Cutaneous melanoma latest developments

Introduction

In this review, new treatment regimens found to improve melanoma survival in randomized controlled trials (RCTs) are presented. Long-term data from RCTs of sentinel lymph node biopsy (SLNB) and subsequent completion lymphadenectomy (CL) and the role of ultrasound (US) and fine needle aspiration (FNA) using "Berlin" criteria for primary melanoma over 1 mm Breslow thickness are reviewed. Controversies in the use of certain newer medications and the requirement to undergo SLNB to participate in clinical trials is discussed.

Ipilimumab

Ipilimumab is a monoclonal antibody that activates the immune system[1]. It is delivered intravenously. Robert[1] evaluated patients with metastatic melanoma treated with ipilimumab and dacarbazine versus dacarbazine alone. Although dacarbazine has been used for 30 years, its efficacy in managing melanoma is poor[2]. However, it was considered the best agent available for a comparison with newer pharmaceuticals. 20.8% of ipilimumab plus dacarbazine patients were alive at 3 years versus 12.2% for dacarbazine alone. Ipilimumab was subsequently found to slow progress in patients with brain metastases[3]. Complications from therapy are concerning with over half of patients suffering either grade 3 or 4 adverse events (Table 1). Immune related colitis along with liver impairment are among the concerning sequalae recognized. Other reported complications are diarrhea, dehydration, fatigue, confusion and skin rashes[1,3]. More recent trials of ipilimumab were in combination with PD1 drugs. (See below).

BRAF inhibitors - including Vemurafenib and Dabrafenib

The other group of drugs that first demonstrated a survival benefit for melanoma patents are the BRAF inhibitors. BRAF is a human gene that encodes a protein called B-Raf. This protein's full name is serine/threonine-protein kinase B-Raf. BRAF is a gene integral to the signaling pathway known as the RAS/MAPK pathway, which controls several important cell functions[4,5]. Inhibiting the BRAF pathway has been shown to prolong survival in melanoma patients with the V600E mutation. Some other variations of BRAF mutation also respond to BRAF inhibitors[6]. These BRAF mutations occur in around half of melanoma patients[6].

Vemurafenib. In the same edition of the New England Journal of Medicine as the ipilimumab trial above[1], Vemurafenib was shown to benefit melanoma patients[4]. Delivery is oral, avoiding hospitalization. Overall survival at 6 months was 84% with vemurafenib versus 64% with dacarbazine, which acted as the control agent[4]. Just over half of melanoma patients with the BRAF mutation gain a response to vemurafenib[6]. Melanoma patients with brain metastases can benefit from vemurafenib therapy[7].

Dabrafenib. The second BRAF inhibitor studied extensively is dabrafenib. In a large RCT of metastatic melanoma patients with the BRAF mutation median progression free survival with dabrafenib was 5.1 months versus 2.7 months with dacarbazine[5]. This drug has an established role in patients with brain metastases[8].

The **adverse events** associated with BRAF inhibitors include fatigue, alopecia, photosensitivity, nausea and diarrhea. Arthralgia can be severe and lead patients to ceasing therapy[4,6]. The adverse event profile is similar with both BRAF inhibitors. Moreover, around a quarter of patients developed cutaneous squamous cell carcinomas (SCCs) following BRAF inhibitor management[4,5,7,8].

MEK inhibitors in combination with BRAF inhibitors

A major step forward was achieved when it was identified that adding an MEK inhibitor to BRAF inhibitor treatment produced an additive therapeutic effect whilst reducing the adverse event profile of BRAF inhibitors alone[9,10]. The MEK (mitogen-activated protein kinase) enzymes work in another step of the RAS/MAPK pathway[9].

Trametinib is the predominant MEK inhibitor studied. Delivery is oral, and patients with metastatic melanoma felt better and lived longer on the combination approach[10]. 12-month survival was shown to be 72% with combination dabrafenib / trametinib treatment versus vemurafenib alone (65%)[9]. Importantly the development of new SCCs associated with BRAF inhibitors is almost eliminated with the combined approach[9]. Incidence of alopecia is also lower on the combined therapy, though gastrointestinal adverse events, pyrexia and peripheral oedema increase in incidence[11].

It is now standard for melanoma patients to receive combination therapy rather than BRAF therapy alone when BRAF therapy is indicated. Even patients previously treated with BRAF therapy may benefit when re-challenged with combination therapy[12]. Combined therapy can be continued for many years with patients continuing to receive benefit [11].

Nodal involvement. While early trials showed benefit in BRAF positive melanoma patients with distant metastases, recent trials have shown a role for MEK / BRAF therapy in patients that have nodal disease but no evidence of metastases elsewhere. These Stage 3 patients had a 3-year survival rate of 86% compared to 77% managed with placebo[13]. Patients in this trial had their involved nodes completely resected prior to drug intervention.

PD-1 drugs – including pembrolizumab and nivolumab

Perhaps the most encouraging new melanoma drugs are the programmed cell death (PD1) drugs. PD-1 is a checkpoint protein on T-cells that inhibits their activity when PD-1 attaches to PD-L1 proteins on some normal and cancer cells[1]. Cancer cells may have large amounts of PD-L1 which inhibits a beneficial immune response. PD-1 drugs inhibit this reaction and boost the immune response[3].

Pembrolizumab. Schachter et al[14] completed an RCT comparing intravenous (IV) pembrolizumab versus IV ipilimumab for melanoma patients with advanced disease. At two years 55% of the pembrolizumab patients were alive versus 43% for ipilimumab. Pembrolizumab has also been found effective in melanoma patients with nodal involvement[15]. 15% of patients on pembrolizumab developed grade 3 to 4 adverse events (Table 1). Hypothyroidism (14% of patients) and other endocrine disorders are recognized possible adverse events. Immune related adverse events included colitis.

Nivolumab. Weber et al compared nivolumab to ipilimumab[16] with stage III and IV melanoma patients. Recurrence free survival at twelve months was 70.5% with pembrolizumab versus 60.8% with ipilimumab. Grade 3 or greater adverse events are similar with both PD1 drugs[16-18] (Table 1).

Combination therapy. Nivolumab can also be combined with ipilimumab. However, 59% of patients developed severe (Grade 3) adverse events on combination therapy[18] (Table 1). Three-year survival was statistically improved being 58% in the combination therapy group versus 52% on nivolumab alone. There is a particular role of combined therapy for patients with brain metastases[17]. Other studies also suggest a role for patients receiving both pembrolizumab and ipilimumab[19].

Some question whether this improvement in survival from combined therapy is in the patient's best interests considering the concerning adverse events profile. This is a matter always needing considerable discussion with patients, with individual patient preferences and needs being taken into consideration.

Sentinel lymph node biopsy

SLNB became a common part of melanoma management because it might save lives.

By far the two most important long term prospective randomized trials of SLNB are the multicenter selective lymphadenectomy trial, denoted MSLT1 and MSLT2.

The MSLT1 randomized patients with a primary melanoma over 1.2 mm in thickness to SLNB and subsequent CL versus observation alone. MSLT1 demonstrated that SLNB and subsequent CL does not improve ten-year melanoma specific survival[20].

The MSLTII trial randomized patients who had a positive sentinel node into those having CL versus observation. Once again, no survival benefit was identified[21].

SLNB is still offered because it can provide added prognostic information for melanoma patients. However, even when the test is offered, it is important that those who are found positive do not then receive CL.

Ultrasound and FNA

SLNB is not required to detect early nodal involvement in melanoma patients. Disease can be accurately detected with US along with FNA using the "Berlin" diagnostic criteria. These are different from conventional US methods for other tumours. [22,23]. The Berlin US morphology criteria grades peripheral perfusion, loss of central echoes and balloon shape. The prognostic accuracy of this approach compares favorably with SLNB. Patients can be spared SLNB and its potential complications except for small numbers of patients where the US is suspicious but FNA is negative[23]. Availability of this approach remains limited in Australia, despite considerable usage in Europe. Given its confirmed role, imaging departments in Australia are further encompassing this approach.

Controversy

The Eggermont et al[15] RCT of pembrolizumab required node positive patients to have CL regardless of the Breslow thickness of the primary tumour. The trial found a one-year recurrence free survival of 75.4% in the pembrolizumab group versus 61% for controls. Recruitment commenced in 2015 prior to the MSLTII publication that found no survival benefit from CL[21]. Trial subjects were thus required to have surgery not demonstrated to improve their survival in order to possibly receive a drug that might.

We have previously expressed our ethical concern that high-risk primary melanoma patients could be *"den(ied) participation in clinical trials of potentially curative therapy"*[24] because they choose **not** to have a further surgical procedure with no proven survival benefit as demonstrated in completed RCTs. Surely cancer patients should only be encouraged to undertake procedures and therapies that have a demonstrated potential therapeutic benefit.

Pathology assessment of excised melanomas alone provides an array of accurate mortality prognostic information. This includes Breslow thickness, ulceration, tumour site, vascular invasion, and mitotic activity and age[20,25] (Table 2). It is yet to be demonstrated and seems implausible that SLNB, requiring a separate surgical procedure, is necessary to identify patients for drug trials rather than an algorithm of all information obtained from the excision along with nodal US and FNA.

We are concerned patients are still encouraged or required to have SNLB to enter trials[24]. If this is the key reason for the surgery, and not improved health outcomes, then health insurers, governments and patients should be alerted to the ethical, equity and financial issues arising from such clinical trial designs.

When drug trials have demonstrated a benefit for the intervention[13,15,16], applicability may be erroneously restricted to those having positive nodes detected by SLNB. This could cement a clinical role for a procedure without proven survival value, and will thus have far-reaching ethical and resource allocation implications for future patients who may be able to benefit from new interventions. Patients who decline to have SLNB must not be denied access to drugs that can treat their disease.

Discussion

Several newer drugs are now available that prolong survival in patients with high risk melanoma. Their role is especially established in those with metastatic disease. Some drug regimens require IV administration. Other combinations are available orally allowing greater flexibility for melanoma patients who may prefer this to having to attend a chemotherapy centre for treatment.

Long term benefit. The survival benefit of these drugs offers added months and potentially added years for patients with melanoma. In every RCT of these drugs thus far, the Kaplan Meier graphic analysis shows a continuing reduction in survival over time. Whether there is a five year or ten-year survival benefit from these drugs, including drug combinations, remain unknown. Long term outcomes from these trials will become available in time.

Adverse events. With all drugs studied, including combination therapies, the severe adverse events demonstrated are concerning both in percentage and nature. Many patients choose to withdraw from the therapies through intolerance of adverse events. Some patients will choose not to commence these therapies after balancing the potential for extra survival against the risk of side effects.

Second primary melanoma. Anecdotally, there some melanoma patients who develop a second cutaneous primary melanoma are not offered surgery for the new melanoma because they are on one or more of the drugs listed above. To suggest that the drugs can also treat a primary melanoma is not reasonable, not based on evidence and outside of guidelines. Further, one cannot assume that a new primary melanoma will have the same mitoses and / or drug responsive characteristics of the first

tumour. Patients on drug treatment who develop a new primary melanoma should still undergo wide local excision.

Sentinel node biopsy morbidity. SLNB is expensive and can affect ongoing quality of life. Complication rates of 10%[26] can include anaphylaxis, persistent seroma[27], lymphedema[27], tattooing at primary site from dye[28], mobility impairment[28], recurrent infection[27,] chronic site pain[28], joint pain and nerve damage[27]. Given that the purpose of SLNB is to determine early nodal involvement, and that this can achieved more safely through ultrasound and FNA, we would hope that usage of SLNB would now be infrequent.

Conclusion

Recent years have seen significant advances in management of metastatic melanoma including patients with nodal spread. SLNB provides prognostic information but has not been demonstrated to improve survival in an RCT. When a sentinel node is positive, removing the remaining nodes offers no survival benefit. US and FNA in skilled hands can provide comparable long-term prognostic advice for the melanoma patient as SLNB.

While the new drugs are prolonging life, they are not a cure. All of the new drugs demonstrate disease specific survival that continues to fall with time. We still do not know the long term (10 year plus) outcomes of these new drugs.

We are concerned that there remains pressure on patients to have SLNB surgery known not to be necessary in order to qualify for drugs that can be used to prolong their life. The General Practitioner is well placed as the gate keeper to monitor their melanoma patients including a role as an advocate for patients.

The role of the GP in managing melanoma, in collaboration with melanoma units where appropriate, may involve ongoing skin surveillance, management of new primary tumours (both melanoma and non-melanoma skin cancer) and management of adverse effects of the new medications. GP management also extends to palliative care and psychological support as the disease progresses.

Abstract

Background Several new drugs have been shown to improve survival in high risk melanoma patients.

Objective We discuss the new drugs, outline their role, the expected benefit from each and the risk of adverse events. We explain the place of sentinel lymph node biopsy SLNB and ultrasound with fine needle aspiration (US-FNA) in assessing and treating melanoma patients.

Discussion Ipilimumab has limited efficacy and a very concerning complication profile. Over half of patients suffer severe or life-threatening adverse events. BRAF inhibitors have greater efficacy and fewer adverse events than ipilimumab. Combining BRAF inhibitors with MEK inhibitors gives enhanced effect and improves the overall adverse event profile. BRAF inhibitors are only effective when the melanoma has a BRAF gene mutation, - something only found in half of cases. PD1 drugs are also more effective and have a much more acceptable adverse event profile than ipilimumab.

Both SLNB and US-FNA can detect early node involvement in melanoma patients. US-FNA is safer.

Call out box 1. - Key points for General Practice

- Drugs are available that prolong survival in patients with metastatic melanoma including nodal spread.
- Long term (five + years) benefits of currently available drugs for melanoma patients is unknown.
- Adverse events on available drugs can be serious or life threatening.
- Neither sentinel lymph node biopsy (SLNB) nor subsequent completion lymphadenectomy has been shown to have a melanoma survival benefit in a RCT.
- US and FNA using "Berlin" criteria provides prognostic information that can be achieved comparably, more cheaply and with less adverse events than through SLNB.
- Melanoma patients on melanoma drugs still need their remaining melanoma care continued, including regular skin checks.
- New suspicious skin lesions in established melanoma patients also need appropriate biopsy and surgical excision on their merits.

Table 1. Common terminology criteria for adverse events with drugs. (Ipililumab = IPI)

Grade	Meaning	IPI	BRAF + MEK	PD1 drugs	PD1 + IPI
Grade 1 MILD	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.				
Grade 2 MODERATE	minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL				
Grade 3 SEVERE	medically significant but not immediately life-threatening; hospitalization or hospital prolongation indicated; disabling; limiting self-care ADL	**56%** [1] **46%** [16]	**8%** [12] **15%** [29]	**14%** [16] **15%** [15]	**45%** [19] **59%** [18]
Grade 4 LIFE THREAT	Life-threatening consequences; urgent intervention indicated		**Nil**[12]		**55%** [17]
Grade 5 DEATH	Death related to adverse events of therapy	**Nil** [1] **2** [16]	**Nil** [8]		**Nil** [19]

Table 2. Multivariate hazard ratios for death for patients with intermediate thickness melanoma *

Prognostic indicator	Hazard ratio	95% confidence limits
Breslow thickness per 1 mm increase [20]	**1.59**	1.21 – 2.09
Sentinel node status – positive versus negative [20]	**2.40**	1.61 – 3.56
Location on trunk – compared with arm or leg [20]	**1.91**	1.26 – 2.88
Ulceration [20] – present or absent	**1.79**	1.24 – 2.58
Mitotic activity [25]	**1.04**	1.012 – 1.067
Age [25] – per 1 year increase	**1.009**	1.003 – 1.016

***Note that Clark level and gender are NOT independent predictors on multivariate analysis**

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