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Review Article

Novel Personalized Biologic Driven Strategies in Head and Neck Cancers – Empirical Cancer Care Leaping Towards Precision Care

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Abstract

Precision medicine is the targeted therapy with personalized approach to cancer treatment, ultimately Resulting in more precise targeting of tumor cells and spares the normal tissues and with minimal toxicities. The currently practised precision/targeted approaches in head and neck cancer are either based on the patient-specific or tumor-specific characteristics which includes the underlying etiology, tumor microenvironment or the genomics. The concept of precision medicine in oncology is focused on identifying therapies that are based on the genetic characterization of a patient's tumor, thereby tailoring the cancer treatment to a specific gene mutation in an individual patient's cancer. Though radiation oncology with the recent advancements with image guidance and functional imaging provides a more individualized treatment, it can be further optimized by the incorporation of novel biologic driven strategies, by consolidating the data obtained from genomics and radio genomics. This upgrades the treatment options with de-intensification or intensification based on the patient and tumor characteristics and etiology. This is currently achieved by various immunotherapeutic agents already in practice with monoclonal antibodies and signal transduction inhibitors and can be further expanded by identification of neoantigens for cancer vaccines and checkpoint inhibitor gene panels, with predictive and prognostic objective in addition to therapeutic benefits.

Introduction

Molecular and Genomic cancer research has become a rapidly expanding branch of biomedical sciences during the last two decades, which has contributed to many advances in our understanding of cancer. These innovative techniques have helped to modify the specific gene of interest, to manipulate the temporal and spatial expression of these genes, to study the entire genome and proteome of cancer cells, and thereby to specifically interfere with signal transduction or target a particular molecule or gene [1]. This novel biology-driven strategies helps in the selection of individualized treatment decisions, based on the specific characteristic of the individual as well as the tumor. Targeted treatment with personalized approach to cancer treatment, ultimately results in more precise targeting of tumor cells and spares the normal tissues, hence with minimal toxicities is broadly termed as precision medicine, by identifying and targeting molecular structures in many diseases, including cancer [2].

Why Precision Medicine in Oncology

A tumor is a heterogeneous population of cells with transformed cancer cells, supportive cells and tumor-infiltrating cells. This intra-tumor heterogeneity is further enhanced by clonal variation and microenvironmental influences on the tumor. The cancer stem cell model provides an explanation for this heterogeneity among cancer cells. This phenotypic and functional heterogeneity arise within the same tumor as a consequence of genetic change, environmental differences, and reversible changes in cellular properties [3], which can be specific for each individual, and each tumor in the same individual. This heterogeneity can also be responsible for treatment failure. Instead of providing an empirical treatment with the conventional chemotherapeutic agents and radiation, which destroys both tumor and normal cells, we need to expand our knowledge to incorporate biologically relevant-molecular level information to make the cancer treatment more personalized, hence tailored to each patient and their tumor characteristics [4], thereby providing the most specific/precise treatment. Precision medicine aims at targeting cancer cells specifically, by uncovering molecular alteration of the malignancy. Also, because the molecular biology generates more heterogeneity among tumors, cancer is to be treated in a more personalized way. The concept of precision medicine in oncology is focused on identifying therapies that are

based on the genetic characterization of a patient's tumor, and hence identifies the treatment modality, the agent and even the dose that will be the most effective for each patient based on genetic characterization of their cancer. This makes the term Precision medicine, be interchangeably used with Personalized medicine or Individualized medicine, which are basically selection of the right patients for a given systemic agent [5]; and precision medicine in oncology aims at tailoring the cancer treatment to a specific gene mutation in an individual patient's cancer.

Precision Medicine in Radiation Oncology

Radiation oncology in the current era with the advancements in treatment delivery with image guidance for better conformality, and incorporation of functional imaging, is already considered to abide by the concept of precision medicine [6]. The individualized approach in the radiation treatment planning, can be seen from contouring of patient-specific tumor and normal tissues, selection of beam energies, placement of beam angles and beam shapes based on patient-specific anatomy, to the selection of optimal treatment plans according to the patient-specific dose-volume-histograms of normal tissues and target volume coverage designed to maximize the therapeutic ratio. Furthermore, tumor-specific factors are also considered with altered fractionation based on the radiobiology of the tissue of origin and based on the intent of treatment [6]. It is required to incorporate the advances in cancer genomics and cancer biology, for further personalization of treatment, instead of offering radiation therapy with the same conventional radiation dose, taking into consideration the molecular features of the individual cancer. Precision Radiation Oncology can be broadly divided into two categories: Physical/Imaging-based precision radiation and Biological-driven precision radiation that includes Genomics and Radiogenomics [4]. Recent advances in radiotherapy with functional imaging and image guidance with on-board live tracking of tumor allows the application of Physical-based precision radiation oncology, by expanding the horizon of precise and accurate treatment delivery or Adaptive radiotherapy. These accounts for inter-fractional variations due to tumor response, which is specific to the individual geometry, or to allow dose escalation boost, thereby to spare maximum normal tissues with better disease control. This potential of improved therapeutic ratio by Physical-based precision radiation, can be optimized to the individual patient by measuring the 'genomic' determined or 'intrinsic' radiosensitivity of a tumor. In head and neck cancers, this helps in selective sparing of normal adjacent organs like spinal cord, parotid and submandibular glands, pharyngeal constrictors and larynx, and thereby effectively preventing any acute or long-term sequelae of radiation and hence promises a better quality of life. This could be further individualized by adjusting radiation dose, considering the use of concurrent chemotherapy or molecular targeted therapy, especially in tumors genomically predisposed to radio-resistance [4].

Genomics is the most recent tool for precision medicine, which is the study of whole genomes of organisms. Genomics, unlike genetics which considers one gene or one gene product at a time considers full complement of hereditary material, incorporating elements from genetics. Genomics uses combination of recombinant DNA, DNA sequencing methods, and bioinformatics to sequence, assemble, and analyse the structure and function of genomes [7]. Radiogenomics is the study of link between the imaging features of a particular disease referred to as Imaging phenotype and various genetic and molecular characteristics of that disease referred to as Genomic phenotype [8]. The practical application of Genomics and Radiogenomics in guiding radiation therapy delivery, may be implemented with use of hypoxia-metrics, functional imaging and tumor proliferative potential, to guide the intensity of radiation dose delivery. This also provides predictive and/or prognostic information to identify potential new treatment targets and treatment choices. These tumor genomic features are used to further personalize the treatment recommendations. This requires an understanding of the vast heterogeneity and complexity of tumors as well as the processes that drive this heterogeneity. Hence, the currently practised precision/targeted approaches in head and neck cancer are either based on the patient-specific or tumor-specific characteristics which includes the underlying etiology, tumor microenvironment or the genomics.

Targeted Treatment in Head and Neck Cancer Based on Etiology

In Head and neck cancers, the two widely accepted tumor factors to implement personalized modification of radiation dose are Human papilloma Virus (HPV)-associated and tobacco-associated pathologies. HPV-associated Head and Neck Cancers (HNC) are clinically and biologically distinct from tobacco-related HNC, which makes their therapeutic response also recognizable. HPV-positive Oropharyngeal Carcinoma (OPC) shows better outcome with respect to overall survival and is still maintained after a longer median follow-up, with similar distribution of toxicity profile, compared to HPV-negative HNC [9] and with low risk of distant metastases [10]. This paved the way for exploring the options of more individualized treatment with radiation dose de-escalation to reduce toxicity, without compromising tumor control in HPV-associated oropharyngeal cancers. The option of treatment de-intensification by avoiding chemotherapy and treating with radiation alone using altered fractionation was also possible with this approach [10]. While in HPV-unrelated, or smoking/tobacco-related locally advanced HNC, treatment intensification is demanded, the resulting toxicity is likely to limit further intensification of radiation and traditional chemotherapy. In such scenarios, the addition of novel targeted agents may be considered [11].

Targeted Treatment in Head and Neck Cancer Based on Tumor Microenvironment

Tumor hypoxia, being the tumor characteristic associated with aggressive malignant phenotype, hence makes poorly oxygenated tumors as a target in the field of precision treatment. These tumors

are less likely to respond to radiotherapy or chemotherapy and are more likely to develop early distant metastasis after treatment, with more risk of treatment failure independent of tumor stage and therapeutic modality. The agents used in HNCs that act indirectly by sensitizing hypoxic cells are MISONIDAZOLE, ETANIDAZOLE and NIMORAZOLE, which are electron-affinic compounds which oxidises radiation-induced free radical damage to produce increased cell kill [12]. While the targeted agents act directly on the hypoxic cells by, and include TIRAPAZAMINE, MITOMYCIN C and PORFIROMYCIN [13]. These being bio-reductively activated compounds are cytotoxic to poorly oxygenated cells and also potentiates the action of Cisplatin [13,14]. The practical approach to hypoxia by the use of hypoxia modifiers are still not very appealing, may be attributed to expensive or logistically difficult techniques to measure hypoxia.

Targeted Treatment Based on Tumor Genomics

Targeted cancer treatment uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells. Based on the mechanism of action it can be broadly classified as Monoclonal Antibodies (MABs), Signal transduction inhibitors or Receptor targeted drugs and Cancer vaccines. MABs are molecules engineered to serve as substitute antibodies which restore, enhance or mimic the immune system's attack on cancer cells. Receptor-mediated or signal transduction pathway-mediated targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Targeted therapy may have fewer side effects than other types of cancer treatment and are labelled as Immunotherapy that uses body's own immune system to fight cancer cells, hence considered as the 'fourth modality of cancer treatment' [15]. These belong to the class of substances known as biological response Modifiers, which stimulates or restores the patient's immune system against the cancer cells, directly or indirectly. These precisely targeted agents are designed to attack specifically the cancer cells either via the antigen produced by them, or via the receptor molecules expressed on their surface, or by inhibiting the cancer promoting pathways. Recent efforts are to integrate radiation and systemic therapy with such molecularly targeted agents based on the presence or absence of mutation, with overexpression, amplification, translocations or deletion of specific genes.

Epithelial Growth Factor Receptor (EGFR) is the most studied and often addressed in HNC, being upregulated in almost 90% of HNSCC and associated with poor prognosis [16]. EGFR can be targeted either directly by blocking the receptor by using specific antibodies against the receptor or by inhibiting the signal cascade of EGFR pathway after activation. Cells receive external signals that are transmitted into the cell by receptors, like tyrosine kinase receptors transmitting signals through phosphorylating tyrosine residues of proteins. Deregulated activation of tyrosine kinases is characteristic of most cancers [17]. CETUXIMAB- an anti-EGFR IgG1 MAB, has shown improved outcomes with respect to median overall survival in recurrent and metastatic disease [18,19] with more acute skin toxicities. Other anti EGFR MABs used in metastatic setting in conjunction with radiation includes Panitumab [20], Zalutumumab [21]. GEFTINIB and ERLOTINIB- which are potent and selective small-molecule inhibitors of kinase activity of wild-type and certain activating mutations of EGFR, resulting in in inhibition of EGFR signaling [17]. This in turn inhibits critical mitogenic and antiapoptotic signals involved in proliferation and metastases, and response to chemo- or radiotherapy. are the most commonly tried targeted drugs in head and neck. Treatment directed against other molecular targets are VEGFR, attributed to the two-fold increase in disease specific mortality associated with overexpression of VEGF in HNSCC, the drug used to be Bevacizumab [22]. The implications of immunotherapeutic drugs in HNC are in recurrent or metastatic diseases not amenable for local therapies or refractory to first line platinum-based chemotherapy, is by inhibition of PD-1 by Nivolumab [23] and Pemrolizumab [24], which improves overall survival.

Ongoing and Upcoming Studies: Future of Precision Medicine in Head And Neck Cancer Management

With the gaining knowledge in genomic surveillance and molecular level analysis, with development of novel molecularly targeted agents and immune-modulating anti-cancer therapeutics, the potential to examine the combination of radiation therapy with these agents for additive or synergistic effects are being explored more lately. The most recent one is the model of seven immune checkpoint-related genes, to construct reliable gene signatures for better risk stratification and thereby to facilitate subsequent individualized treatment options. The 7 genes studied in the gene panel were PPP2R1B, MYD88, CD86, CD80, MAP2K1, TRIB3 and ICOS [25]. This model showed that the 80 Differentially Expressed Genes (DEGs) were enriched in the MAPK signalling pathway, PI3K – Akt signalling pathway, and the assessment of prognosis by the risk stratification based on this model showed that the high-risk patients were having a poor prognosis. This model hence puts forward an effective method to predict and stratify overall survival in HNSCC patients [25], and thereby the optimal treatment selection based on outcomes. Cancer vaccine is another ground-breaking advancement in field of precision medicine in HNC. Cellular immunity to neoantigens have a direct impact on clinical outcomes in HNSCC, as it is considered to have relatively high mutation burden compared to other cancer types [26] and hence as a source of neoantigens to get targeted by antigen-specific T cells. These neoantigens can be tumor-associated antigens or tumor -specific antigens. Studies are ongoing for identification of somatic mutation derived neoantigens and the appropriate selection of antigens to be targeted with the vaccines [26], in those patients who do not benefit from other modalities, as a therapeutic approach. Use of Anti-HPV vaccines with prophylactic approach for HNSCC, which are already approved and widely used for cervical and anal cancer prevention is also currently under consideration, which will be a promising step towards head and neck cancer prevention [27].

Advantages and Challenges

There are many potential advantages for application of precision medicine, which includes accurate and timely diagnosis, with more certain and more favourable treatment outcomes, allowing more patient and tumor specific treatment decisions, which ultimately helps in improvement of treatment outcomes with respect to survival and toxicities, and thereby of quality of life. It also aids for access to clinical trials, for more common as well as for rare diseases [5]. This is possible with a proper patient selection strategy based on matching the genomic features like driver mutation, amplification or pathway overexpression, is required which will lead to a rapid and successful outcome, with least related toxicities; but absence of a selection strategy may lead to a null effect. Though the precision medicine tools theoretically cause much less systemic toxicity due to their targeted approach than the non-specific cytotoxicity of classical chemotherapy, there are certain concerns over its efficacy. Since signalling in most cancers is not strictly via oncogene addiction pathways and due to the cancer heterogeneity and plasticity, targeted therapies may get primed for resistance, making the targeted pathway be bypassed by alternate rescue signalling [28]. There are certain practical challenges as well, from patient perspective like limitations for timely access, affordability, uncertainty in the potential harm resulting from data sharing or data security issues, uncertainties in impact of personal genetic information on family members and relatives [5]. Incomplete knowledge of implications of biomarkers or lack of understanding of risk prediction and interpretation, and the differences among treatment options raises concerns from the treating physician perspective. There are certain logistic concerns also like, preparedness for prognostic features and future insurance coverage, and regarding the practicality of providing a truly informed consent [5].

Conclusion

Genomic Surveillance is fast emerging as a routine part of cancer diagnostics and therapeutics, for targeted drugs with immunotherapy, as an adjunct to radiation therapy and conventional chemotherapy as biomarkers for treatment response and resistance. The individualized approach with targeted treatment and further expansion by molecular analysis will provide biomarkers for more personalized therapies that eliminate malignant cells sparing normal cells, improving the therapeutic ratio, survival and quality of life.

References

1. Grade M, Becker H, Ghadimi BM (2004) The impact of molecular pathology in oncology: The clinician's perspective. Cell Oncol 26(5–6): 275–278.
2. Baumann M, Krause M, Overgaard J, Debus J, Bentzen SM, et al. (2016) Radiation oncology in the era of precision medicine. Nat Rev Cancer 16(4): 234–249.
3. Dagogo-Jack I, Shaw AT (2018) Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol 15(2): 81–94.
4. Baschnagel AM, Vijayakumar S, Li A, Schultz CJ, Wilson GD, West CML, et al. (2017) Current Opportunities and Future Vision of Precision Medicine in Radiation Oncology. Int J Radiat Oncol Biol Phys 101(2): 267-270.
5. Biltaj E, Brixner D, Barr C, Oberg J, Shandhu G (2020) Being Precise About Precision Medicine: What Should Value Frameworks Incorporate to Address Precision Medicine? A Report of The Personalized Precision Medicine Special Interest Group. Value Heal [Internet] p. 1–11.
6. Kirsch DG (2017) Current Opportunities and Future Vision of Precision Medicine in Radiation Oncology. Radiat Oncol Biol [Internet] 101(2): 267–270.
7. Nogrady B (2020) How cancer genomics is transforming diagnosis and treatment. Nature 579(7800): S10-S10.
8. Shui L, Ren H, Yang X, Li J, Chen Z, et al. (2020) Era of radiogenomics in precision medicine: an emerging approach for prediction of the diagnosis, treatment and prognosis of tumors. Front Oncol 10: 3195.
9. Nguyen-Tan PF, Zhang Q, Ang KK, Weber RS, Rosenthal DI, et al. (2014) Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol 32(34): 3858.
10. O'Sullivan B, Huang SH, Perez-Ordonez B, Massey C, Siu LL, et al. (2012) Outcomes of HPV-related oropharyngeal cancer patients treated by radiotherapy alone using altered fractionation. Radiother Oncol 103(1): 49–56.
11. Ghi MG, Paccagnella A (2019) Therapeutic Intensification and Induction Chemotherapy for High-Risk Locally Advanced Squamous Cell Carcinoma. Curr Treat Options Oncol 20(2): 2.
12. Adams GE, Stratford IJ, Sheldon PW (1984) Hypoxia-mediated drugs for radio-and chemotherapy. In: Cancer Chemotherapy and Selective Drug Development. Springer pp. 241–247.
13. Haffty BG, Wilson LD, Son YH, Cho EI, Papac RJ, et al. (2005) Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: final results of a randomized clinical trial. Int J Radiat Oncol Biol Phys 61(1): 119–128.
14. Dobrowsky W, Naudé J (2000) Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancers. Radiother Oncol 57(2): 119–124.
15. Bell RB (2017) Immunotherapy for head and neck cancer: integrating the fourth modality into treatment. Int J Oral Maxillofac Surg 46: 5.
16. Temam S, Kawaguchi H, El-Naggar AK, Jelinek J, Tang H, et al. (2007) Epidermal growth factor receptor copy number alterations correlate with poor clinical outcome in patients with head and neck squamous cancer. J Clin Oncol 25(16): 2164–2170.
17. Caponigro F, Romano C, Milano A, Solla R, Franchin G, et al. (2008) A phase I/II trial of gefitinib and radiotherapy in patients with locally advanced inoperable squamous cell carcinoma of the head and neck. Anticancer Drugs 19(7): 739–744.
18. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, et al. (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354(6): 567–578.
19. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA (2005) Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 23(34): 8646–8654.
20. Wirth LJ, Allen AM, Posner MR, Haddad RI, Li Y, et al. (2010) Phase I dose-finding study of paclitaxel with panitumumab, carboplatin and intensity-modulated radiotherapy in patients with locally advanced squamous cell cancer of the head and neck. Ann Oncol 21(2): 342–347.

21. Machiels JP, Subramanian S, Ruzsa A, Repassy G, Lifirenko I, et al. (2011) Zalutumumab plus best supportive care versus best supportive care alone in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck after failure of platinum-based chemotherapy: an open-label, randomised phase 3 trial. Lancet Oncol 12(4): 333–343.

22. Yoo DS, Kirkpatrick JP, Craciunescu O, Broadwater G, Peterson BL, et al. (2012) Prospective trial of synchronous bevacizumab, erlotinib, and concurrent chemoradiation in locally advanced head and neck cancer. Clin Cancer Res 18(5): 1404–1414.

23. Sato Y, Fukuda N, Wang X, Urasaki T, Ohmoto A, et al. (2020) Efficacy of nivolumab for head and neck cancer patients with primary sites and histological subtypes excluded from the CheckMate-141 Trial. Cancer Manag Res 12: 4161.

24. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, et al. (2019) Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 394(10212): 1915–1928.

25. Song D, Tian J, Han X, Li X (2021) A model of seven immune checkpoint-related genes predicting overall survival for head and neck squamous cell carcinoma. Eur Arch Oto-Rhino-Laryngology p. 1–11.

26. Shibata H, Zhou L, Xu N, Egloff AM, Uppaluri R (2021) Personalized cancer vaccination in head and neck cancer. Cancer Sci 112(3): 978.

27. Shewale JB, Gillison ML (2019) Dynamic factors affecting HPV-attributable fraction for head and neck cancers. Curr Opin Virol 39: 33–40.

28. Burdach SEG, Westhoff M, Steinhauser MF, Debatin K (2018) Precision medicine in pediatric oncology. Curr Opin Pediatr 30(1): 17-24.

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