The role of interleukin-6 in malignant mesothelioma

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Abstract: Malignant mesothelioma (MM) still remains a dismal disease with a median overall survival between 9-12 months. During the past decade since the introduction of the multi-folate antagonist, pemetrexed, there have been no significant advances in its systemic treatment, particularly with novel therapeutics that have exhibited varying degrees of success in other solid tumours. In recent years, the pleiotropic proinflammatory cytokine, interleukin-6 (IL-6) has emerged as a mediator of pivotal processes such as cell proliferation and chemoresistance within the mesothelioma tumour microenvironment in addition to clinical symptoms commonly witnessed in this disease. This manuscript provides a brief summary on the pathophysiology and clinical management of MM, followed by the role of IL-6 in its tumourigenesis and the rationale for utilising anti-IL-6 therapeutics alongside standard chemotherapy and targeted agents in an attempt to prolong survival.

Keywords: Interleukin-6 (IL-6); malignant mesothelioma (MM); chemoresistance; STAT3

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Introduction

Malignant mesothelioma (MM) is a rare aggressive solid tumour that is invariably incurable. Current first-line chemotherapy regimens have minimal impact on overall survival and poor outcomes are compounded by the lack of an established second-line or maintenance therapy. Moreover, this bleak outlook is typified by the disappointing results yielded from recent clinical trials of novel targeted and cytotoxic agents. In industrialized countries, the incidence of MM is expected to rise in the next 20 to 30 years by 10-15% per year (1). Males represent 70-80% of cases (2) and from studies in US, UK and Japan, the combined MM-related death toll is predicted to sum up to more than 260,000 by 2050 (1-3). Meanwhile in Australia alone, such cases will increase to about 18,000 by 2020 (4). The nomenclature for MM is typically based on the sites of origin, which in order of prevalence are pleural (80%), peritoneal (10-20%), and pericardial (5%) (1). From a histological perspective, MM can be categorised into three subtypes; epithelioid (80%), sarcomatoid (10%), and biphasic or mixed (10%) (5). Previous reports have demonstrated greater variation of these statistics, namely 50%, 34% and 16% for epithelioid, biphasic and sarcomatoid respectively (6). The median overall survival (OS) rate of MM remains poor at approximately 10 months from the onset of symptoms (7). In a US study on pleural MM, 94% of patients died within 24 months from diagnosis and only less than 1% survived up to 5 years (8). Although the epithelioid subtype is consistently more prevalent, the non-epithelioid subtypes generally carry a worse prognosis (9).

The most significant aetiological factor of MM is asbestos exposure (10). After US, UK and France, Australia ranked 4th among the western world in the gross consumption of asbestos-cement products and is the highest on per capita basis (11). Indeed, the rising prevalence has also been attributed to non-occupational asbestos exposure (e.g., home renovation) causing a potential third wave of asbestos related disease. Moreover, the expected surge in MM diagnosis in the next few decades is due to the latency...
period between the first asbestos exposure and onset of symptoms which can last between 15-67 years (7). Other aetiological factors including exposure to minerals such as fibrous zeolite and fluoredenite amphibole (10). The onset of MM clinical symptoms most commonly present between ages 50-70 years (2). Most prevalent symptoms are chest/bone pain, dyspnoea, dysphagia and paraneoplastic syndrome namely thrombocytosis with an incidence of 30-40% (12). Other paraneoplastic phenomena may present such as endocrinopathies [e.g., syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypoglycaemia, hypercalcaemia] and amyloid A amyloidosis (12-14). Radiological findings in this disease typically include pleural effusions and/or thickening (2). Poor prognostic factors of MM are non-epithelioid subtypes, male gender, >75 years of age, poor performance status as well as thrombocytosis (platelets ≥400x10^9/L), white blood cell ≥8.3x10^9/L and lactate dehydrogenase ≥500 IU/L (2). In addition, high levels of C-reactive protein (CRP), interleukin (IL)-4Ra and angiogenesis have also been established as poor prognostic factors (15-17).

Various cytotoxic agents have exhibited a modicum of efficacy in MM (Table 1) with a plethora of monotherapeutic and combinatorial trials showing superior efficacy with platinum-containing regimes in comparison with either single agent or non-platinum based therapies (28-30). However, a gold-standard first line treatment has only been established recently. In this setting for pleural MM, Vogelzang et al. investigated the comparative efficacy of a novel platinum-doublet consisting of cisplatin and pemetrexed (multifolate antagonist) against cisplatin monotherapy with an overall response rate (ORR) of 41.3% and 16.7% respectively (P<0.0001). Similarly, both median time to progression (5.7 vs. 3.9 months; P=0.001) and OS (12.1 vs. 9.3 months; P=0.02) favoured the combination arm which also had an acceptable safety profile (21). Although the authors reported toxicities including neutropenia, leukopenia, nausea, vomiting and fatigue, severe side effects could be effectively ameliorated with the administration of vitamin B12 and folic acid without compromising the anti-folate activity of pemetrexed (18). While no formal comparison with best supportive care (BSC) has been performed, it is estimated that this doublet regimen would confer an OS advantage of 3 months over BSC (31). With respect to peritoneal mesothelioma, there are a paucity of studies focusing on this particular subset of patients and current treatment strategies are based on data extrapolated from aforementioned trials with pleural MM. However, a study by Deraco et al. investigated the effect of perioperative systemic chemotherapy in patients who had undergone cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Unfortunately, there was no significant impact on OS and substantial post-operative morbidity was reflected in the considerable surgical and medical complications encountered (32). Depressingly, in over a decade since the Vozelgang study there has been no significant progress in systemic treatment for MM which is further exemplified by the absence of a widely accepted standard second-line therapy. This is in discordance with the management of most other solid tumours (33). Although recent successes have been forged with targeted therapies in a myriad of malignancies, this

| Table 1 Clinical trials of single and combined chemotherapy agents for MM |
|---------------------------|----------------|-----------|---------|--------|
| Chemotherapy              | No. patients | ORR (%)   | OS (months) | Refs. |
| Cisplatin                 | 222           | 16.7      | 9.3       | (18)  |
| Pemetrexed                | 64            | 14.1      | 10.7      | (19)  |
| Raltitrexed               | 24            | 20.8      | 20.8      | (20)  |
| Vinorelbine               | 29            | 24.0      | 10.6      | (21)  |
| Gemcitabine               | 27            | 7.0       | 8.0       | (22)  |
| Carboplatin               | 31            | 16.0      | 8.0       | (23)  |
| Cisplatin/raltitrexed     | 213           | 23.6      | 11.4      | (24)  |
| Cisplatin/pemetrexed      | 226           | 41.3      | 12.1      | (18)  |
| Carboplatin/pemetrexed    | 76            | 25.0      | 14.0      | (25)  |
| Gemcitabine/cisplatin     | 25            | 16.0      | 9.4       | (26)  |
| MVP (mitomycin/vinorelbine/cisplatin) | 150      | 15.3      | 7.0       | (27)  |

ORR, overall response rate; OS, median overall survival; MM, malignant mesothelioma.
has not translated to the clinical treatment of MM (Table 2), with no appreciable extension in either progression free survival (PFS) or OS seen beyond that evident with cisplatin and pemetrexed. This lack of significant progress also extends to the sphere of radiotherapy and surgical management of MM. Although radiotherapy is often effective in palliating symptoms, it does not prolong OS (45). Furthermore, hemithoracic radiation alone has an associated 17% mortality rate while intensity modulated irradiation therapy (IMRT) is allied with significant pleural toxicity (2). With respect to surgery, the most common approaches include surgical pleurodesis via video assisted thoracoscopic surgery (VATS), surgical debulking and extra pleural pneumonectomy (EPP) (2). Debulking surgery has lower mortality rates (<5%) but the procedure seldom results in complete tumour resection. While EPP reduces local recurrence and may prolong OS, the morbidity rate was 60% (46,47).

Indeed, a tri-modality treatment approach involving surgery, chemotherapy and radiation therapy has recently been compared with chemotherapy alone. The Mesothelioma and Radical Surgery (MARS) feasibility study compared three cycles of neoadjuvant chemotherapy followed by EPP and radical radiotherapy to chemotherapy alone (2). Poor outcomes and high morbidity were associated with trimodality therapy alongside significant complications including such as grade 3 fatigue, pain, dyspnoea and paraplegia in 5 out of 8 patients who had undergone radical radiotherapy after EPP and chemotherapy (48). Interestingly, the one year survival was also higher in patients who did not receive EPP (73.1% vs. 52.2%) and in conclusion, the trimodality approach was not feasible (48). These poor treatment outcomes and lack of established second-line therapies indicate an unmet need for effective treatment strategies against MM. A potential approach to address this lies with identifying chief orchestrators of processes facilitating disease progression. In this regard, factors associated with inflammation are burgeoning areas of research. Indeed, the chronic inflammatory response triggered by prolonged asbestos exposure is thought to reduce anti-tumour immunity and subsequently enhance MM pathogenesis (49). This hypothesis was derived from the discovery of immunocompetent T-cells that produce the proinflammatory cytokine, IL-6, during asbestos exposure. The aetiological role of chronic inflammation in MM is also supported in a study by Hillegass et al. where elevation of inflammatory cytokines including IL-6 were observed (50). Furthermore, several other MM studies have consistently confirmed elevated IL-6 concentrations in serum and pleural fluid, suggesting a pivotal role for this cytokine in MM (51-55). These observations are also mirrored in numerous malignancies such as breast, gastrointestinal, leukaemia, lymphoma, lung, melanoma, multiple myeloma, pancreatic, prostate, renal cell and gynaecological malignancies (56,57). Significantly, several reports have highlighted the integral role of IL-6 in facilitating key pathways and processes within the respective tumour microenvironments of these diseases (Table 3).

### Table 2: Studies of second-line chemotherapies and targeted therapies for MM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. patients</th>
<th>RR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Year (Refs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cediranib(^1)</td>
<td>47</td>
<td>9</td>
<td>2.6</td>
<td>9.5</td>
<td>2011, (34)</td>
</tr>
<tr>
<td>Sorafenib(^1)</td>
<td>10</td>
<td>6</td>
<td>3.6</td>
<td>9.7</td>
<td>2012, (35)</td>
</tr>
<tr>
<td>Sunitinib malate(^1)</td>
<td>51</td>
<td>12</td>
<td>3.5</td>
<td>6.1</td>
<td>2012, (36)</td>
</tr>
<tr>
<td>Erlotinib(^2)/bevacizumab(^1)</td>
<td>24</td>
<td>0</td>
<td>2.2</td>
<td>5.8</td>
<td>2008, (37)</td>
</tr>
<tr>
<td>NGR-hTNF(^1)</td>
<td>57</td>
<td>2</td>
<td>2.8</td>
<td>12.1</td>
<td>2010, (38)</td>
</tr>
<tr>
<td>Belinostat(^3)</td>
<td>33</td>
<td>0</td>
<td>1.0</td>
<td>5.0</td>
<td>2009, (39)</td>
</tr>
<tr>
<td>Dasatinib(^4)</td>
<td>43</td>
<td>4.7</td>
<td>2.3</td>
<td>6.5</td>
<td>2012, (40)</td>
</tr>
<tr>
<td>Bortezomib(^5)</td>
<td>23</td>
<td>4.8</td>
<td>2.1</td>
<td>5.8</td>
<td>2012, (41)</td>
</tr>
<tr>
<td>Gemcitabine/docetaxel(^6)</td>
<td>37</td>
<td>18.9</td>
<td>7.0</td>
<td>16.2</td>
<td>2011, (42)</td>
</tr>
<tr>
<td>Gemcitabine/oxaliplatin(^5)</td>
<td>29</td>
<td>6.9</td>
<td>2.3</td>
<td>6.1</td>
<td>2008, (43)</td>
</tr>
<tr>
<td>Gemcitabine/vinorelbine(^5)</td>
<td>30</td>
<td>10</td>
<td>2.8</td>
<td>10.9</td>
<td>2008, (44)</td>
</tr>
</tbody>
</table>

RR, response rate; PFS, progress-free survival; OS, median overall survival; Refs, references; NGR-hTNF, coupling of the N-terminus of human TNF-α with the C-terminus of a tumor-homing peptide (NGR); MM, malignant mesothelioma; \(^1\), angiogenesis inhibitor; \(^2\), EGFR inhibitor; \(^3\), HDAC inhibitor; \(^4\), src family inhibitor; \(^5\), proteasome inhibitor; \(^6\), chemotherapy combinations.
and immunocompetent cells involved in MM development, there is compelling evidence to suggest that IL-6 has a significant role within the MM tumour microenvironment and may serve as a potential therapeutic target.

**Functions of IL-6**

IL-6 is a pleiotropic cytokine produced by various cells including macrophages, B cells, T cells, syncytiotrophoblasts, fibroblasts, epidermal keratinocytes, monocytes, endothelial cells and mesangial cells (86). Primary physiological functions involve induction of antibody production and acute phase reactions by stimulating B cells and hepatocyte respectively (87). It also plays a role in antigen-specific immune responses and inflammatory reactions (87). Besides mediating proliferation of T cells, thymocytes and synovial fibroblasts, IL-6 assists in the differentiation of cytotoxic T cell, macrophages, megakaryocytes and osteoclasts (87). In haematopoiesis, IL-6 promotes formation of multilineage blast cell colonies by acting synergistically with IL-3 (87). With respect to endothelial cells, it enhances expression of adhesion molecules and production of monocyte chemoattractant protein-1 (MCP-1) (87). Alongside its role in the recruitment of mesenchymal vascular cells and subsequent promotion of neoangiogenesis (87,88), there is ample evidence to support the significance of IL-6 in vital cellular processes.

**IL-6 receptors and signalling**

The IL-6 receptor consists of two polypeptide chains which exist in transmembrane and soluble forms (88). The α chain, known as gp80 (IL-6R), is an 80 kDa glycoprotein which binds specifically to IL-6 with high avidity (88). However its expression is restricted to hepatocytes and specialized subsets of leucocytes (monocytes, neutrophils, T-cells and B-cells). Unlike gp80, the 130kDa β chain; gp130, is ubiquitously expressed and mediates IL-6 signalling transduction (88). Alongside IL-6, gp130 binds to the additional cytokines namely IL-11, IL-27, leukaemia inhibitory factor, ciliary neurotrophic factor, oncostatin M, cardiotrophin-1 and neurotrophin-1 (88), which together comprise the IL-6 superfamily.

There are two predominant modes of IL-6 signalling. The binding of IL-6 to membrane bound gp80 and subsequent association with gp130 mediates ‘classical signalling’ (Figure 1) (89) through which IL-6 principally exerts its homeostatic functions.

The soluble IL-6 receptors, sgp80 (or sIL-6R) and sgp130, result from either cleavage of the transmembranous proteins (via metalloproteinases) or translation from alternative spliced mRNA. Interestingly, unlike most soluble receptors, sgp80 behaves as an agonist, which contrasts with the inhibitory activity of sgp130 (89). Signalling as a result of IL-6/sgp80 complex binding to transmembranous gp130 is referred to as ‘trans-signalling’, which allows induction of IL-6 signalling in cells that lack membrane-bound gp80 (Figure 1) (89). This form of signal transduction is the fulcrum for tumourigenic processes attributed to IL-6 (89). Until recently, sgp130 was thought to inhibit only trans-signalling and not classical signalling as IL-6 does not interact with gp130 directly (89). However, a report has demonstrated that sgp130 also inhibits classical signalling indirectly by trapping IL-6/sgp80 complex hence

### Table 3 Roles of IL-6 in other cancers

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Roles of IL-6</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma</td>
<td>Tumour survival factor, proliferation and chemoresistance</td>
<td>(58-60)</td>
</tr>
<tr>
<td>Prostate</td>
<td>Tumour survival factor, proliferation, tumour burden, migration, adhesion and chemoresistance</td>
<td>(61-66)</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>Proliferation, angiogenesis, chemoresistance and tumour burden</td>
<td>(57,67,68)</td>
</tr>
<tr>
<td>Renal</td>
<td>Prognostic factor and chemoresistance</td>
<td>(69,70)</td>
</tr>
<tr>
<td>Oesophageal squamous</td>
<td>Chemoresistance</td>
<td>(71)</td>
</tr>
<tr>
<td>Colon</td>
<td>Tumour progression, proliferation and migration</td>
<td>(72,73)</td>
</tr>
<tr>
<td>Lung</td>
<td>Tumourigenesis</td>
<td>(74)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Tumour progression and chemoresistance</td>
<td>(75,76)</td>
</tr>
<tr>
<td>Breast</td>
<td>Chemoresistance, proliferation and tumour progression</td>
<td>(77-80)</td>
</tr>
<tr>
<td>Castleman’s disease</td>
<td>Clinical features and systemic manifestations</td>
<td>(81,82)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Anaemia, poor patient survival, proliferation</td>
<td>(83-85)</td>
</tr>
</tbody>
</table>
eliminating free surrounding IL-6 which subsequently negates any binding to membrane-bound gp80 which would otherwise exert classical signalling induction (90).

Within the sphere of the tumour microenvironment, the malignant repertoire of IL-6 appears to be prominently manifested through Signal Transducers and Activators of Transcription (STAT) signalling. In response to IL-6 binding, gp130 activates Janus Kinase (JAK)1 and JAK2 which subsequently phosphorylates a tyrosine residue of STAT3 (91). STAT3 dimerizes then translocates into the nucleus from the cytoplasm. The phosphorylated STAT3 dimer then binds to the IFN-γ activated sequence (GAS) element which induces expression of apoptotic regulatory genes (Bcl-xL, XIAP, Mcl-1, Fas, and c-myc). In addition, STAT3 binds to p53 to further impede apoptosis regulation. This signalling is terminated by suppressor of cytokine signalling (SOCS) and protein inhibitor of activated STAT (PIAS). IL-6 is also known to signal via additional pathways including RAS/MAPK/ERK, AP1/JNK, Cox-2, PI3K/AKT, Notch3/Jagged-1 and Wnt (91).

**Figure 1** IL-6 signalling. (A) The classic mode of IL-6 signalling involves IL-6 complexing with membrane bound IL-6R. Trans-signalling is mediated via IL-6-sgp80 complexes. Both modes involve association with membrane bound gp130 to induce downstream signalling; (B) sgp130 abrogates both classic signalling and trans-signalling by preferentially binding to IL-6-sgp80 complexes.
IL-6 and MM

Clinical symptoms

Elevated concentrations of circulating IL-6 in MM have been reported to confer clinical features commonly observed in MM patients. A study by Bielefeldt-Ohmann et al. found that high serum levels of IL-6 were associated with cachexia, liver damage, diarrhoea and abdominal distension in addition to cell depletion and functional depression in the peripheral lymphoid organs (52). Notably, most of these clinical symptoms were effectively abrogated in an in vivo mouse model treated with anti-IL-6 monoclonal antibody (mAb) and recombinant human (rh) IFN-α. However, there was no direct effect on retarding tumour cell proliferation (52). Other biological processes associated with increased levels of IL-6 include fever, chronic inflammation, thrombocytosis and Amyloid A amyloidosis (13,31,53,55). Interestingly, an in vivo ovarian cancer study discovered that the underlying mechanism of paraneoplastic thrombocytosis revolves around the production of hepatic thrombopoietin which is facilitated by tumour derived IL-6 (92). Hence, this could feasibly support a similar function for IL-6 in thrombocytosis associated with MM.

Autocrine growth factor

Despite the clinical associations with IL-6, there appear to be conflicting reports with respect to its role as an autocrine growth factor in MM. Schmitter et al. have previously concluded that IL-6 was not an autocrine growth factor as addition of rhIL-6 to MM cell lines did not induce DNA synthesis in the cells (54). These results are mirrored in the aforementioned in vivo study by Bielefeldt-Ohmann et al. whereby anti-IL-6 therapy had negligible effects on tumour growth. Contrastingly, Adachi et al. conducted the first study in MM that described a putative role for IL-6 as an autocrine growth factor; an effect mediated via STAT3 signalling (93). This report emphasized the crucial role of sIL-6R for signalling in MM cell lines in vitro as cells lacking these receptors did not stimulate cell proliferation in response to IL-6 exposure compared to those treated with both IL-6 and rhsIL-6. Furthermore, this growth mediated by IL-6/sIL-6R was effectively inhibited with humanized anti-IL-6R antibody (93). Such observations further consolidate the notion of IL-6 mediating tumorigenic processes through transsignalling (89). There is also a suggestion that IL-6 exerts autocrine functioning indirectly through the high affinity receptor for alpha melanocyte stimulating hormone (α-MSH); melanocortin 1 receptor (MC1R). Catania et al. demonstrated that MC1R enhances MM cell line secretion of IL-6 in addition to IL-8 and TGF-β. Interestingly, MC1R inhibition with synthetic α-MSH significantly impeded cell proliferation (94).

Angiogenesis

IL-6 is a well-established proangiogenic factor in a variety of tumour types (57,95,96). Hence it follows that a causal relationship exists between IL-6 and angiogenesis within the MM tumour microenvironment. The aforementioned Adachi study confirmed that stimulation of MM cells in vitro by IL-6/sIL-6R increased vascular endothelial growth factor (VEGF) expression via JAK2/STAT3 signalling (93). Moreover, inhibition of IL-6 using an anti-IL-6R mAb abrogated VEGF expression stimulated by IL-6/sIL-6R (93,97). As with the effects on cell proliferation, this study also highlights the significance of sIL-6R for VEGF induction in MM. Significant increases in the concentrations of VEGF in MM is further supported in a study by Kao et al. (98). They demonstrated strong correlations between circulating VEGF levels and OS. In a Phase II study in MM patients treated with thalidomide alone or in combination with cisplatin and gemcitabine, subjects with high VEGF levels (> median levels) which decreased to < median levels within 8 weeks of therapy had significantly prolonged survival compared to patients who had increased VEGF (P<0.05). Despite this, no such correlations with survival were witnessed with IL-6 and sIL-6 in this study. Hence, in light of the aforementioned preliminary data, future studies will be required to elucidate whether the potent proangiogenic effects of IL-6 established in other tumour types are also evident in MM (98).

Chemoresistance

Chemotherapeutic responses in MM are often short lived and tumour progression can often present within a year of treatment completion. In a study of pleural MM, within 12 months, 59% of the tumours developed chemoresistance to vinorelbine, 31% against gemcitabine and 27% against cisplatin (99). Furthermore, epithelioid tumours were more chemoresistant compared to the non-epithelioid subtypes (33% vs 18%), which appears counterintuitive in view of the poorer prognosis associated with the latter histotype. An additional study with pleural MM cell
lines demonstrated varying degrees of chemoresistance towards standard first-line chemotherapy with cisplatin and pemetrexed; as monotherapies or in combination (100). A study by McLaren et al. found that the reduction of the cell growth correlated with a decrease in IL-6 levels even at low doses of cytotoxic agents (101). At increasing doses, however, a surge of IL-6 was observed. The authors associated this phenomenon with the temporary exacerbation of toxicities commonly seen in patients undergoing treatment and suggested the side effects would eventually be abated since IL-6 undergoes rapid plasma clearance. However, a further study observed a gradual reduction of IL-6 concentrations until 14 days following cisplatin and irinotecan treatment which was subsequently followed by a resurgence of IL-6. Hypothetically, this increase could mediate tumour progression (53).

Although the link between IL-6 and chemoresistance has been commonly attributed to its anti-apoptotic functions, within the realms of MM research there are few studies which focus on this aspect. Indeed, Adachi et al. concluded that IL-6/sIL-6R does not prevent apoptosis of MM cell lines induced by chemotherapy agents (93); a conclusion inferred from the observation that apoptotic cells were barely visible in the medium lacking IL-6/sIL-6R. This was linked to other studies which had demonstrated induction of apoptosis in MM cell lines by regimens such as cisplatin, progesterone and lovastatin. However, this contradicts the evidence of IL-6 behaving as a survival factor against drug-induced apoptosis in other tumour types as summarized in Table 3. Moreover, two separate in vitro and in vivo studies of pleural MM had demonstrated down-regulation of anti-apoptotic factors (e.g., Bcl-xl and Mcl-2) downstream of IL-6, leading to cisplatin- and TNF-α-induced apoptosis of the MM cells (102,103). Cytoplasmic or nuclear expression of another anti-apoptotic factor induced by IL-6, survivin, was also shown to be elevated in peritoneal MM patients and survivin gene knockdown had enhanced both spontaneous and drug-induced apoptosis (104). Interestingly, in pleural MM the high expression of survivin was found to correlate with higher level of apoptosis and proliferation of tumour cells (105). While Hmeljak et al. reported higher survivin expression in patients who responded to chemotherapy than those who had stable or progressed disease, Cregan et al. established that knockdown of survivin gene did not affect sensitivity of the pleural MM cell lines against cisplatin in vitro (105,106).

In addition, Fischer et al. have recently demonstrated that inhibition of PI3K signalling, which plays a role in regulating cellular drug trafficking, had reduced the chemoresistant population of MM cells and increased their sensitivity to pemetrexed (107). Furthermore, Giovannetti et al. reported that vandetanib, an EGFR/VEGFR-2/RET inhibitor that blocks Akt phosphorylation, had enhanced carboplatin and pemetrexed cytotoxicity as well as inducing apoptosis in pleural MM cell lines (108). In view of PI3K/Akt representing a prominent IL-6 signalling pathway, these studies suggest a possible indirect role for IL-6 mediated chemoresistance in MM.

**IL-6 and MM prognosis**

Although elevated serum concentrations of IL-6 has been implicated as a poor prognostic factor for advanced non-small cell lung cancer and metastatic breast carcinoma (80,109), such a role in MM has not been firmly established. However, there is certainly evidence associating IL-6 with established poor prognostic factors of MM including thrombocytosis, elevated CRP and IL-4Rα. This is exemplified by a study carried out by Nakano et al. that demonstrated significant correlations between IL-6, elevated platelet counts and CRP levels (53). Burt et al. also concluded that although IL-4Rα is a poor prognostic factor in MM, IL-4 has no direct effect on apoptosis or proliferation of the MM tumours (16). Administration of IL-4 increases the production of IL-6 significantly in pleural MM cell lines which may contribute to its poor prognosis. Conversely, when observing the relationship between plasma levels of IL-6 and patient survival, no significant difference has been reported (53,98). Hence, it is a possibility that IL-6 per se does have a detrimental effect on survival and is not an independent prognostic factor in MM. However, sIL-6R could potentially be assessed as a poor prognostic indicator due to its significant role in promoting cell proliferation.

**Future directions**

Amongst all solid malignancies, undoubtedly MM is viewed as one of the bleakest diseases in terms of its inherent chemoresistance which results in poor survival rates and the vastly disappointing responses to novel agents which have shown some promising activity in a selection of other tumour types. Taking these facts into consideration, there is an obvious urge to refresh the approach to developing systemic therapies that will forge new horizons in effective
clinical management. This review has synthesized literature to support the validity of targeting the inflammatory cytokine IL-6 in an attempt to achieve this goal. IL-6 exhibits pleiotropy within the MM microenvironment by promoting cell proliferation, chemoresistance and clinical symptoms such as cachexia, thrombocytosis and immunosuppression. However, it must be stressed that the failure of monotherapeutic targeted salvage therapy (Table 2) would certainly preclude adopting similar approaches with anti-IL-6/anti-IL-6R mAb in future clinical trials for this disease. Although the biology of MM is indeed complex, perhaps the lack of success with novel therapeutics could also be explained by the paucity of studies looking at appropriate combinations of such drugs with inhibitors of targets responsible for inducing their intrinsic and acquired resistance. Interestingly, IL-6 is emerging as a potential mediator of resistance to standard cytotoxic agents used in MM (101). Furthermore, it has a role in the development of anti-angiogenic therapy resistance in numerous malignancies (96). Hence there is a sound rationale for developing trials with anti-IL-6 therapies utilised as adjunctive therapies to chemotherapy and anti-angiogenic agents either in combinatorial or maintenance settings. Appropriate stratification of patients likely to gain benefit through targeting IL-6 also requires further investigation. For example, both thrombocytosis and CRP are predominantly induced by IL-6 and could feasibly represent surrogate markers for IL-6 bioactivity. Whether these respective levels are robust predictors of response to anti-IL-6 therapies remains to be seen, but further basic research is a necessity to enable efficient translation of this approach.

Acknowledgements

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