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Therapeutic Potential of α-Her-2 Medications in Colorectal Adenocarcinomas: Do We Have Enough Evidence?

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Abstract

Colorectal cancer is a substantial health concern. The potential role of Human epidermal growth factor (Her-2) in breast and gastric cancer is extensively exploited. α-Her-2 therapy (Trastuzumab/Herceptin) in breast cancer has shown a dramatic response whereas α-Her-2 therapy for gastric cancer has also been approved. Role of this potential therapeutic marker in colorectal cancer is still highly debatable. In this mini review, we have attempted to represent the available data regarding the over expression of Her-2 and its therapeutic potential in colorectal cancer.

Keywords: Her-2; Colorectal cancer; Trastuzumab

Introduction

Worldwide colorectal cancer ranks to be the 3rd most common cancer [1]. Although its mortality is low, cure rates estimated for patients in advanced stages for colorectal cancer remains poor. Management modalities of colorectal cancer depend on the disease severity and stage. Surgery is the keystone treatment along with chemotherapy and radiotherapy. In recent years, functional studies and cancer genome studies has introduced Trastuzumab (α-Her-2) as targeted therapy in various tumors including breast and gastric cancers [2,3].

Her-2 is also known as Neu, CD-340 or p-185 and is encoded by the proto-oncogene ErbB2 [4]. It is a member of "Her" family of proteins and with its normal expression it promotes cellular proliferation and growth (Figure 1) [5]. Over-expression of Her-2 has been most notably associated with increased cellular survival, increased proliferation and decreased apoptotic potential of cells leading to malignant transformation and maintenance of malignancy. This marker is noted to be over expressed in various tumors including oesophagus, lung, ovary, bladder, head & neck [6]. Her-2 over expression in colorectal cancer is quite debatable, showing a wide range of variability (0-83%) [7]. Some studies reported only membranous Her-2 over expression while others reported membranous as well as cytoplasmic expression [8-12]. These variable data could be attributed to several factors including use of different antibodies, different sample size, use of non-uniform scoring system for interpretation of results amongst others [13]. Moreover, the role of Her-2 over expression in colorectal cancer survival remains unclear. Her-2 over expression has been reported as a poor predictor by some researches [10,14-16]. While some studies stated that it was negatively associated with patient survival [16-18].

In the past, phase II trial was conducted amongst colorectal cancer patients who expressed 8% positivity of Her-2 over expression. Although the expression rate was low but these patients responded to trastuzamab and irinotecan therapy [19]. In this new era of personalized medicine, mounting evidences are being made to enhance the therapeutic potential of α-Her-2 therapy for colorectal cancer.

Conclusion

In summary, this review addressed the data concerning Her-2 over expression in colorectal cancer. However, to reduce the variability in its expression, a uniform scoring is highly suggested. Moreover, large scale clinical trials are also required to deal with the therapeutic benefit of this emerging α-Her-2 therapy.

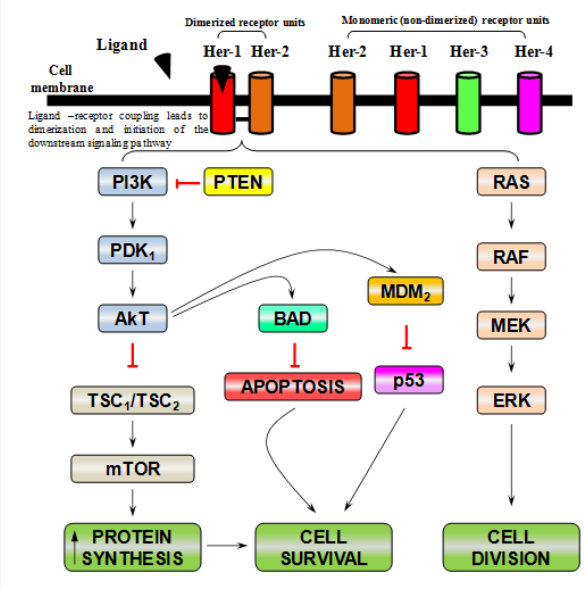

Figure 1: Her family of proteins consists of four structurally related receptors Her-1, Her-2, Her-3 and Her-4. When a ligand (usually a growth factor) binds with these receptors, they dimerize with each other resulting in phosphorylation of intracellular portion of these receptors and activate different pathways. PIK3/AKT a pro-survival pathway, BAD an antiapoptotic protein and MAPK through RAF, RAS, and MAP2K/MEK & ERK leads to survival & proliferation of cells [5,20].

Her=Human epidermal growth factor; PI3K/AKT=Phosphoinositide 3-kinase; PDK1=Pyruvate dehydrogenase kinase; TSC=Tuberous sclerosis; mTOR=Mammalian target of rapamycin; PTEN= Phosphatase &tensin homolog; BAD=Bcl2 associated death promoter protein; MDM2=Mouse double minute 2 homolog; p53=Tumor suppressor gene; RAS=Rat sarcoma; RAF=Rapidly accelerated fibrosarcoma; MEK=Mitogen activated protein kinase; ERK=Extracellular signal regulated kinases.

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