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Role of Anticancer Drugs in the Treatment of Oral Carcinomas-A Review of Literature

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Abstract: ***Oral cancer is the sixth common tumour world- wide [1]. Oral cancer is the fourth leading cause of cancer death for males [2]. Oral squamous cell carcinoma (OSCC) is the most common neoplasia and is found frequently in oral cavity in the cheek, gingiva and tongue [3]. Although cigarette and alcohol are considered as two major etiological factors of oral carcinogenesis [4], occurrence of oral cancer was seen to be associated with betel quid chewing.[4,5]. Oral chemotherapy is attractive because of its convenience and ease of administration, particularly in the palliative setting. This article focuses on the various anticancer drugs and their action.***

Keywords: oral cancer, anticancer, cytotoxics

1. Introduction

Oral chemotherapy is appropriate where prolonged drug exposure is desirable as with schedule dependent agents such as topoisomerase I inhibitors or the fluoropyrimidines. With an increasing number of oral agents emerging, there can be a rapid rise in the use of oral chemotherapy.

More than 20 oral cytotoxics are already available. One reason is that many oral cytotoxics are new formulations of existing compounds. Oral etoposide is active against a wide range of tumours but enthusiasm for its use has been limited by concerns over toxicity. Currently, probably the widest use of oral chemotherapy is with 6-mercaptopurine, methotrexate and busulphan in patients with leukaemia and lymphoma.

2. Cytotoxics

Over the last decade oral chemotherapy has generally failed to keep pace with increasing use of i.v. cytotoxics. Many emerging oral cytotoxics are new formulations of drugs routinely given i.v. Topotecan is equally effective in small cell lung cancer by the i.v. and oral routes but oral treatment has a better toxicity profile with less myelosuppression (6). The ability to administer taxanes orally would offer considerable advantages, particularly with paclitaxel where the chremophore EL vehicle can be responsible for hypersensitivity reactions. Co- administration of cyclosporin A, a potent inhibitor of p-glycoprotein, results in oral bioavailability for taxanes in excess of 50%. Several oral taxanes are also in development (7,8) and likely to become available in the next few years.

5-fluorouracil (5-FU) is highly schedule dependent, but oral administration is unreliable and causes diarrhoea, this has been a particular focus of efforts to develop oral alternatives. These have included pro-drugs that are absorbed unchanged (capecitabine, tegafur), addition of inhibitors of the enzyme DPD that catabolises 5-FU (uracil, eniluracil), or a combination of the two (UFT, S1, emitefur) (9)

Eniluracil is a very effective DPD inhibitor that renders 5-FU highly bioavailable after oral administration. The combination of UFT and folinic acid is active in fluoropyrimidine sensitive tumours.

The future of S1 and emitefur is also unclear. The exception is capecitabine which is now approved across the world in two common solid tumours, breast and colorectal cancer. It is also active as a single agent in taxane resistant breast cancer. Results of a recent trial in patients with anthracycline resistant breast cancer show that the addition of capecitabine to docetaxal significantly prolongs survival (10). The success of capecitabine means that the profile of oral chemotherapy is set to rise.

3. Limitations of Cytotoxic Agents

There are a number of problems with the safety profile and efficacy of chemotherapeutic agents. Cytotoxics predominantly affect rapidly dividing cells so do not specifically target cancer cells in the resting phase. They also only influence a cell's ability to divide and have little effect on other aspects of tumour progression such as tissue invasion, metastases or progressive loss of differentiation. Finally, cytotoxics are associated with a high incidence of adverse effects. The most notable examples include bone marrow suppression, alopecia, mucositis, nausea and vomiting.

4. Novel Agents

Potentially even more important in the medium and long-term will be 'smart' drugs, targeted to components of intra-cellular signalling pathways such as protein kinases (11). Imatinib inhibits the c-abl and c-kit tyrosine kinases. It has excellent oral bioavailability and remarkable activity (12) (13), which are 'driven' by the BCR-ABL fusion protein and c-kit, respectively. Iressa (ZD 1839) is an oral anilinoquinazoline inhibitor of EGFR tyrosine kinase activity given once daily by mouth that is active in non-small cell lung cancer (13). A reversible acneiform rash has been observed with both iressa and tarceva (OSI-774),

another oral quinazoline EGFR tyrosine kinase inhibitor is active in head and neck cancers (15;16).

5. Choice of Chemotherapy in Oral Cancer

The single agents active in oral cancer, with response rates between 15 and 40 percent, include methotrexate, cisplatin, carboplatin, fluorouracil, ifos- famide, bleomycin, paclitaxel and docetaxel. Cisplatin is particularly popular for use either as a single agent or in combination with other drugs because for a long it was viewed as one of the most active drugs in squamous head and neck cancer (17) Taxoids and gemcitabine are now gaining favour and are being incorporated into many current drug trials. [18,19,20]

6. Chemotherapy Strategies

6.1 Combination chemotherapy

Combinations of cytotoxic agents are widely used for many cancers and may be more effective than single agents. Possible explanations for this include:

- Exposure to agents with different mechanisms of action and non overlapping toxicities;
- Reduction in the development of drug resistance;
- The ability to use combinations of drugs that may be synergistic.

In practice, the predominant dose-limiting toxicity of many cytotoxic drugs is myelosuppression and this limits the doses of individual drugs when used in combination.

6.2 Adjuvant chemotherapy

This is the use of chemotherapy in patients known to be at risk of relapse by virtue of features determined at the time of definitive local treatment (e.g. tumour grade, lymph node status, etc.). The intention of adjuvant chemotherapy is therefore the eradication of micro metastatic disease. Randomised trials assessing the use of adjuvant chemo-therapy for the patients with head and neck squamous carcinoma do not suggest a significant benefit (21).

6.3 Neoadjuvant chemotherapy

Neoadjuvant, or induction chemotherapy, is the use of chemotherapy before definitive surgery or radiotherapy in patients with locally advanced disease. The intention of this strategy is to improve local and distant control of the disease in order to achieve greater organ preservation and overall survival. Numerous phase III trials have considered the benefit of neoadjuvant chemotherapy followed by definitive surgery, by surgery and radiotherapy, or by radiotherapy alone as compared to definitive management without chemotherapy. Unfortunately, these studies have not demonstrated a survival advantage. To date, only subset analyses of trials using neoadjuvant cisplatin and 5-fluorouracil combination chemotherapy compared with locoregional treatment alone have shown a small survival gain. In addition, neoadjuvant chemotherapy has been shown to have little impact on reducing loco regional failure. This is perhaps surprising given the consistently observed high initial tumour response rates of up to 70–85 percent. The role of neoadjuvant chemotherapy therefore continues to remain controversial and further studies are planned, particularly looking at more effective drug combinations (22).

6.4 Concurrent chemo-radiation

This involves the synchronous use of chemotherapy and radiotherapy. Multiple randomised trials comparing con-current radiotherapy and chemotherapy with radiotherapy alone have shown significant improvement in loco regional control, relapse-free survival and overall survival rates in patients with locally advanced, unresectable disease (23). These results may reflect the influence of chemotherapy on micro metastatic disease or its ability to enhance tumour radio sensitivity (24). Some chemotherapy agents are recognised to be more active in certain radio resistant cell types. Other drugs may act synergistically with radio-therapy by hindering the repair of radiation-induced DNA damage (cisplatin), by synchronising or arresting cells during radiosensitive phases (hydroxyurea, paclitaxel) or by hindering regrowth between fractions of treatment.

Many different drug combinations and radiation schedules have been evaluated. Each combination clearly has unique toxicities, risks and benefits. At present, there is still debate regarding the optimum chemo radiotherapy regimen that should become the standard of care.

6.5 High-dose chemotherapy

Many chemotherapy drugs have a linear dose–response curve, but their use at high doses is limited by myelosuppression. This may be overcome by using bone marrow or peripheral stem cell infusions. While high- dose chemotherapy appears to have a role in the management of leukaemias, myeloma and certain lymphomas, little benefit has been demonstrated in common solid tumours.

6.6 Chemoprevention

This is a novel approach with the aim of reversing or halting carcinogenesis with the use of pharmacologic or natural agents. Retinoids have been tested in head and neck carcinogenesis both in animal models and against oral premalignant lesions and in the prevention of secondary tumours in humans, with initial encoura- ging results (25,26). Studies are also looking at the benefit of using cyclo-oxygenase 2 (COX-2) inhibitors in a similar role (27).

6.7 Novel Therapies for the Future

Despite the introduction of new cytotoxic drugs, such as antimetabolites (capecitabine) and topoisomerase I inhibitors, the management of advanced head and neck cancer remains challenging. Over the last years interest has focussed more on novel agents with a more targeted mechanisms of action. Targeted therapy aims to specifically act on a well- defined target or biologic pathway that, when inactivated, causes regression or destruction of the malignant process. The main strategies of research have looked at the use of monoclonal antibodies or targeted small molecules.

6.8 Monoclonal antibodies

In the early 1980s, it became apparent that targetted therapy using monoclonal antibodies (MAb) might be useful in the detection and treatment of cancer. Mono- clonal antibodies can be derived from a variety of sources: murine: mouse antibodies;chimeric: part mouse/part human antibodies; humanised: engineered to be mostly human; human: fully human antibodies. Murine monoclonal antibodies may themselves induce an immune response that may limit repeated administration. Humanised and, to a lesser extent, chimeric antibodies are less immunogenic and can be given repeatedly.
There are several proposed mechanisms of action of monoclonal antibodies (28).These include:

Direct Effects:
- Induction of apoptosis;
- Inhibition of signalling through the receptors needed for cell proliferation/function;
- Anti-idiotype antibody formation, determinants amplifying an immune response to the tumour cell;

Indirect Effects:
- Antibody-dependent cellular cytotoxicity (ADCC, conjugating the 'killer cell' to the tumour cell);
- Complement-mediated cellular cytotoxicity (fixation of complement leading to cytotoxicity).

7. NSAID's as Anticancer Drugs

Several recent reviews (29-31) have summarised the intriguing and accumulating evidence that non steroidal anti-inflammatory drugs (NSAIDs) have promise as anticancer drugs. NSAIDs have been shown experimentally to stimulate apoptosis and to inhibit angiogenesis, two mechanisms that help to suppress malignant transformation and tumour growth. Numerous epidemiological (nonrandomised)studies(32,33)have found that long-term users of aspirin or other NSAIDs have a lower risk of colorectal adenomatous polyps and colorectal cancer than nonusers, al- though one study has not (34-36). Randomised clinical trials have confirmed that two NSAIDs, the prodrug sulindac (37-39) and the selective cyclooxygenase (COX)-2 inhibitor celecoxib (40), effectively inhibit the growth of adenomatous polyps. Despite these positive findings, the efficacy and safety of long-term NSAID prophylaxis against colorectal or other cancers remain unproven. In addition, unresolved questions about the mechanism by which these drugs act, the optimal drug, dose, treatment regimen, and the balance of risks and benefits in specific populations must be answered.

8. Conclusion

The majority of conventional chemotherapeutic agents cause cell death by directly inhibiting the synthesis of DNA or interfering with its function. This means that they are often not tumour-specific and are associated with considerable morbidity. Trials have demonstrated that combination chemotherapy regimens can cause dramatic regression of head and neck tumours, especially when used concomitantly with radiotherapy. Unfortunately, this has not been associated with an increase in survival rates.

There is considerable excitement over the development of new target-directed cytotoxic agents. These have been developed to modulate or inhibit specific molecular targets critical to the development of or control of cancer cells. Particular interest has focussed on the field of monoclonal antibody development, particularly in relation to the epidermal growth factor. Other drugs affecting signal transduction, programmed cell death, transcription regulation, matrix invasion and angio- genesis are currently involved in clinical trials. The results of these are obviously eagerly awaited and will potentially radically change current therapeutic strategies.

References

[1] Ng SH, Yen TC, Liao CT, Chang JT, Chan SC, Ko SF, Wang HM, Wong HF: 18F-FDG PET and CT/MRI in oral cavity squamous cell carcinoma: a prospective study of 124 patients with histologic correlation. J Nucl Med. 2005, 46: 1136-1143.
[2] Chung TT, Pan MS, Kuo CL, Wong RH, Lin CW, Chen MK, Yang SF: Impact of RECK gene polymorphisms and environmental factors on oral cancer susceptibility and clinicopathologic characteristics in Taiwan. Carcinogenesis. 2011, 32: 1063-1068. 10.1093/carcin/bgr083.
[3] Chen YK, Huang HC, Lin LM, Lin CC: Primary oral squamous cell carcinoma: an analysis of 703 cases in southern Taiwan. Oral Oncology. 1999, 35: 173-179. 10.1016/S1368-8375(98)00101-8.
[4] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: Global Cancer Statistics. Ca-a Cancer Journal for Clinicians. 2011, 61: 69-90. 10.3322/caac.20107.
[5] Trivedy CR, Craig G, Warnakulasuriya S: The oral health consequences of chewing areca nut. Addiction Biology. 2002, 7: 115-125. 10.1080/13556210120091482.
[6] von Pawel J, Gatzemeier U, Pujol JL, Moreau L, Bildat S, Ranson M, Richard- son G, Steppert C, Riviere A, Camlett I, Lane S, Ross G (2001) Phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer. J Clin Oncol 19:(6): 1743 – 1749.
[7] Polizzi D, Pratesi G, Monestiroli S, Tortoreto M, Zunino F, Bombardelli E, Riva A, Morazzoni P, Colombo T, d'Incalci M, Zucchetti M (2000) Oral efficacy and bioavailability of a novel taxane. Clin Cancer Res 6:(5): 2070 – 2074
[8] Rose WC, Long BH, Fairchild CR, Lee FY, Kadow JF (2001) Preclinical Phar- macology of BMS-275183, an Orally Active Taxane. Clin Cancer Res 7:(7): 2016 – 2021
[9] Lamont EB, Schilsky Rl (1999) The oral fluoropyrimidines in cancer chemotherapy. Clin Cancer Res 5: 2289 – 2296
[10] O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, Fumoleau P, Jones S, Lui WY, Mauriac L, Twelves C, Van Hazel G, Verma S, Leonard R (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-

pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 20(12): 2812 – 2823.
[11] Rajagonopalan S, Hanson-Painton O, Cooper DR (2000) Protein kinases as therapeutic targets. Pharma Res 17:(11): 1345
[12] Kantarjian HM, Talpaz M (2001) Imatinib mesylate: clinical results in Phila- delphia chromosome-positive leukemias. Semin Oncol 28:(5 Suppl 17): 9 – 18
[13] van Oosterom AT, Judson I, Verweij J, Stroobants S, Donato di Paola E, Dimitrijevic S, Martens M, Webb A, Sciot R, Van Glabbeke M, Silberman S, Nielsen OS; European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (2001) Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet 358:(9291): 1421 – 1423
[14] Baselga J (2001) The EGFR as a target for anticancer therapy – focus on cetux- imab. Eur J Cancer 37:(Suppl 4:): S16 – S22
[15] Perez-Soler R, Chachoua A, Huberman M, Karp D, Rigas J, Hammond L, Rowinsky E, Preston G, Ferrante KJ, Allen LF, Nadler P, Bonomi P (2001) A phase II trial of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor OSI-774, following platinum-based chemother- apy, in patients with advancecd, EGFR-expressing, non-small cell lung cancer. Proc ASCO 20: 310
[16] Senzer NN, Soulieres D, Siu L, Agarwala S, Vokes E, Hidalgo M, Silberman S, Allen L, Ferrante K, Fishers D, Marsolais C, Nadler P (2001) Phase 2 eleva- tion of OSI-774, a potent oral antagonist of the EGFR-TK in patients with advanced squamous cell carcinoma of the head and neck. Proc ASCO 20: 2
[17] Henk JM. Concomitant chemotherapy for head and neck cancer: saving lives or grays? Clinical Oncology (Royal College of Radiologists (Great Britain)). 2001; 13: 333–5. Brief summary of important issues and trials with respect to the role of chemotherapy and radiotherapy in head and neck cancers.
[18] Henk JM. Concomitant chemotherapy for head and neck cancer: saving lives or grays? Clinical Oncology (Royal College of Radiologists (Great Britain)). 2001; 13: 333–5. Brief summary of important issues and trials with respect to the role of chemotherapy and radiotherapy in head and neck cancers.
[19] Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet. 2000; 355: 949–55. Main meta- analysis on the effect of chemotherapy on nonmetastatic head and neck squamous-cell carcinoma.
[20] Forastiere A, Koch W, Trotti A, Sidransky D. Head and Neck Cancer. New England Journal of Medicine. 2001; 345: 1890–1900. Very good summary of the important advances in the treatment of patients with head and neck cancer and the future importance of molecular biology.
[21] Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet. 2000; 355: 949–55. Main meta- analysis on the effect of chemotherapy on nonmetastatic head and neck squamous-cell carcinoma.
[22] Haffty BG. Concurrent chemoradiation in the treatment of head and neck cancer. Hematology/Oncology Clinics of North America. 1999; 13: 719–42.
[23] Forastiere A, Koch W, Trotti A, Sidransky D. Head and Neck Cancer. New England Journal of Medicine. 2001; 345: 1890–1900. Very good summary of the important advances in the treatment of patients with head and neck cancer and the future importance of molecular biology.
[24] Haffty BG. Concurrent chemoradiation in the treatment of head and neck cancer. Hematology/Oncology Clinics of North America. 1999; 13: 719–42.
[25] Hong WK, Endicott J, Itri LM, Doos W, Batsakis JG, Bell R et al. 13-Cis retinoic acid in the treatment of oral leukoplakia. New England Journal of Medicine. 1986; 315: 1501–5.
[26] Hong WK, Lippman SM, Itri LM, Karp DD, Lee JS, Byers RM et al. Prevention of second primary tumours with isotretinoin in squamous-cell carcinoma of the head and neck. New England Journal of Medicine. 1990; 323: 795–801.
[27] Chan G, Boyle JO, Yang EK, Zhang F, Sacks PG, Shah JP et al. Cyclooxygenase-2 expression is up-regulated in squamous cell carcinoma of the head and neck. Cancer Research. 1999; 59: 991–4.
[28] Green MC, Murray JL, Hortobagyi GN. Monoclonal antibody therapy for solid tumours. Cancer Treatment Reviews. 2000; 26: 269–86.
[29] Taketo M. Cyclooxygenase-2 inhibitors in tumorigenesis (part I). J Natl Cancer Inst 1998;90:1529–36.
[30] Taketo M. Cyclooxygenase-2 inhibitors in tumorigenesis (part II). J Natl Cancer Inst 1998;90:1609–20.
[31] Janne PA, Mayer RJ. Chemoprevention of colorectal cancer. N Engl J Med 2000;342:1960–8.
[32] Isomaki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. J Chronic Dis 1978;31:691–6.
[33] Friedman GD, Coates AO, Potter JD, Slattery ML. Drugs and colon cancer. Pharmacoepidemiol Drug Safety 1998;7:99–106.
[34] Paganini-Hill A, Chao A, Ross R, Henderson B. Aspirin use and chronic diseases: a cohort study of the elderly. Br Med J 1989;299:1247–50.
[35] Paganini-Hill A, Hsu G, Ross RK, Henderson BE. Aspirin use and inci- dence of large-bowel cancer in a California retirement community [letter]. J Natl Cancer Inst 1991;83:1182–3.
[36] Paganini-Hill A. Aspirin and colorectal cancer: the Leisure World cohort revisited. Prev Med 1995;24:113–5.
[37] Labayle D, Fischer D, Vielh P, Drouhin F, Pariente A, Bories C, et al. Sulindac causes regression of rectal polyps in familial adenomatous pol- yposis. Gastroenterology 1991;101:635–9.
[38] FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, et al. Treatment of colonic and rectal adenomas with sulindac in fa- milial adenomatous polyposis. N Engl J Med 1993;328:1313–6.
[39] Nugent KP, Farmer KC, Spigelman AD, Williams CB, Phillips RK. Ran- domized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell

proliferation in patients with familial adenomatous polyposis. Br J Surg 1993;80:1618–9.
[40] Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000;342:1946–52.