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Review

Ewing sarcoma: The clinical relevance of the insulin-like growth factor 1 and the poly-ADP-ribose-polymerase pathway

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Abstract ***Background:*** In the last three decades the outcome for patients with localised Ewing sarcoma (ES) has improved significantly since the introduction of multimodality primary treatment. However, for patients with (extra-) pulmonary metastatic and/or non-resectable relapsed disease the outcome remains poor and new treatment options are urgently needed. Currently the insulin-like growth factor 1 receptor (IGF-1R) pathway and the poly-ADP(adenosinediphosphate)-ribose-polymerase (PARP) pathway are being investigated for potential targeted therapies.
IGF-1R: The IGF-1R pathway is known to be deregulated by the *EWSR1-FLI1* translocation which makes it a potential target for therapy. Clinical trials have been reported in which only ES patients were treated with an IGF-1R inhibitor, either as single agent or in combination. In total 291 ES patients were included in these trials, in which two (0.7%) complete responses, 32 (11%) partial responses of which some durable, and 61 (21%) stable diseases were observed.
PARP: In the presence of a PARP inhibitor DNA strand breaks cannot be efficiently repaired, leading to cell death. The first phase II trial with ES patients was recently published and showed no clinical responses, which may have been due to the drug being non-effective as a single agent.
Discussion: The IGF-1R pathway is an interesting target for ES and should be explored further, as biomarkers to select patients that might benefit from treatment are lacking. PARP

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inhibitors as single agent have so far failed to show improvement in outcome. Future directions include dual insulin receptor/IGF-1R blockade with linsitinib as well as chemotherapy –PARP combinations. Both therapeutic strategies are currently being explored.

1. Background

Ewing sarcoma (ES) is the third most common primary bone sarcoma after osteosarcoma and chondrosarcoma. However it is still rare with an overall incidence of 2.9 new cases/1,000,000 every year in the United States [1]. In children and adolescents ES is mainly localised in bone, with a peak incidence at 15 years of age [2]. In adults, ES localises more frequently primarily in soft tissue or organs. The tumour is diagnostically defined by a reciprocal translocation, causing a fusion of the *EWSR1*-gene on chromosome 22 with a member of the ETS (E26 transformation-specific) family of transcription factors [3]. The most common translocation (85%) is the t(11;22)(q24;q12), fusing *EWSR1* to *FLI1*. Other rare ETS and non-ETS fusion partners have been described, and so far it is unclear whether the latter should be considered a separate entity [3]. The *EWSR1*-ETS translocation type does not influence the outcome or reaction on chemotherapy [4,5]. Proven genetic prognostic factors are TP53 mutations [6], CDKN2A deletions [7], 1q gain [8] and Stag2 mutations [9–12].

With current multimodal treatment options, including surgery, conventional chemotherapy and radiotherapy, the 5-year survival for localised disease is 60%. However, for patients that present with metastatic disease other than lung involvement only, the 5-year survival is below 20%. The outcome for patients with relapsed or refractory ES is even worse with a 5-year survival as low as 10% [13]. Therefore, new treatment strategies are urgently needed. Currently the insulin-like growth factor 1 receptor (IGF-1R) pathway and the poly-ADP-ribose-polymerase (PARP) pathway are being investigated for potential targeted therapies. In our opinion these two pathways represent the main area of early clinical studies in ES in the recent years deserving an in-depth review. Therefore, here we summarise current knowledge in an attempt to stimulate further treatment development for ES.

2. Insulin-like growth factor 1 receptor pathway in Ewing sarcoma

2.1. Insulin-like growth factor 1 receptor pathway

IGF-1R is a tyrosine kinase receptor which is 84% homologous to the insulin receptor (IR) and is widely expressed in human tissues [14]. Binding of the ligands (IGF-1 and IGF-2) to the IGF-1R or the IR induces receptor dimerization, resulting in trans-autophosphorylation of the receptors (Fig. 1). This receptor phosphorylation recruits the downstream signalling proteins IR substrate (IRS) 1, 2 and 4 and the Src homology 2 domain containing transforming proteins to the cell membrane [14]. The subsequent phosphorylation of these proteins induces the activation of the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinases (MAPK) pathways resulting in stimulation of cellular proliferation, cell motility and inhibition of apoptosis [14]. IGF-1 and IGF-2 are mainly produced by the liver in response to the presence of growth hormone and are found in the circulation bound to the IGF binding proteins (IGFBP1-6), which regulate their bioavailability in peripheral tissues. The bioavailability of IGF-2 is also regulated by the IGF-2R, which does not confer intracellular signalling [15]. IGFBP3 is the most abundant IGF binding protein, which forms a ternary complex with insulin-like growth factor acid-labile subunit and accounts for 80% of all IGF binding. In addition to its role in normal cellular development (foetal growth and linear growth of the skeleton and other organs), the IGF signalling pathway has been implicated in malignant transformation and disease progression [16–18]. Interestingly, patients with congenital deficiency of IGF-1 seem protected from the development of malignancies [19] and cells with a dominant negative mutation in IGF-1R fail to undergo malignant transformation and *in vivo* tumourigenesis [20]. Furthermore, many tumours and cell lines have increased expression of IGF-1 or IGF-1R [21]. In addition, numerous studies have shown that higher plasma concentrations of IGF-1 are associated with increased cancer risk, in particular for breast, prostate and colon cancer [22–31].

2.2. Insulin-like growth factor 1 receptor pathway activity and its inhibition in Ewing sarcoma: preclinical data

Interestingly, the peak incidence of primary bone ES correlates with the increased levels of the IGF ligands in puberty. In 1990 it was already shown that IGF1 is expressed in ES carrying a t(11;22) translocation and that blocking the IGF-1 loop inhibits cell growth [32]. Subsequent studies using ES cell lines confirmed these findings [33]. In 1997 a study using fibroblast cell lines from an IGF-1R knock-out mouse and a wild type