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Small molecules and targeted therapies in distant metastatic disease

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Chemotherapy, biological agents or combinations of both have had little impact on survival of patients with metastatic melanoma. Advances in understanding the genetic changes associated with the development of melanoma resulted in availability of promising new agents that inhibit specific proteins up-regulated in signal cell pathways or inhibit anti-apoptotic proteins. Sorafenib, a multikinase inhibitor of the RAF/RAS/MEK pathway, elesclomol (STA-4783) and oblimersen (G3139), an antisense oligonucleotide targeting anti-apoptotic BCl-2, are in phase III clinical studies in combination with chemotherapy. Agents targeting mutant B-Raf (RAF265 and PLX4032), MEK (PD0325901, AZD6244), heat-shock protein 90 (tanespimycin), mTOR (everolimus, deforolimus, temsirolimus) and VEGFR (axitinib) showed some promise in earlier stages of clinical development. Receptor tyrosine-kinase inhibitors (imatinib, dasatinib, sunitinib) may have a role in treatment of patients with melanoma harbouring c-Kit mutations. Although often studied as single agents with disappointing results, new targeted drugs should be more thoroughly evaluated in combination therapies. The future of rational use of new targeted agents also depends on successful application of analytical techniques enabling molecular profiling of patients and leading to selection of likely therapy responders.

Key words: B-Raf, c-Kit, inhibitor, melanoma, mTOR, multikinase

introduction

Treatment of melanoma once it has metastasised beyond locoregional sites remains unsatisfactory. A range of different treatments based on chemotherapy, biological agents or a combination of both (reviewed elsewhere) has had little impact on survival [1–3].

Single-agent chemotherapy produces responses in 10–20% of patients with advanced melanoma, although there is no evidence that this translates into a survival advantage. Complete responses occur in ~2% of the cases; median survival associated with chemotherapy is 9 months and 13% of patients are alive at 2 years [4]. Commonly used compounds include dacarbazine (DTIC), temozolomide, fotemustine, cisplatin, carboplatin, vinblastine, paclitaxel and docetaxel [5].

As a single agent, DTIC has been most commonly used even when it has not been formally compared with other agents or with observation alone. The usual dose is 1000 mg/m^2 every 3–4 weeks (given either in 1 day or at five daily doses of 200 mg/m^2). Some centres substitute DTIC with temozolomide for its convenience of administration [2]. Temozolomide demonstrated efficacy equal to that of DTIC in a phase III trial at a dose of 200 mg/m^2/day for 5 days every 28 days [6]. Recent results from a large, randomised phase III trial (EORTC 18032), which examined the efficacy of an extended schedule of temozolomide (week on-week off, 150 mg/m^2/day for 7 days repeated every 14 days) compared with standard dose single-agent DTIC, showed no difference in overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) between the two arms [7].

Combination chemotherapy is associated with a response rate of 30–50%, but with <5% complete responses and a median survival of 9 months [2, 5]. The better-known combinations are cisplatin–vinblastine–dacarbazine (CVD) and cisplatin–dacarbazine–BCNU–tamoxifen (Dartmouth regimen) [8, 9]. Although preliminary reports favoured the use of these regimens over single-agent chemotherapy, further comparisons with DTIC alone did not show differences in survival or even in response rate [10]. In addition, combination chemotherapy produces significant toxicity. Poor results with single-agent or combination chemotherapy regimens have remained

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unchanged for decades and underscore the need for application of fundamentally different strategies in treatment of advanced melanoma.

Substantial advances have been made in understanding the genetic changes associated with the onset of this malignancy. As reviewed elsewhere [11], consensus is emerging about primary events involved in the development of melanoma largely from comparative genome hybridisation (CGH) [12]. These include (a) up-regulation of the RAS/RAF/MEK pathway [12, 13]; (b) down-regulation of the retinoblastoma protein (RB) by increased cyclin D1 or CDK4 activity [12, 14]; and (c) inactivation of the CDKN2A p16 suppressor of CDK4 and 6, in >50% of melanoma [12, 15]. Activating mutations in c-Kit or FGF may occur in some melanoma [16]. Inactivation of the CDKN2A gene may also affect production of p14 ARF (alternate reading frame), which is important in maintenance of p53 protein levels by inhibiting the HDM2-mediated ubiquitination of p53 that leads to its degradation.

signal pathway inhibitors

Numerous studies have shown that several signal pathways related to survival of cancer cells are frequently up-regulated in melanoma. Arguably the most important of these is the RAF/RAS/MEK pathway, which is involved in proliferation and resistance to apoptosis. The pathway can be turned on by activating mutations in *NRAS* or *BRAF* or by endogenous receptor–ligand interactions. Importantly, activation of the pathway was shown to be related to progression of the disease [17] and resistance to apoptosis [18, 19]. Another survival pathway is the PI3K/Akt3 pathway, activated in 5–10% of melanomas by a mutation in the phosphatase and tensin (PTEN) protein, receptor–ligand interactions or activating mutations in *NRAS* [20–22]. The Src/Stat3 pathway was reported to be variably activated in some melanoma lines and metastatic melanoma *in vivo* [23]. Expression of c-Met/HGF receptors was also associated with progression of melanoma [24–26].

A number of new drugs have been developed that target members of these pathways. These are summarised in Tables 1 and 2. Many of these agents are still being evaluated in preclinical studies, and very few have been evaluated in randomised phase III studies. Sorafenib is a multikinase inhibitor with selectivity for B-Raf, C-Raf, VEGFR-2 and -3, platelet-derived growth factor receptor (PDGFR) and c-Kit. When used as a single agent, it stabilised the disease in 19% of stage IV patients, and when given with carboplatin and paclitaxel, it induced promising objective responses and PFS [27]. A randomised phase II trial comparing DTIC with or without sorafenib at twice-daily, 400 mg doses was conducted in 101 patients. The group receiving sorafenib had a PFS of 21.1 weeks compared with 11.7 weeks in the DTIC-alone group. Response rates were 24% and 12%, respectively [28]. Another phase II trial with a complex design investigated sorafenib in combination with temozolomide. Again, encouraging response rates were reported [29]. Skin rashes and haematologic toxicity were the main side-effects reported. A phase III trial recruited 270 patients into a second-line study and compared carboplatin plus paclitaxel with or without sorafenib. The median PFS was 17.9 and 17.4 weeks in the placebo and sorafenib groups, respectively. The ORR was 11% in both groups [30]. Although the addition of sorafenib did not improve PFS or ORR in this second-line patient population, the utility of carboplatin plus paclitaxel with sorafenib in chemotherapy-naïve advanced melanoma patients remains to be determined. The Eastern Cooperative Oncology Group (ECOG) is conducting a similar trial in previously untreated patients that is now closed to accrual (ECOG 2603). The results of the trial and further studies on sorafenib plus DTIC are awaited with interest.

The specific MEK inhibitor AZD6244 was evaluated in a randomised phase II trial of 200 patients with stage IV melanoma. Patients were randomised to AZD6244 or temozolomide; recently reported results indicate that there was no significant difference in PFS between those arms [34]. However, AZD6244 monotherapy resulted in lasting remissions mainly in patients with documented B-Raf mutations. Combinations with other agents, such as a taxanes, are being planned. Taxanes are known to activate the anti-apoptotic MEK pathway [48], and combination therapy with inhibitors of this pathway may be beneficial.

The other two B-Raf inhibitors, RAF265 and PLX4032 (Table 1), have high affinity for the mutated B-Raf and are in dose-finding and early phase II studies. The MEK-specific inhibitor PD0325901 was associated with some retinal disturbances, and its further evaluation was halted. Tanespimycin (KOS-953), an inhibitor of heat shock protein 90 (Hsp90), targets proteins protected (chaperoned) by Hsp90. This includes RAF, Akt and other signal pathway proteins. The drug was tested in a phase II study in previously treated stage IV melanoma patients and administered twice weekly for 2 weeks out of 3 weeks. Results from a treatment of 14 patients met the criteria for further evaluation in the second stage of the trial [31]. Another group,

Table 1. RAS/RAF/MEK signal pathway inhibitors

Agent	Class of inhibitor	Target protein(s)	Reference
Sorafenib	Multikinase inhibitor	C-Raf; B-Raf; VEGF-2, -3; PDGF; Flt-3; c-Kit	[27–30]
Tanespimycin (KOS-953, 17-AGG)	Hsp90 inhibitor	Hsp90 (client proteins, B-Raf, Akt, others)	[31]
RAF265	Multikinase inhibitor	Mutant B-Raf, VEGFR-2	[32]
PLX4032, PLX4720	Selective B-Raf kinase inhibitor	Mutant B-Raf	[33]
PD0325901	Non-ATP-competitive specific MEK inhibitor	MEK1, 2	[32]
AZD6244	Non-ATP-competitive specific MEK inhibitor	MEK1, 2	[34]
Tipifarnib (R115777)	Farnesyl transferase inhibitor	Prenylated proteins	[35, 36]

farnesyl transferase inhibitors, should in theory inhibit activation of RAS. However, when used as a single agent this group of drugs has been disappointing [35, 36].

Most of the agents in Table 2 are at early stages of investigation and are listed to indicate the rich supply of agents that remain to be evaluated in treatment of melanoma. Given that activation of the Akt pathway has been implicated in resistance to chemotherapy [22], trials with inhibitors of this pathway or downstream targets such as mTOR, GSK3β or HDM2 are awaited with much interest.

A key downstream target of Akt—mTOR exists in two complexes, mTORC1 and mTORC2. The latter is not inhibited by rapamycin or its analogues and is believed to be responsible for rapamycin-induced activation of Akt and PKC-α [49]. Newer inhibitors, which target the mTORC2 complex or those that inhibit both PI3K and mTOR (XL765), should avoid this problem. XL765 has proved to be well-tolerated in phase I studies [42].

A rich supply of inhibitors of receptor tyrosine kinases (RTKs), such as those against Bcr-Ab1, c-Kit, PDGFR, epidermal growth factor receptor (EGFR), c-Met and Src, may have a role in the treatment of some melanomas. For example, a high percentage of mucosal or acral melanoma and some cutaneous melanoma have amplified and mutated c-Kit and may respond to imatinib, sunitinib or dasatinib [44, 45]. Four phase II trials with sunitinib or imatinib in patients with c-Kit melanoma mutations are ongoing. A subgroup of melanoma with overexpression of phosphorylated c-Kit and CDK4 were resistant to B-Raf inhibitors but sensitive to imatinib [50].

Several agents of indeterminate action such as histamine [51] and lenalidomide (CC-5013) [52] are no longer under investigation. Elesclomol (STA-4783) is a new agent that appears to increase reactive oxygen species. Results from a recent randomised phase II study of elesclomol in combination with paclitaxel indicated a significant benefit for chemotherapy-naïve patients in PFS (HR = 0.315, $P = 0.02$) [53]. Evaluation of this combination therapy has progressed to a phase III trial [54]. Axitinib (AG-013736), an oral inhibitor of VEGFR-1, -2 and -3, c-Kit, PDGR-α and PDGR-β, is also at an early stage of evaluation in melanoma [55], and recent results from a phase II study demonstrated its single-agent activity in a subgroup of melanoma patients [56].

Table 2. Akt, receptor tyrosine kinase (RTK) and Stat signal pathway inhibitors

Agent(s)	Target protein	Reference
PI 103	PI3K/mTOR	[37]
SF1126 (LY294002-prodrug)	PI3K	[38]
Perifosine, PX-866	Akt	[22]
CMEP	Akt	[39]
Temsirolimus (CCI-779)	mTOR	[40]
Everolimus (RAD001)	mTOR	[40]
Deforolimus (AP23573)	mTOR	[41]
XL765	P13K/mTOR	[42]
SB216763, DW1/2	GSK3β	[43]
Imatinib, dasatinib, sunitinib, erlotinib	RTKs	[44]
Dasatinib	Src	[45]
S31-M2001	Stat3	[46]
SUI1274	c-Met/HGF	[24, 47]

inhibitors of anti-apoptotic proteins

Another group of new drugs targets the anti-apoptotic proteins. Mitochondria-dependent apoptotic pathways are regulated mainly by the Bcl-2 family of proteins, which, as reviewed elsewhere [57–60], consists of a family of BH3-only pro-apoptotic proteins, two multi-domain pro-apoptotic proteins (Bax and Bak) and several multi-domain anti-apoptotic proteins (Bcl-2, Bcl-XL, Bcl-W, Mcl-1 and A1). In one model, binding the anti-apoptotic proteins to the BH3 proteins displaces Bax or Bak from the anti-apoptotic proteins, allowing them to bind to mitochondria and induce mitochondrial outer membrane permeabilisation (MOMP) [58, 61]. Certain BH3 proteins have selectivity for different anti-apoptotic proteins. In particular, Noxa binds selectively to Mcl-1. The latter also binds Bak, and hence Noxa may displace Bak from Mcl-1, allowing it to bind to mitochondria [62, 63].

It is of particular interest that immunohistological studies on tissue sections from melanoma have shown that Mcl-1 and Bcl-XL increase in expression with progression of the disease whereas Bcl-2 decreased during progression of the disease [64]. Further studies are needed to define the regulators of these proteins more closely, particularly Mcl-1, as current studies suggest it is up-regulated as part of the unfolded protein response to endoplasmic reticulum stress [65].

These findings are important in the design of treatment strategies in melanoma. As shown in Table 3, a number of new agents can be used clinically to target the anti-apoptotic proteins. Oblimersen is an antisense agent targeted to mitochondrial Bcl-2. Results from a randomised phase III trial comparing DTIC combined with oblimersen with DTIC alone in 771 patients showed improved PFS (2.6 months compared with 1.6 months, $P < 0.01$) and response rate (13.5% compared with 7.5%, $P = 0.007$) but no statistical difference in overall survival (9.0 months compared with 7.8 months, $P = 0.077$) [66]. Problems with study design and failure to measure tumour Bcl-2 expression made these results difficult to interpret. A significant interaction between baseline serum lactate dehydrogenase (LDH) and treatment was noted, with oblimersen significantly increasing survival in patients with normal LDH (11.4 months compared with 9.7 months, $P = 0.02$). Another agent, ABT-737, has high affinity for Bcl-2,

Table 3. Targeting anti-apoptotic proteins

Agent	Target protein(s)	Reference
Oblimersen (G3139)	Bcl-2 (specific)	[66]
YM155	Survivin	[67]
ABT-737 (ABT-263)	BH3-mimetic (inhibits Bcl-2 group: Bcl-2, Bcl-XL, Bcl-W, not Mcl-1)	[68–70]
Gossypol (AT-101)	BH3-mimetic (inhibits Bcl-2 group)	[71]
Obatoclax (GX015-070)	BH3-mimetic (inhibits Bcl-2 group)	[72]
TW37	Bim-mimetic (inhibits Bcl-2 group)	[73]
Smac mimetic	Inhibitor of $IAP_{1,2}$, XIAP	[74]

Bcl-XL and Bcl-W, but not Mcl-1. Preclinical studies have shown that many tumours are resistant to this agent due to its failure to inhibit Mcl-1 in cancer cells; down-regulation of Mcl-1 resulted in sensitivity to ABT-737 [68, 69]. ABT-263 is an orally active form of ABT-737 [70]. Sorafenib or MEK inhibitors may down-regulate Mcl-1 and may thus be useful in combination studies. As shown in Table 3, however, a number of protein inhibitors have selectivity for all the anti-apoptotic proteins. One of these inhibitors, obatoclax, is now in preliminary trials in patients with haematological malignancies [75] and was shown to overcome Mcl-1 resistance to apoptosis [76]. At this stage, we would expect that these broad-spectrum inhibitors would be more effective when given in combination with a treatment that induces apoptosis, such as immunotherapy or chemotherapy.

conclusions

We may already have agents that would control the disease if targeted to patient subgroups or if given in appropriate combinations. A number of new agents are in various stages of clinical evaluation. The current strategy of testing new targeted drugs as single agents is necessary, but should be regarded as the first step in evaluation of the agent for future combination with other agents. For example, agents that induce apoptosis, such as taxanes, platinum compounds or immunotherapy, can be combined with agents that inhibit anti-apoptotic proteins. Failure of a drug as a single agent is probably no guide to the ultimate effectiveness of the drug when given in combination and planning for trials of combined agents would appear to be an important part of drug evaluation (e.g. as carried out in the evaluation of the elesclomol–paclitaxel combination). Future research will also need to develop approaches that help to select subgroups of patients that are more likely to respond to particular agents. Combining high-density single-nucleotide polymorphism arrays and the mutation analysis of relevant oncogenes might provide the rational basis for a sophisticated use of new agents in the treatment of melanoma [77]. To improve the outcome of melanoma treatments and to determine the biological mechanisms of efficacy or failure, future studies with small molecules and targeted therapies will also require strict monitoring of biological end points.

conflict of interest disclosures

L. Bastholt has had an advisory role with Schering Plough, Celgene, Pfizer, Genmab and AstraZeneca, and has received honoraria for educational lectures from Schering-Plough and AstraZeneca; V. Chiarion-Sileni has received research funding from Bristol-Myers Squibb and Synta and provided an expert testimony for Schering-Plough; G. Cinat has served as advisor for Pfizer and received lecture honoraria from Pfizer; R. Dummer has received research funding from AstraZeneca, Novartis, Cephalon, Merck Sharp & Dohme, Transgene, and Bayer, and has served as a consultant or on advisory boards with AstraZeneca, Novartis, Cephalon, Merck Sharp & Dohme, Transgene, Genta, Bayer and Schering Plough; A. M. M. Eggermont has been consultant for Schering-Plough; E. Espinosa has received honoraria from Schering-Plough; A. Hauschild has served on advisory boards with Onyx Pharmaceuticals/Bayer (USA/Germany), AstraZeneca (Germany), Synta Pharmaceuticals/GlaxoSmithKline and Genta Pharmaceuticals (USA); C. Robert has had an advisory role with Bayer, Pfizer, Bristol-Myers Squibb, Johnson & Johnson and Novartis; D. Schadendorf has had an advisory role with Bristol-Myers Squibb, AstraZeneca, GlaxoSmithKline, Schering-Plough, Synta Pharmaceuticals, Bayer and Altona, and has received research support from Schering-Plough.

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