

# ADVANCES IN OUR UNDERSTANDING AND MANAGEMENT OF SARCOMAS – RARE BONE AND SOFT TISSUE CANCERS

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### Abstract

Bone and soft tissue sarcomas are rare, accounting for approximately 1% of all adult solid malignant tumors. Although these cancers are categorised under the same banner of 'sarcoma', they in fact represent more than 70 distinct tumor subtypes, correct diagnoses of which are becoming increasingly important in delivering tailored and optimal medical care. The dramatic impact of imatinib on the management of gastrointestinal stromal tumor has served as a prototypic model for the development of other molecularly-targeted therapies. However, patients and their families affected by sarcomas still face significant challenges in accessing appropriate cancer care, as do their counterparts affected by other rare cancers. This review paper summarises recent advances in management of sarcomas, and in particular highlights the importance of progress in molecular genetics of sarcomas and how these findings have enabled the discovery of targeted therapeutic agents.

Sarcomas are a heterogeneous and relatively rare group of malignant tumours that develop in bone and soft tissue, accounting for approximately 21% of all paediatric solid cancers and less than 1% of all adult cancers.<sup>1</sup> Patients and their families affected by sarcomas face a number of similar challenges in receiving optimal cancer care as their counterparts with other rare cancers do, from delays in making a correct diagnosis to a lack of readily available clinical expertise and access to effective therapies, given a limited opportunity to participate in clinical trials and even limited access to reimbursed agents. Sarcoma patients are markedly over-represented by adolescents and young adults, leading to an even greater impact on number of years of life lost to this disease, when compared to other cancers.

There are more than 70 distinguishable subtypes of sarcomas, which exhibit different behaviors, incidence and response to treatment.<sup>2</sup> Despite these challenges, the diversity in disease subtypes, many of which are defined by molecular phenotypes, has in fact served as a fertile ground in driving therapeutic development of agents to target these, as exemplified by the success of imatinib in transforming the prognosis of patients affected by advanced gastrointestinal stromal tumour (GIST) – a subtype of soft tissue sarcoma. We review recent advances in sarcoma management, highlighting the success story of imatinib therapy for patients with advanced GIST as a flag bearer for what can

be achieved when rationally applying an expanding knowledge of molecular biology to the development of targeted agents.

### Imatinib success story in advanced GIST

Success stories of improvements in survival in rare cancers are not complete without re-addressing the development of imatinib for treating advanced GIST. Historically, patients with metastatic or inoperable GIST had a very poor prognosis because of the highly resistant nature of these tumours to conventional chemotherapy.<sup>3</sup> In the late 1990s, a Japanese group at the University of Osaka first showed that GIST was driven by activating mutations in the c-kit oncogene.<sup>4</sup> The first clinical trial using imatinib – a tyrosine kinase inhibitor known to target the KIT and PDGF receptors – showed dramatic improvements in disease control and led to its accelerated approval by the US Food and Drug Administration in 2001, only three years after the Hirota paper was published.<sup>4,5</sup>

In a disease in which median survival was less than a year for patients with advanced/metastatic disease, survival is now at least five years.<sup>6,7</sup> Subsequently, in 2008, imatinib received further accelerated approval for adjuvant use in patients with resected GIST,<sup>8</sup> with further data demonstrating an even greater impact in patients with high risk for recurrence following potentially curative resection.<sup>9</sup> A multitude of further insights have

come through a greater depth of understanding of KIT biology, including how specific mutations in KIT or PDGF predict response to imatinib and next-generation kinase inhibitors,<sup>10,11</sup> and in mechanisms of resistance to imatinib have led GIST to be considered a model disease in how to implement a personalised approach to treating cancers.<sup>12</sup> Therapeutic applications of imatinib have also expanded to other soft tissue sarcomas such as dermatofibrosarcoma protuberans, with the discovery of a characteristic translocation leading to an autocrine dependence on PDGF signalling also targetable by imatinib.<sup>13</sup>

### **Molecular complexities and heterogeneity of sarcomas**

Bone and soft tissue sarcomas are marked by their heterogeneity and complexity in histology and molecular biology. Sarcomas are collectively rare and individual subtypes comprise many rarer entities, posing significant challenges to pathologists outside specialist sarcoma centres. There are more than 50 distinct subtypes of soft tissue sarcoma alone.<sup>2</sup> Delays in reaching a correct diagnosis is the first limiting step in accessing appropriate care for patients with sarcomas. The misclassification rate of sarcomas based on histopathology alone, was reported to be up to 20% in the early 1990s.<sup>14</sup> Unfortunately this still remains true with potentially devastating consequences. We now have consistent, albeit low level, evidence that expert review results in a change to diagnosis in a significant proportion of cases ranging from a minor discordance in tumour grade to a false positive or false negative diagnosis of malignancy.<sup>15-17</sup> Therefore, whenever a sarcoma is suspected clinically or biopsied, or even possibly resected outside a sarcoma specialist setting, a timely review of the diagnosis is strongly recommended.

### **Current management of bone and soft tissue sarcomas**

The mainstay of sarcoma management in 2014 remains a multimodality approach using surgery, chemotherapy and radiotherapy, which are dependent on high quality radiology, pathology and increasingly molecular pathology input. Not all patients diagnosed with sarcomas require all three modalities, and the subtleties in managing a complex and rare disease are therefore critically dependent on an expert multidisciplinary approach. As an example, the survivorship of children with osteosarcoma and Ewings sarcoma in the last 30 years has changed significantly, from less than 20% to a five-year disease free survival in excess of 60% for those with localised disease, mainly due to the integration of intense chemotherapy regimens with surgery and radiotherapy.<sup>20,21</sup> In addition, limb-preserving surgery has evolved to the point that amputation is rarely required, leading to significant improvements in quality of life for affected patients.<sup>22</sup>

The role of chemotherapy remains controversial for patients with soft tissue sarcoma, with a lack of evidence in survival benefit in the treatment of operable disease.<sup>23,24</sup> It is generally reserved for patients with metastatic disease in palliating symptoms. Integrating our knowledge on risk stratification of sarcoma subtypes is enabling better patient and treatment selection for specific systemic therapies, and once again requires high quality expert care delivered through specialist sarcoma services.

### **Multidisciplinary management – a tautology**

The utmost importance of involving a multidisciplinary team cannot be overstated in sarcoma management. Sarcoma treatments vary by tumour subtype, grade and stage. The duration and intensity of sarcoma therapy can often be intensive and prolonged, with combinations of chemotherapy, surgery and at times radiotherapy required to maximise the chance of cure, as is typically the case in Ewing sarcomas or osteosarcomas. Many published series consistently report inferior outcomes for patients whose sarcoma treatment is initiated in non-specialist centers, with some studies estimating that up to half of all patients with soft tissue sarcoma are managed outside specialist centres.<sup>18,19</sup>

Given the rarity and often complexity in diagnosis and treatment, a sarcoma expert centre can facilitate access to appropriate imaging, biopsy and histopathology review by expert pathologists. From there, cases are discussed in a multidisciplinary meeting, similar to the ways in which other more common tumor streams manage their patients these days. In Australia, there are several dedicated sarcoma centres, which are affiliated with Australasian Sarcoma Study Group, the national cooperative group driving sarcoma research in this region.

### **Recent development in novel therapies**

An ever increasing number of novel agents are being explored and added to our expanding armamentarium against specific subtypes of soft tissue sarcoma. The recent addition of pazopanib to the Pharmaceutical Benefits Scheme listing for the indication of non-adipocytic soft tissue sarcomas in Australia will assist patients' access to this targeted option.<sup>25</sup> Despite its activity in certain soft tissue sarcoma subtypes, access to trabectedin unfortunately remains difficult for patients in Australia. Interestingly, some of the new agents with the highest impact have been in rare and classically chemo-resistant subtypes, which not surprisingly are known to now have strong single oncogenic drivers.<sup>26-28</sup> Despite some extraordinary responses in these rare sarcomas, obtaining regulatory approval and reimbursement in Australia remains unlikely with our current mechanisms, an issue that is increasingly becoming a challenge with

even 'common' cancers when broken down into their requisite subgroups.

The next wave of new treatments in sarcomas will likely continue to come from translating the molecular findings from the first generation of in-depth genomic studies that will continue to provide insights into targetable subtypes, even if rare.<sup>29</sup> In addition to this, efforts will also need to focus on understanding the functional impact of the many translocations that are well defined in many sarcoma subtypes, and how these can be targeted.

Sarcomas are considered favourable models for the development of novel agents targeting specific molecular aberrations because these alterations are often well characterised. However, the heterogeneity of sarcomas and limited number of patients per individual sarcoma subtype pose significant challenges in developing clinical trials. Despite this, the international sarcoma community has recognised this as a challenge that must be overcome, and now places a high priority on collaborative efforts to conduct trials even in extremely rare subtypes, as critical for us to make any progress. Until recently, opportunities were scarce in Australian centres to lead or participate in sarcoma-focused trials. However, this has improved considerably in recent years due to the establishment of local and international collaborative infrastructure.<sup>30</sup> With challenges in getting timely approval to novel agents, trials remain an important potential source of access to novel agents for patients with sarcomas and other rare cancers.

## Conclusion

Over the past decade we have witnessed remarkable developments in our understanding of the molecular genetics of cancer. As we continue to unravel the molecular mechanism of sarcoma pathogenesis, more opportunities will arise in discovering potential targets and novel therapeutic approaches in treating patients with bone and soft tissue sarcomas. In parallel, developing and implementing new methodologies for well-designed clinical trials will become crucial in moving us closer to delivering truly personalised cancer care to patients affected by this rare and diverse group of cancers.

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