the treatment when possible. The new immunotherapy drugs and the development of targeted therapy, with a face towards personalised therapy, bring up the question of the place of surgical treatment in the rapidly changing medical field. Surgical treatment is the gold standard for resectable cases and takes an important part in staging determination, but despite its values, it may lead to complications and morbidity. Therefore, a question about the potential of advanced medical treatments to replace surgical treatment has to be asked, at least for cases of mutilating resection surgeries.

Triple therapy for BRAF-mutant patients: the standard of care for BRAF-mutant melanoma patients is either BRAF/MEK inhibitor therapy or immunotherapy. There are three studies that have assessed anti-PD1+BRAF inhibitors +

MEK inhibitors. Firstly, IMspire 150 [25] was the only study with significant results; it showed that Atezolizumab + Cobimetinib improved PFS compared to targeted therapy + placebo. This regimen is not commonly used because usually one needs to begin with BRAF-targeted therapy (Vemurafenib + Cobimetinib) before administering Atezolizumab, which may be complicated. In addition, Atezolizumab is often considered to be inferior compared to anti-PD-1 therapy, even though there is no directly comparative data to support this. The second trial, KEYNOTE-022 [26], showed no significant difference in PFS between triple therapy and targeted therapy. The third trial, COMBI-I [27], also showed no significant support for triple therapy using Sparta-DabTram therapy. There is currently an ongoing phase 3 STARBOARD trial [28] assessing the triple combination of Encorafenib + Binimetinib + Pembrolizumab versus Pembrolizumab alone. This is highly relevant because, as opposed to previous studies, STARBOARD is using front-line anti-PD-1 immunotherapy for comparison, as opposed to BRAF/MEK inhibitors, which currently are rarely used as first-line therapy for melanoma treatment. In general, triple therapy is only considered the best treatment approach in patients with high disease burden that is rapidly progressing.

New immunotherapy combinations: A new study, RELATIVITY-047, suggested using combined immunotherapy for unresectable or metastatic melanoma with anti-PD-1 and anti-lymphocyte-activation gene 3 (LAG-3) as active agents [29]. While anti-PD-1 is a known and proven agent, anti-LAG-3 is a relatively new immune checkpoint inhibitor, and its role as an inhibitory target seems promising [30]. RELATIVITY-047 [29] compared Relatlimab (a new checkpoint inhibitor) + nivolumab to nivolumab alone and found a significantly improved PFS in favour of the combination therapy. This trial showed that inhibition of these two immune checkpoints provided a significant benefit compared to anti-PD-1 alone with regards to progression-free survival. Currently there are ongoing studies researching the efficacy of this combination therapy as an adjuvant therapy [31]. There are currently pre-clinical studies supporting the use of T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT), an inhibitory receptor known as Vibostolimab, in metastatic melanoma [32]. A phase III clinical trial is expected to begin relatively soon to compare TIGIT in combination with anti-PD-1 therapy vs. anti-PD-1 therapy alone as an adjuvant therapy for stage IIB, C, III and IV resectable cutaneous melanoma. In addition, there are current, ongoing trials assessing the addition of the BCL-2 inhibitor navitoclax to the combination of dabrafenib + trametinib [33]. There is also a phase 2 BAMM2 trial examining the addition of hydroxychloroquine to dabrafenib + trametinib in patients with stage IIIC and IV BRAF-positive melanoma [34]. Lastly, the use of ipilimumab/nivolumab + the interleukin 6 (IL-6) receptor blocker tocilizumab in patients with untreated, unresectable advanced or metastatic melanoma has been reported. Results are promising, and the study is ongoing [35]. In a very recent study, the phase I AMBER study presented at the 2022 ASCO Annual Meeting, dual T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) with anti-PD1 showed promising anti-tumour activity. This study utilized Cobolimab, a selective anti-TIM-3 monoclonal antibody [36].

An additional study assessed a TOLL-like receptor (TLR)-9 agonist: vidutolimod. This drug has shown promise in patients as a monotherapy as well as in combination with anti-PD-1 therapy, with a response rate of approximately 20% in both regimens; however, it is more durable when combined with anti-PD-1 therapy [37].

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