Angiogenesis and Cancer

Tumors measuring 1-2 (mm)³ lack blood supply and neovascularization is a major process orchestrated by over-production and release of pro-angiogenic growth factors causing sequential step-wise formation of blood vessel capillaries in tumors. Molecular mediators of tumors angiogenesis include VEGF family, IL-8, EGF receptor ligands, basic and acidic FGF, PDGF etc. There are natural endogenous inhibitors of tumor-origenesis (TSP-1, Vasostatin). Negative feedback mechanisms do exist to control/regulate tumor angiogenesis. Angiogenesis is detrimental to tumor progression favouring transition from hyperplasia to a neoplastic state, influencing cancer cell dissemination besides exerting an independent negative prognosis. Tumor vasculature is dysfunctional, heterogeneous in the tumor mass in terms of density leading to a limited/retarded diffusion of drugs especially certain antibodies, gene therapy vectors, immune-effector cells through interstitium of these tumors. The hypoxic zones in tumors are the areas of resistance to the chemotherapy. Angiogenesis is upregulated in tumorigenesis leading to over-production of pro-angiogenic growth factors that have become targets for anticancer drug development.

The era of angiogenic drugs began with the publication in NEJM in 1971 by Folkman and since then FDA has approved several agents for systemic treatment in advanced and metastatic cancers.

VEGF family of growth factor expression is associated with ascites formation, malignant progression and poor prognosis in Ovarian cancer. There is a rationale for anti-angiogenic therapy in ovarian cancer having an impact on overall survival, quality of life, however, an optimal use of such agents needs further investigation. GOG-0218 used standard chemotherapy with Bevacizumab followed by Bevacizumab

maintenance having PFS statistically superior to the standard chemotherapy, however, the interpretation of survival is limited at this point. The treatment was well tolerated with adverse events similar to previous Bevacizumab studies in non-gynaecologic cancers. ICON-7, a closely related European trial demonstrated a statistically significant improvement in PFS. Single agent activity has been determined for TKI such as Cedireneb having an objective response rate of 17% and 38% six month PFS. This finding led to first time use of non-classic anti-angiogenic agent AMG 386, acting by preventing the interaction of angiopoietin with its receptor. Some newer anti-angiogenic agents like Sunitinib, Sorafenib, Pazopanib are undergoing trials in Ovarian cancer at present. In metastatic Lung cancer (NSCLC) the management has moved from the best supportive care, to the introduction of frontline chemotherapy, to active cell lines, to molecular targeted agents in the last 40 years. The median OS has moved from 4 months in 70's to upto 12 months in mid 2000's. In parallel 1 year OS has improved from 10% to upto 50%. Bevacizumab is the only approved antiangiogenic agent in the treatment of advanced NSCLC. 2 large phase 3 trials show improvements in the response rates and PFS and OS in one of these trials. A pooled meta-analysis of AVAIL and ECOG 4599 reveals positive results for OS in ECOG trial and not in the former trial, nevertheless, the pooled study analysis still shows positive OS results with a hazard ratio of 0.89. There has been an improved response rate and PFS in 2 randomised phase 3 trials with improved OS in pooled analysis. Compared to CT alone, Bevacizumab increases median OS by 2 months in overall 4599 population and 3.9 months in Adenocarcinoma patients. An enhanced efficacy was observed in phase 4 trials (SAIL, ARIES). Bevacizumab has an acceptable safety profile in patients with Non-squamous NSCLC benefitting from Bevacizumab based

therapy in the first line setting. Other antiangiogenic agents for NSCLC include Vandetinib, Sunitinib, Sorafenib, BIBF 1120 and Cedirenib. Similarly antiangiogenic agent Bevacizumab has been tried in the treatment of metastatic colorectal cancer with improved results. ECOG(Trials E220B, ECOG 3200) revealed an efficiency in terms of response rates and NO16966 in terms of PFS.

The rubrics of fight against cancer in context of antiangiogenic therapy is evolving and incremental. Presence of large number and diverse molecular changes detected in

endothelial cells of the tumor blood vessels suggest a multitude of antiangiogenic agents, newer targets and enhancing of efficiency of chemotherapy by such agents including a newer concept of maintenance treatment with antiVEGF therapy after a maximal response with parent chemotherapy. Molecular predictors for anti-angiogenic therapy are yet to be established. An intrinsic/acquired resistance to antiangiogenics is a newer challenge that is being addressed to and soon smart guidelines shall follow to tailor and optimize cancer treatment with such agents.

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