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Research Article

PRECISION & PERSONALIZED SURGI CAL ONCOLOGY MANAGEMENT BASED ON IMMUNOLOGIC FACTORS. IS THERE SPACE FOR TARGET INHIBITION IN THE FIELD OF CANCER RECURRENCE AND METASTASIS

Giannios John[1], Delis Spiros[2] and Sofoudis Chrisostomos[3]

[1]MD/MBBS, Prof in Genomic and Cancer Medicine, BSc (Biol & Chem), Post-Cert (Transl Med with Distinction) Med School, Univ of Edinburgh, PostDipl (Transl Med with Distinction) Med School, Univ of Edinburgh, MSc (Transl Med) Med School, Univ of Edinburgh, Post Dipl (Genomic Medicine & Healthcare), Univ of South Wales, Cardiff, Professional Doctorate in Translational Cancer Medicine, University of Middlesex, London, UK, Leader of the Postgraduate Programme in Genomic Medicine and Healthcare, USW, and Prof in Medical Oncology, UoB, UK

[2]MD, PhD, Director of HPB Unit Konstantopouleio Hospital, Athens, Greece, Cooperative Prof of Surgical Anatomy, Univ of Athens, ASTS Fellow, Univ of Miami, USA

[3].MD, PhD, MPH, Post Doc, Consultant, 1st Department of Obstetrics and Gynecology, Elena Venizelou, Maternal Hospital, Athens, Greece

Corresponding author

Dr. Chrisostomos Sofoudis, MD, PhD, MPH, Post Doc
Adress: Ippokratous 209,11472, Athens, Greece

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Abstract

Now days, enormous increase of medical expertise and especially medical technology reflect assiduous diagnosis and therapeutic mapping, decrease operative or postoperative potential complications and most of all increased overall survive and patient's quality of life.

Although oncologic-resection is required for treating solid-tumors, surgical tissue-trauma, fasting, metabolic-derangements, hypothermia and other factors, it may lead to enhanced tumor-outgrowth, and activation of the metastatic-process.

Pathophysiologic pathways can explain thoroughly all potential mechanisms which consist cornerstone of metastatic process.

Aim of our study represents pathophysiologic depiction of all complicated medical cataracts, certifying potential negative outcomes of surgical oncologic interventions.

All factors which are promoting cancer-recurrence and metastasis after systemic-effect of surgery-induced stress are following composed.

KEY WORDS: Immunosuppression, inflammation, cancer cells, dissemination

Introduction

IMMUNOSUPRESSION represents a mechanism which tumor-cells utilize for circumventing immune-attack leading to enhanced progression of tumor-formation [1].

During first fourteen-days postoperatively, clinical-effects of systemic immunosuppression become more severe due to the synergistic action of additional-factors consisting of blood-transfusions, anesthetic-agents, inflammation, elevated levels of neutrophils or Treg-cells, reduced levels of NK-cells, etc.

More analytically, surgery induced stress during the perioperative-period may alter the function of immunocomponents, such as the NK-cells which are large-granular cytotoxic-lymphocytes (LGL) involved in the innate immune-system [2].

Activated NK-cells may overexpress coreceptors CD-4 , and a small-subset of CD-8. During perioperative-period, prostaglandins, glucocorticoids and catecholamines may suppress the ability of NK-cells to release the macrophage-activating glycosylated-protein IFN-γ, and surgical-stress may inhibit programmed tumor lysis (PTL) by impairing NK-cells, while promoting cloaking of the fibrin, and platelet coating all around tumor-cells

leading to impairment of tumor-clearance facilitated by NK-cells.

Another immunocomponents, such as Treg-cells may be involved in the postoperative-immunosuppression process in the primary-tumor, and the dissemination of cancer-cells which may metastasize [3].

Thus, elevated levels of Treg-cells in solid-tumors after surgery, and reduced levels of cytotoxic T-cells, and T helper-cells have been linked to poor-prognosis due to systemic-complications including enhanced release of immunosuppressive acidic-proteins, and cortisol. Therapeutic modification of T cell-populations may lead to the prevention of cancer-recurrence after surgery.

Neutrophils which mediate-inflammation and protect our bodies by neutralizing invasive pathogenic-microorganisms may also be involved in the process of postoperative-immunosuppression leading to metastasis of tumor-cells affecting vital-organs in the human-body, where CTCs bind with WBCs to form CTC-WBC-clusters that may promote systemic-progression of the cell-cycle of CTCs enhancing their metastatic-potential [4]. Additionally, postoperative systemic-inflammation may promote CTC-migration via the activation of neutrophils which are releasing NTEs, and subsequently HMGB-1 which may activate TLR9-pathways and promote proliferation, adhesion, migration, invasion, and triggering metastatic-dormancy due to postsurgical-IRI, and inflammation after extravasation of tumor-cells [5].

Furthermore, postoperative elevated levels of CD11b/CD33 myeloid derived suppressor-cells or MDSC may lead to poor-prognosis due to cancer-recurrence after promotion of angiogenesis, MMP9-release, premetastatic-niches, tumor-growth and invasion of tumor-cells. A therapeutic-approach against the postoperative-functions of MDSC consists of downregulation of ROS, IL4-Ra and ARG-1 via the administration of PDE5- inhibitors, such as sildenafil-citrate which may activate the tumoricidal-activity of NK-cells decreasing postsurgical cancer-recurrence.

INFLAMMATION is induced by surgical-wound infection that recruits neutrophils, monocytes and macrophages which release elevated levels of inflammatory-factors including IL1, TNFa, VEGF and MMP leading to tumor-progression [6].

PGE2-production which is facilitated by the COX2-pathway induces angiogenesis, cell-proliferation and tumor-progression after downregulation of E-cadherin, upregulation of MMP-9 and induction of immunosuppression. Moreover, enhancement of tumor-promoting Treg-cells, alteration of cytokine-release induced by T helper-cells, induction of anticancer-effects by influencing the transition-pathway of dormant to proliferative-stage of disseminated tumor-cells in the bone-microenvironment, and reduction of activated-populations of CD8 T-cells are reported as inflammation and PGE2 promoters. Other postoperative-promoters of inflammation consist of elevated-levels of TCC, and C3A of the complement-system which may lead to the reduction of antitumor-immunity, promotion of angiogenesis, and stem cells-enhancement of CSCs.

SYMPATHETIC NERVOUS-SYSTEM responses by enhancing the levels of circulating-catecholamines, such as noradrenaline and adrenaline may activate beta adrenergic-receptors or b-ARs leading to subsequent remodeling of the tumor-microenvironment or TME, metastasis, acceleration of solid tumor-growth, and enhanced quantity of invasive tumor-cells with invadopodia leading to cancer-recurrence, and metastasis [7].

The activated autonomic nervous-system or ANS may enhance the secretion of prometastatic-factors in the tumor-microenvironment (TME), such as IL6, IL8, VEGF or MMP-9 which may lead to the stimulation of tumor-growth by inducing angiogenesis, and inflammatory-pathways that may cause remodeling of tumor associated blood, and lymphatic vasculatures leading to the dissemination of tumor-cells. Furthermore, the activated sympathetic nervous-system or SNS may exert immunosuppressive action by suppressing NK-cell antitumor-activity.

CIRCULATORY-SYSTEM by establishing a hypercoagulable-state, and ischemia/reperfusion injury (IRI) by upregulating TLR-9 may activate ICAM1 in endothelial and/or immune-cells, and NFkB in M1-macrophages that regulates adaptive and innate immunity, and inflammasome [8].

Furthermore, it is activating the CD-95/CD-5L which may lead to apoptosis or programmed cell death type-1 of normal-cells that may infiltrate cytotoxic-lymphocytes leading to enhanced tumor-progression. Also, IRI can lead to modifications of secret omics in cancer-cells involving LCN-2 which may be upregulated in solid-tumors due to inflammatory, and hypoxic pathways leading to enhanced survival and proliferation of tumor-cells, and subsequent metastasis by the induction of EMT and elimination of the iron-ion. Moreover, upregulation of Angptl-4 may promote cancer-growth, angiogenesis, anoikis-resistance, disruption of redox and metabolic homeostasis, and other oncogenic-pathways in solid-tumors. Furthermore, IRI may influence the tumor-microenvironment or TME promoting tumor-cell growth, migration to body-organs, cancer-cell adhesion, and metastasis. Other cells, such as the endothelial-progenitor cells or EPC may promote tumor-growth and angiogenesis. A very promising therapeutic target consists of inhibiting the MMP9 which is overexpressed by IRI promoting micro metastasis. Moreover, IRI may enhance endothelial E-selectin that facilitates adhesion of tumor-cells, and metastasis in synergy with additional IRI-effects in neutrophils.

Is DISSEMINATION OF CANCER-CELLS IN UCED BY SURGICAL TRAUMA?

Although is not proved yet surgical trauma may act as an immunosuppressive-niche that is facilitated via the lymphatic, and vascular systems which may lead to migration in distant body-organs causing tumor-regrowth, cancer-recurrence and poor-survival via heterogeneous CTCs in the blood-circulation, and DTCs in sentinel lymph-nodes and bone-marrow [9].

Their significant population enhancement may be used as a biomarker involving prognosis, diagnosis and even therapeutic-response in solid-tumors. Surgery including postsurgical complications is reported that promotes migration of tumor-cells in a complex manner with the use of catecholamines, inflammatory-factors including proinflammatory-prostaglandins, chemokines and cytokines, prometastatic proteolytic and no proteolytic enzymes including hyaluronidases, heparanase, MMPs, cathepsins and plasminogen activators. These may lead to propagation, and metastasis of disseminated tumor-cells which are characterized by high genomic-heterogeneity, and clonal-expansion.

ANESTHESIA consisting of intravenous, and inhalational anesthetic-agents may cause postoperative cancer-recurrence by affecting directly signaling-pathways of tumor-cells, and indirectly by interfering with functions of the immune, and neuroendocrine systems [10].

INTRAVENOUS-ANESTHETICS such as ketamine (ketalar) which blocks the ionotropic-glutamate receptor NMDA may reduce the NK-cell activity, and enhance the rates of cell-survival and metastasis of solid tumors. Another intravenous anesthetic-agent, the oleophilic-barbiturate thiopental-sodium which acts on the GABAA receptor-channel with its thiol group may modify the activity of the IkB-kinase leading to the inhibition of NK cell-activity that may enhance solid tumor-cell survival, and subsequent metastasis.

On the other hand, the general intravenous anesthetic-agent of alkyl-acids propofol especially with EPA or DHA conjugates may exert potent anticancer action by inducing PCD Type-I or apoptosis and inhibit tumor-cell adhesion, migration or invasion via the blockage of oncogenic

mRNA-translation, and modulation of the GTPase-RhoA which may improve the overall-survival (OS) rates of patients with solid-tumors.
It is very significant that the administration-method of anesthetic-agents may affect differently the rate of cancer-recurrence. For instance, regional-anesthesia which is mediated with local-anesthetics, and epidural-anesthesia may reduce the rate of cancer-recurrence while improving overall-survival (OS) in patients with solid tumors.

INHALATIONAL-ANESTHETICS for general-anesthesia, such as the halogenated-hydrocarbon isoflurane which blocks the conduction of potassium-channels may upregulate HIF-1 and 2 and reduce the immune activity of NK-cells leading to enhanced migration of tumor-cells, and subsequent promotion of cancer-recurrence [11].

Even nitrous-oxide which is the least potent inhalational-anesthetic is characterized by the most powerful metastatic-stimulating action of all other anesthetics, reducing overall-survival in cancer patients with solid tumors who had been through cancer-surgery. Thus, the use of inhalational anesthetics during cancer surgeries should be limited for reducing cancer recurrences, and metastases [12].

It is very important to include the local-anesthetic systemic-toxicity or LAST which is an adverse-event that may be life threatening due to diverse cellular-effects in the CNS, and cardiovascular-system (CVS). LAST may be minimized or circumvented with the use of pharmacogenomics.

MODIFIED APPROACHES TO ENHANCE SURGICAL OUTCOMES

NSAIDs, such as Parecoxib, Meloxicam, Celecoxib or ASA which are blocking isozymes COX1 or COX2 (PTGS-1 or PTGS-2, respectively) exert analgesic, and mainly anti-inflammatory action especially after cancer-surgery by preventing the blockade of NK-cell activity, and subsequently circumventing in some degree tumor-growth, and even the metastatic-cascade [13].

Furthermore, NSAIDs may exert immunoprotective-effects, and some degree of apoptotic action in solid tumors. Antihypertensive-drugs, such as beta adrenoreceptor-antagonists including metoprolol or propranolol which are used for the treatment of heart-failure (HF), hypertension and tachycardia may block the release of surgical-stress induced monoamine-neurotransmitters, such as catecholamines reducing the perioperative elevated-levels of activated regulatory T-cells (Treg), while blocking the synthesis of thromboxane that suppresses aggregation of platelets leading to significant inhibition of solid tumor-progression, cancer-recurrence, and metastasis leading to the enhancement of the overall-survival of cancer patients after surgery.

Anticoagulants or antithrombotic consisting of warfarin, heparin or ASA may block fibrin-formation and subsequent platelet-clots preventing metastastatic cascade and subsequently improving the overall-survival (OS) after surgery [14].

Statins which are characterized by pleiotropic effects are clinically indicated to be used against hyperlipidemia that may cause atherosclerosis, and CVD. Statins, such as atorvastatin, lovastatin, fluvastatin, pravastatin, simvastatin, rosuvastatin and pitavastatin are used as LDL-cholesterol lowering drugs, since they are inhibiting HMG-CoA reductase that is used for synthesis of cholesterol [15].

In addition to their stabilizing action in atherosclerotic-plaques, they also have vaso-dilatatory, antioxidant, anti-inflammatory and mainly antitumor/ant metastatic action.

Antiangiogenic-agents, such as bevacizumab which is a recombinant humanized MAb IgG1 blocks VEGF-A that is a cell-surface protein promoting angiogenesis, and subsequent metastasis [16].

Its perioperative-administration may improve overall-survival in patients with solid tumors. In addition to antiangiogenic MAbs, such as ranibizumab which blocks VEGF-A or olaratumab that inhibits PDGFRa. There are oligonucleotide-aptamers, such as pegaptanib, recombinant fusion-proteins including aflibercept, mTOR-inhibitors, such as temsirolimus, immunomodulatory-agents including lenalidomide or thalidomide, and tyrosine-kinase inhibitors, such as sunitinib, sorafenib, axitinib, vandetanib, apatinib, cabozantinib, ponatinib, pazopanib, etc.

Perioperative anticancer medicine may be improved tremendously with the implementation of Genomic-Medicine that must also focus on antiangiogenic drug-resistance factors, such as informal-angiogenesis via intussusceptions-angiogenesis or vessel-mimicry, autophagosomes, tumor-recruitment of pericellular-cells for covering blood-vessels or bone-marrow derived endothelial-progenitor cells, and compensatory-profactors, such as HGF, PDGF, PIGF, bFGF, etc.

Inhibition of these factors of antiangiogenic-resistance may improve prevention of cancer-recurrence, and metastasis after cancer surgery.
PDE5-inhibitors, such as tadalafil or sildenafil which are indicated for treating erectile-dysfunction may exert a perioperative-antitumor action by downregulating the expression of ROS, IL4-Ra, and ARG-1 [17].

Immunostimulating-drugs including checkpoint-inhibitors, vaccines or toll like receptor-agonists may be used as perioperative-antitumor agents because they may activate immune-cells, such as NK-cells [18].

These immunotherapy-drugs may circumvent the suppression of immune-cells which is caused by cancer-surgery. More analytically, TLR-9 and TLR-4 agonists, such as CpGC-oligonucleotides and GLASE, respectively, may reduce cancer-metastasis by enhancing NK cell-cytotoxicity after cancer-surgery. Also, immune checkpoint-inhibitors, such as cemiplimab, nivolumab, and pembrolizumab are mitigating the dysfunction of T-cells after cancer-surgery by targeting, and blocking PD1-protein that is acting as an off-switch preventing T-cell attack against tumor-cells. When these immunotherapeutic-agents are combined with prostaglandin-inhibitors, they are capable of restoring completely the antitumor-action of T-cells after cancer-surgery. Furthermore, vaccines which may activate immunity, such as influenza-vaccination combined with cancer-surgery may reverse perioperative-dysfunction of NK-cells reducing metastasis. Viruses used for infecting multiple-autologous tumor-types, such as the Newcastle-Disease Virus or NDV after being injected as a vaccine to cancer patients who had been through tumor-resection may enhance their overall survival (OS). Pharmacogenomics may predict genomic-variation to drug response by detecting genetic loci which predispose cancer-patients to adverse events or IrAE for ICIs, such as antiPD1 (pembrolizumab and nivolumab), anti-PDL1 (atezolizumab and durvalumab) and anti-CTLA4 (tremelimumab and ipilimumab).

Promising potential therapeutic approaches for perioperative surgical oncology may consist of the administration of NECROSTATIN-1 which is a small molecular inhibitor of RIPK-1 that may initiate NECROPTOSIS, form the necrotic-complex and vasculogenic-mimicry that is providing a blood-supply to tumor-cells independently of endothelial-cells [19].

In addition, creates an immune-suppressive tumor microenvironment (TME), and cause intrinsic/extrinsic-resistance to immune-checkpoint blockade. The administration of necrostatin-1 in cancer patients may inhibit all these oncogenic functions, suppress inflammation and tumorigenesis, induce type-1 PCD or apoptosis, and mainly inhibit perioperative-metastasis.

Another potential approach for blocking the metastatic-cascade consists of inhibiting the IL6-STAT3-SAA1,2 tumorigenic signaling-pathway which may lead to inhibition of inflammatory polymorph nuclear-neutrophils (PMNs) [20].

Also, inhibition of exosome-secretion may block the formation of PMNs blocking the colonization, extravasation of CTCs, organ tropic-metastasis, and growth of tumor cells.

It is imperative to avoid postoperative administration of glucocorticoids, such as dexamethasone, prednisone or cortisone for reducing metastatic-colonization, and enhancing survival-rates.

Another therapeutic approach consists of the miRNA mediated upregulation of AKAP-8 that is a splicing-regulatory factor acting as a metastasis-suppressor by impeding EMT, and inhibiting tumor-cell proliferation, cancer-growth, invasion and mainly metastatic-colonization [21].

Immunologic target in addition to colonization consists of dormant or growing-micrometastasis that is potentiated by systemic-effects consisting of activated-platelets, immunosuppression due to reduced NK-cells, and enhanced catecholamines, tumor growth-factors, angiogenic-factors (VEGF) or inflammatory mediators, such as MMP or COX.

All these factors may be derived from perioperative-stress modulators consisting of blood-transfusion, metabolic-disturbances, hypothermia, pain and even anxiety.

Other potential therapeutic-approaches may consist of antibodies targeting and inhibiting additional intertumoral-interactions including intercellular-crosstalk pathways mediated by ECM adhesion-molecules, and protease-release or intravasation which refers to the local- invasion of tumor-cells in the lumen of blood or lymph-vessels [22].

Approaches, such as neoadjuvant-therapies for shrinking tumors before cancer surgery, and adjuvant-therapies for reducing the risk of cancer recurrence after surgery may consist of chemotherapies including paclitaxel, etoposide, cisplatin etc., radiotherapies, such as IMRT, EBRT etc., immunotherapies consisting of atezolizumab, pembrolizumab, nivolumab etc., targeted-therapies including osimertinib, sotorasib, crizotinib etc., hyperthermia, hormone-therapy, radiofrequency-ablation, etc [23].

Pharmacogenetics and pharmacogenomics facilitated with targeted, exome and whole genome sequencing via NGS may be used for circumventing resistance to anticancer-agents, adverse drug reactions (ADR), drug-drug interactions, peripheral-neuropathies, secondary-tumors, infertilities, early-menopause, permanent damages to vital organs, etc. For the implementation of precision, and personalized medicine approaches additional omics may be employed, such as transcriptomics mediated by single cell RNA sequencing, RNA sequencing, SAGE, EST, CITE,ECCITE,REAP-seq, microarray etc, proteomics analyzed with MALDI-mass spectrometry and reverse phase protein-array or RPPA, metabolomics analyzed with mass spectrometry and NMR, epitranscriptomics analyzed with m6A- REF-seq, TLC, me- RIP –seq bisulfate RNA-seq, Tunnel –current/single-mol seq, radioactive SAM-incorporation, MS etc., and very importantly epigenomic-alterations which may be reversible leading to the circumvention of chemoresistance with the administration of epidrugs, such as DNMT-inhibitors (Azacitidine, Zebularine, Decitabine, Guadecitabine, RG-108, Fd-Cyd, SGI1027,Td-Cyd, MG-98, etc.), HDAC-inhibitors (Vorinostat or SAHA, Valproic-acid, Tubastatin-A, WK216, Panobinostat, RGFP-966, Belinostat, Romidepsin, etc.), EZH2-inhibitors (GSK-126, Tazemetostat, etc.), LSD1-inhibitors (TAK418, T448, Chalcone, etc.), DOT1L-inhibitors (EPZ-004777, etc.) and additional inhibitors that may be administered according to pharmacoepigenomic-analysis, and noncoding RNA-genes, such as miRNAs which may regulate the expression of disease causative protein coding genes after administration of therapeutic-agents consisting of AMO, LNA or PMO. MiRNA-suppression may be mediated by miRNA-inhibitors, miRNA-sponges, miRNA-masks or miRNA-antagomirs, while miRNA-replacement may be mediated by miRNA-mimics, miRNA expressing-plasmids, miRNA-precursors or miRNA-agomirs. Delivery of miRNAs and antimiRNA-oligonucleotides may be mediated by viral-vectors consisting of adenoviral-vectors, lentiviral-vectors, retroviral-vectors or adeno-associated viral-vectors, and nonviral-vectors composed of inorganic-material based delivery-systems, polymeric-vectors, 3D scaffold based delivery-systems or lipid based nanocarriers.

Additional delivery- vectors are based on dendrimers or cell derived membrane-vesicles. Methods for epigenome-analysis involving epigenetic-alterations, and noncoding RNA-genes, such as miRNAs consist of DNA-methylation sequencing methods, such as scNMT, scTrio, scMT or scM and T sequencing, chromatin-accessibility including SNARE sequencing or sci –CAR, whole-genome bisulfite-sequencing or whole genome-shotgun bisulfite-sequencing (WGSBS), Me DIP sequencing, ChiP sequencing, small-RNA sequencing, miRNA-microarray, nanostring, qRT- PCR, miRNA in-situ hybridization, MIRA sequencing and additional NGS methods.

It is very important that tailored genomic medicine approaches may target all the hallmarks of cancer recurrence, and metastasis involved in cancer surgery. For instance, the implementation of pharmacogenomics may circumvent the blockbuster, or one size fits all empiric-prescribing policy by identifying the individual-genotype of each perioperative cancer patient that may affect drug-efficacy, and adverse-events. Thus, by linking the genetic identity of each patient to his/her pharmacological identity, we may administer the right drug, at the right time and the right dosage to the right cancer patient.

Also, nanodelivery systems may enhance the therapeutic index of perioperative drugs, while reducing their systemic toxicity by protecting drug molecules from biological milieu interactions, and RES elimination. They may also circumvent chemoresistance mechanisms including drug efflux pumps (MDR), and deliver drug molecules to targeted cells by linking antibodies on nanosomal surfaces so they can bind to specific surface (plasma) receptors on tumor-cells, and even cancer stem cells which have been experimentally targeted by myself leading to their eradication by immunotarget- NANOSURGERY as an adjuvant treatment for eradicating metastasis [24].

The administration of the right evidence-based treatment individualized, to the patient, during and after cancer surgery may reduce adverse events, cancer recurrence and metastasis.

Concluding, the implementation of tailored perioperative personalized, and precision medicine approaches based on multiomic evidence to each cancer patient may revolutionize the field of surgical oncology.

Disclosure of interest

All authors declare any financial interest with respect to this manuscript.

Conclusion

Immunologic factors consist of cornerstone requirements concerning precise therapeutic mapping in surgical oncologic cases.

Target inhibition and case recurrence remain controversial issues regarding proper therapeutic strategy.

More studies must be conducted in order to establish assiduous results.

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