The Role of Induction Chemotherapy in the Treatment of Patients with Locally Advanced Head and Neck Cancers: A Review

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Introduction

The majority of patients with head and neck cancers (HNC) usually present at diagnosis with locally advanced (stages III or IV) disease. In an effort to improve on the outcome of these patients, chemotherapy (CT) has been integrated as part of the local treatment(s) of surgery and/or defintive radiotherapy (RT). Induction CT was introduced in the middle 1970s because of the poor results obtained with the current treatments in patients with locally advanced HNC. Induction CT is the use of systemic CT before definitive surgery and/or RT. This was coincided at that time with the introduction of cisplatin as an active agent in patients with recurrent/metastatic HNC. Only patients with unresectable/inoperable cancers were included in these early trials [1-6]. The first trial used only single agent cisplatin. Later most of the phase II studies gave cisplatin and bleomycin with or without a vinca alkaloid of vinblastine or vincristine [1-4]. Without the benefit of randomized trials, it was felt at that time that cisplatin combinations are more effective than single agent cispaltin in patients with locally advanced and previously untreated HNC. All these trials were phase II carried out by single institutions, and CT was given for up to two courses of treatment. In the late 1970s, the National Cancer Institute (NCI) activated the first phase III trial [7]. In this trial, patients with resectable locally advanced HNC were randomized to one of three arms: Arm 1 of "standard" treatment of surgery and post-operative RT; arm 2 of one course of induction cisplatin and bleomycin followed by surgery and post-operative RT; and arm 3 of one course of the same induction CT and local treatments and followed by up to six courses of single cisplatin infusion as an adjuvant therapy. As expected from the design of this trial the overall results were negative. Patients on the third arm with additional adjuvant single cisplatin may have border line improved survival.

In 1980, Al-Sarraf [8,9] introduced the combination of two cycles of cisplatin (P) 100mg/m^2 day one followed by 5FU (F) 4,000mg/m^2 as 96 hour continuous infusion as induction CT in same group of patients with much promising results, and definitely much less and different side effects. Subsequently, the same group concluded that PF regimen with 5FU infusion for 120 hour, and three courses is the most adequate induction CT.

This highly effective regimen gained wide acceptance by most institutions, despite the lack of prospective phase III randomized trial(s) to compare with other cisplatin and bleomycin with or without other agent combinations. Furthermore, PF for three courses was investigated in other settings such as laryngeal preservation, post operative therapy, and as adjuvant treatment. Also, PF was investigated in phase III trials concurrent with single or hyperfractionated RT Vs. the "standard" treatment of total RT alone in patients with unresectable/inoperable HNC.

In the late 1990s and early 2000s with the introduction of active Taxane agents (Paclitaxel & Docitaxel), the three drugs combination of Taxane, Platinol, and 5FU (TPF) was studied in phase II trials [Tables 1 and 2]. This combination was also supported by the pre-clinical evidence that demonstrated synergy when taxanes are added to either platinum and or 5FU. Later, the

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three drugs combination of TPF was compared to PF in at least four phases III randomized studies.

Best Combinations

The early induction combination chemotherapy was the combination of cisplatin and bleomycin with or without additional agent (s), particularly vincristine or vinblastine. In early 1980 Al-Sarraf et al. introduced PF as better tolerated and possibly more effective induction CT [8, 9]. This combination was widely accepted by the majority of centers, and became the "standard" induction chemotherapy. In pre clinical studies synergism between cisplatin and 5FU was demonstrated.

Induction PF combination was investigated in laryngeal preservation in patients with stages III and IV disease. Initially PF was tested in phase II trials and later in phase III studies by the VA Administration hospitals in the USA and the EORTC in Europe [10-12]. These investigations resulted in "standard" use of induction two courses of PF and patients evaluated for response to the CT. Those patients with partial response (PR) or complete response (CR) had a third course followed by definitive RT. Patients with no response to two cycles of PF had laryngectomy followed by post-operative RT.

In addition, induction PF combination followed by standard RT as compared with the standard RT only was investigated in phase III trials in patients with locally advanced HNC especially those with unresectable/inoperable disease [13]. Statistically significant improvement in survival in subset analysis in patients with unresectable/inoperable cancers, but not in those with operable/resectable disease.

In the early 1990s with the introduction of Taxanes (Paclitaxel and Docetaxel) as active agents in these patients [14-17], the two agents combination of platinols (cisplatin or carbopaltin) with either of the Taxanes were investigated in patients with recurrent/metastatic HNC, and those with previously untreated locally advanced disease [Tables 1 & 2] [18-23]. Synergism between T and P has been reported in pre clinical investigations. The effectiveness and safety of TP was extensively demonstrated in HNC patients and other malignant disease (s). The side effects of the TP combination is different from those caused by PF, while the treatment cost of TP is much higher than the cost of equal courses of PF. Randomized phase II/III trials comparing three cycles of PF to the same cycles of TP were carried out in patients with recurrent/metastatic HNC [Table 3] [24],

No. of Agents	No. of Series	Patients	RR (%)
Pac	3	74	33
Doc	4	106	35
Pac, P	13	535	36
Doc, P	8	246	52
TPF	5	104	49

RR: response rate, Pac: paclitaxel, Doc: docetaxel, P: platinols (cisplatin or carboplatin), T: taxans (paclitaxel or docetaxal)

Table 1: Response to single, double, and triple taxans in combination with other agents in patients with metastatic/ recurrent disease: Phase II Trials

Agents	No. of Series	No. of Patients	CR (%)		RR (٪)	
			Range	Mean	Range	Mean
PT	6	220	11-71	25	46-90	62
PFT	9	466	0-87	30	71-100	97

CR: complete response, RR: response rate

P: platinols (cisplayin, or carboplatin), T: taxans (Paclitaxel, or docetaxel),

F: 5-fluorouracil

Table 2: Phase II Trials Response to induction chemotherapy with double and triple taxans in combination with other agents in patients with locally advanced disease

Author	Agents	No.	%		
			CR	RR	
Murphy (24)	P,F,	96	6	22	1-yr survival 41%
	P,Pac	92	5	28	1-yr survival 30%

Table 3: Randomized Trials Comparing PF to PT in Patients with Metastatic/Recurrent Cancers

		%	
	Agents	CR	RR
Cruz (25)	PF	12	71
	PT	15	69

F: 5-Fluorouracil, P: Cisplatin, Pac: Paclitaxel

Table 4: Randomized Trial Comparing Induction Chemotherapy of PF to PT In Patients with Locally advanced Cancers

1.	Induction CT followed by consolidation CT+RT.
2.	Concurrent CT+RT are the best therapy.
3.	Initial CT will down stage the disease and make concurrent CT+RT even more effective.
4.	Early CT is more desirable for the eradication of systemic micro-metastasis.
5.	Give more time to improve patients' nitrogen balance and weight before RT started.
6.	Time needed for teeth care before RT started.
7.	Response to induction CT is the best prognostic factor.
8.	Possible selection for organ preservation.

Table 5: The rational for the effectiveness of Total Treatment of Induction CT followed by Concuurent CT+RT

and those with previously untreated and locally advanced disease [Table 4] [25]. In patients with metastatic/recurrent disease no differences were found in the complete response (CR) and overall response rates (RR) between patients treated with PF vs. those received TP, while the one-year survival for PF treated patients was 41% vs. 31% respectively [25]. In previously untreated with locally advanced HNC, no differences in overall response rate (RR), CR rate, progression disease free (PDF) survival or overall survival (OS) were demonstrated in either group. On the other hand, there were differences in the type (s) and incidence of drugs induced side effects, and of course the actual cost of such chemotherapy.

This is followed by testing the efficacy of the three drugs combination of Taxane, Platinol and 5FU (TPF) in phase II studies in patients with locally advanced and previously untreated HNC [Table 2] and those with recurrent/metastatic disease [Table 1] [18-23]. In most institutions and especially in the USA, Docitaxel was given in this combination, while in most European centers, Paclitaxel was used. Cisplatin was used uniformly in all these combination, and 5FU was given as infusion for 96-120 hour. The majority of the investigators gave three courses of induction CT. It is important to mention here that in vitro synergism between 5FU and Docitaxel but not with Paclitaxel (only additive) was reported. The efficacy of TPF was established and the overall side effects were acceptable. The CR rates seemed higher than that with three courses of PF or TP. Most of these phase II trials were performed in patients with unresectable/inoperable disease, or in patients with potentially operable disease for the purpose of organ (primarily laryngeal) preservation.

This generated many prospectively randomized phase III trials comparing the same number of courses of PF vs. TPF followed by the best local treatments of surgery and/or concurrent chemo-radiotherapy [26-29]. All these studies demonstrated the superiority of the TPF vs. PF regimen with statistically improvement of progression free survival, and the overall survival. The use of TPF is currently considered to be the most widely used and accepted induction CT for patients with

previously untreated and locally advanced HNC in North America and Europe.

Unfortunately, the efficacy of TPF regimen is at the expense of its tolerability, with a high incidence of mucositis, nausea and vomiting, and dehydration that may end more than 30% in the hospital for additional care. Part of the reason of the mucositis is when 5FU given as 96-120 hour infusion mucositis is the primary side effect. The incidence of mucositis is about 7-10% with Docitaxel and more with Paclitaxel. When taxanes are combined with 5FU infusion, the incidence of mucositis is significantly higher than that caused by either agent alone. Another important factor is the emetogenic nature of cisplatin despite of the administration of the newer generations anti-emetic drug (s). Also, usually cisplatin is given with mannitol diuresis to reduce of the incidence of renal impairment. The combination of mucositis, nausea and vomiting (lower oral fluid intake), renal diuresis (because of the Mannitol) will increase of the incidence of the dehydration and electrolytes imbalance that may need urgent attention. The prohibited toxicity of the original TPF regimen led to its modification so that it can be given completely as an out patient administration, as a much less toxic and a better tolerated regimen [30]. The dose of Docitaxel is kept the same (75mg/m^2), where as carboplatin (AUC 5.0) replaced cisplatin, and 5FU is given as 2,600 mg/m^2 as 24 hour infusion given on day 1, 8, 15, instead of prolonged infusion (96-120 hour) every three weeks. The combination is repeated every three weeks for three courses [30]. This combination (TCF) is found to be as effective as the original TPF, much less toxic and well tolerated by most patients, with a reduced incidence of nausea and vomiting, mucositis, renal impairment, ototoxicity and neurotoxicity; the latter toxicities are usually associated with cisplatin administration. The TCF became our standard induction CT and being used increasable by other investigators and practicing Medical Oncologists.

Number of Courses

In the mid 1970s only one course of induction CT was given and this was the basis of the three arms of the HNC NCI protocol [11]. Later, when cisplatin, vincristine, bleomycin (CVB) became the standard induction CT by many investigators and cooperative group (s), only two courses of induction CT were usually given especially in patients with unresectable/inoperable HNC to avoid undue delay in starting RT [1-6]. In late 1979 and early 1980 Al-Sarraf et al started and completed a phase II study of PF with the 5FU 4,000/m2 given for 96 hour infusion for two cycles only [8, 9]. Because this new combination was active and highly well tolerated, a subsequent phase II trial with PF regimen in which 5FU 5,000mg/m^2 was administered for 120 hour infusion, and the PF given for three courses. After the first cycle the overall RR was about 60% and CR rate of less than 10%, which increased to 85% and 25% respectively after the second cycle. With total three courses of induction PF, the overall RR was about 90% and CR rate about 50%. It is important to mention here that RR and especially CR rate is not only related to the type of CT (CVB vs. PF) and number of courses but also may relate to many prognostic factors in which stage and especially the N stage is the most important [2, 31,32]. So the three courses became the "standard" by most centers.

With TPF regiment widely accepted in standard of care, we strongly believe that 3 cycles are the optimal number of cycles to maximize response and patient benefit from treatment. More cycles would not only increase unnecessarily the cumulative toxicities of cisplatin, but may also limit further use of chemotherapy concurrently with RT.

The Role in Resectable/Operable Disease

The early trials of induction chemotherapy studied its role mainly in patient with locally advanced unresectable disease. However, the NCI HNC three arms phase III trial was in patients with locally advanced (stages III and IV) resectable disease [7]. Only one course of cisplatin and bleomycin (PB) was given for the two experimental arms. Overall the study was negative. Other later reports even using PF as induction CT up to three courses before surgery followed by RT and compared those who had the "standard" treatment of surgery and post-operative RT in phase III trials in patients with operable and

resectable cancers were also negative [13]. This resulted in the "general" statement that induction CT does not benefits all the patients with locally advanced HNC regardless of the resectability and/or their operability.

In our strong opinion, patients who are deemed to have operable and respectable disease, surgery should be performed without introducing indication CT. Evidence remains that the extent of the planned surgery is expected to be the same if it was done immediately or after subsequently following induction CT. Unfortunately, in these patients with locally advanced HNC (stage III or IV) this does not mean cure and additional treatment(s) are usually needed to improve on the cure rate and the overall survival. This is why in these patients surgery followed by post-operative RT is considered the "Standard" of care. However still the overall 5-year survival of these patients does not exceed 30%, even in patients who have, negative surgical margins given adjuvant post-operative RT. This poses a pressing need for the oncology community to seek more effective treatments.

Lesson Learned from Laryngeal Preservation Trials

In late 1970s and early 1980s we made the observation and reported that patients who respond to initial CT have higher chance to responds to subsequent RT (CR, and overall RR) [10]. While, those HNC patients who did not respond to initial CT (<than PR) usually will not respond to subsequent RT. This have been confirmed and reported by many centers and investigators [33]. This led us to offer those patients with resectable and operable laryngeal cancers (stages III and IV) and who refused laryngectomy to offer them induction CT. Responders to such initial CT will received total RT, while those who did not respond to CT will go for laryngectomy followed by post-operative RT. Since the overall response rate to three courses of PF is about 90% so only about 10% have lost initially their larynx and the function of speech. This led in the USA for the activation of VA Hospital laryngeal preservation prospectively randomized phase III study [11]. Patients with resectable and operable stages III and IV cancers of the larynx were randomized to receive "standard" surgery followed by post-operative RT vs. two courses of PF and evaluated for response to such induction CT. Responders (CR and PR) received a third course of the same CT followed by total RT, and non-responders (<than PR) after such two cycles CT had surgery and RT. The study was positive in which about 60% of the patients who are a live on the investigation arm had preserved their voice and their larynx. But no difference in overall survival was reported between the two groups as of the initial randomization. This had been confirmed by many investigators and especially the EORTC subsequent phase III trial [12]. The "standard" regimen for organ preservation continued to be induction CT and for the responders (CR plus PR) total RT until this have been changed in the late 1990s to concurrent chemo-radiotherapy after the intergroup trial of 91-11 [34].

More important is what we learned from these trials of organ preservation after induction CT. In those patients who received first induction CT have the same survival to those have initial surgical resection (laryngectomy) followed by RT. Since between the two groups the RT is about the same and constant, so three courses of PF is equal to the surgical resection (laryngectomy) in these patients with locally advanced and resectable cancers.

Lesson Learned from Two Vs. Three Drugs Combinations

In the mid 1990s with the emergent of many phase II studies using the three drugs regimens and especially TPF [Table 2], this led to the activation of many groups phase III and prospective trials comparing induction TPF to the same number of courses of induction PF followed by the best local treatment(s)[26-28]. Most of the patients subsequent to the induction CT received concurrent CT (cisplatin or carboplatin) with total RT. All these studies were positive in favor of the three drugs regimen especially in relationship to progression free survival and overall survival. This is why at the present time the three agents combination and especially TPF or its modification is the "standard" of care for induction CT instead of PF. Since the

treatment(s) (concurrent CT+RT) subsequent to the induction CT was the same in both groups, then one may be able to conclude that induction CT with three drugs combination followed by concurrent CT+RT is superior to only CT+RT in the same group of patients. Although this is an important observation and conclusion, we still support the present active randomized phase III trials trying to answer the question for the need of induction CT for those patients going to receive the "standard" total CT+RT.

The Role in Organ Preservation

From the mid 1980s to late 1990s the "standard" of care for organ preservation and especially laryngeal preservation is induction CT and all the responders (CR+PR) to have organ preservation and to receive total RT [10-12, 33]. With emergent off extensive phase II and phase III trials of the superiority of the concurrent CT+RT vs. RT only, in patients with locally advanced and unresectable/inoperable HNC, concurrent chemo-radiotherapy became the "standard" of care for these patients [35-37]. This led to the activation of the Intergroup 91-11 protocol comparing the "standard" induction CT and responders received total RT, vs. total RT only, vs. concurrent CT+RT for patients with stages III and IV cancers [34]. This important study demonstrated the superiority of the concurrent CT+RT for organ preservation than the other two arms. Until today concurrent CT+RT became the "standard" of care for those patients with laryngeal cancer and for other HNC patients for organ preservation.

As we mentioned above many phase II being reported in the literature for the last ten years given induction CT (two or three agents combination) followed by concurrent CT+RT for patients with unresectable/inoperable HNC or for the purpose of organ preservation [35-37]. Off protocol(s) and since mid 1980s we have been given for patients with resectable, unresectable, nasopharyngeal cancers (NPC), or for organ preservation induction CT followed by concurrent CT+RT. The later group our incidence and those reported by other investigators of organ preservation was about 90%, but we felt strongly and also as reported in the literature by other investigators for the first time there is actual improvement in overall survival of these patients. Although, of protocol induction CT followed by concurrent CT+RT is our and many other investigators are the "standard" of care for organ preservation, we strongly believe in the conduction of prospective randomized trial(s) to answer this important question.

The Role in unResectable/in Operable Disease

As was mentioned above the "standard" of care at the present time for patients with locally advanced and unresectable/inoperable HNC is the concurrent CT+RT [35-37]. Many randomized trials on both sides of the Atlantic are active at the present time to answer the primary question, do we need induction CT before the "standard: of care in these patients with the concurrent CT+RT. Induction CT before total RT was reported to be superior vs. total RT only in the same groups of patients [13]. The induction CT with three drugs combination like TPF followed by the best locally treatment(s) usually CT+RT was superior to the same number of cycles of PF followed by the same best local treatment(s) [26-28].

Table 5 reviews what we can achieve with induction CT before the best of local treatment(s). The overall RR to three courses of CT is more than 90%, and the clinical CR rate is more than 50%. Of those patients achieved clinical CR and had surgical resection or biopsy done about 80% of these will results in no evidence of microscopical cancer (pathological CR) [38]. So after down staging these patients with stages III or IV disease (more than 90%) and then having them received the best treatment we have of concurrent CT+RT, the results achieved by the later have to be superior to those similar patients receiving concurrent CT+RT without induction CT or down staging. In the mean time those patients on induction CT have their teeth care done before the future RT without delay in their therapy, and usually gained most of their lost weight if not more and improved on their nitrogen balance. That will make these patients (on induction CT) much healthier to tolerate the future RT with less interruption in such treatment with less need for nutritional help during the CT+RT course.

Therapy	No. of Series	No. of Patients	5-Year OS(%)	
			Range	Mean
RT	19	8,273	24-62	44
Limited Chemotherapy:				
CT--->RT	11	713	35-83	64
CT+RT	4	172	55-94	67
RT---> CT	5	181	54-80	70
Total Treatment:				
CT+RT---> CT	3	162	70-80	77
CT---> CT+RT	3	92	83-94	86

Table 6: Results of radiation alone, or combined therapy in locally dvanced NPC patients: Phase II Trials

Treatment	% 5-Year Survival
RT without Salvage	<30
RT with Salvage	+40
Concurrent CT+RT	50-55
Sequential CT--->RT	50-55
RT--->CT	50-55
CT+RT--->CT	75
CT--->CT+RT	?90

Table 7: NPC Stage IV: Change in Overall Survival between the Year 1980-2008

So our recommendation at the present time for patients with locally advanced HNC off protocols is induction CT with three agents combination of the investigator(s) choice, and this to be followed by concurrent CT of the investigator(s) choice with total RT. As mentioned above our choice of induction CT is the modification of TPF, TCF with the 5FU given as 24 hour infusion day one and weekly for three weeks. It is worth while to mention here that our choice of concurrent CT after induction chemotherapy is single agent carboplatin AUC 1.5 given day one of the RT and weekly during the irradiation treatment. We have been using carboplatin weekly since the early of 1990s. With the modification of the TPF especially by omitting the cisplatin and replacing it with carboplatin and giving carboplatin concurrent with RT we reduced or avoided many serious side effects and especially nausea and vomiting, renal impairment, loss of hearing, peripheral neuropathy, and the need for gastric tube for feeding during the course of RT. This will improve and increase on the quality of life of all these patients receiving the total treatment.

So with the use of effective and safer induction CT followed by using an effective and safer concurrent CT+RT we not only may improved on the cure rate and overall 5-year survival rate, but we also are achieving a less treatment side effects and better quality of life.

The Role in Nasopharyngeal Carcinomas

The majority of the patients with nasopharyngeal cancers (NPC) usually present at diagnosis with Stages III and IV disease and especially the later. The incidence of systemic metastasis at presentation or after failure of the local treatment(s) is higher than in patients with other HNC sites. NPC is highly sensitive to radiotherapy and chemotherapy [39-46]. Because of the poor results obtained with total RT in these patients with overall 5-year survival in stage IV is less than 30% across the world, the addition of CT had been investigated in these patients since 1980. Chemotherapy given on limited basis as induction, concurrent or adjuvant with total RT improved the overall survival in patients with stage IV cancer to about 50-55% [Tables 6 and 7]. The present "standard" of care for patients with locally advanced NPC (stages III or IV) is our Intergroup protocol of concurrent cisplatin 100mg/m^2 days 1, 22, 43 concurrent with total RT followed by three courses of cisplatin 80mg/m^2 day 1 and 5FU 4,000mg continuous infusion for 96 given every four weeks. The overall survival obtained with concurrent CT+RT followed by adjuvant CT is about 75% [42].

With the increase use of induction CT by us and others in patients with locally advanced HNC, we started giving patients with locally advanced NPC who refused to be on protocol(s), induction CT with PF followed by concurrent

	No. Trials	No. Pts.	% Difference	p Value
All Trials	65	10,850	+4	<.0001
Adjuvant	8	1,854	+1	NS
Induction	31	5,269	+2	NS
PF	15	2,487	+5	.01
Others	16	2,782	0	NS
Concurrent	26	3,727	+8	<.0001

NS= Not significant. Adapted from Pignon, J et al. [47]

Table 8: Effects of Chemotherapy on the 5-Year Survival: From Meta-analysis

CT+RT. This was done for above reasons for possible improvement of efficacy and for better of quality of life. Our personal experience of about twenty such patients, the tolerance to CT and to the overall treatment(s) was better, and the 5-year survival was about 90% [Tables 6 and 7]. Many phase II trials administering induction CT followed by concurrent CT+RT were reported and showed improvement in the 5-year survival over the "standard" regimen of concurrent CT+RT followed by adjuvant CT [44-46]. Unfortunately, no phase III prospective randomized studies comparing induction CT followed by concurrent CT+RT to the "standard" of care in locally advanced NPC are active at the present time. This comparison is needed to definitely result in the best "standard" total treatment for patients with locally advanced NPC previously untreated.

Taxans (Docitaxel, Paclitaxel) are active in this disease as in other HNC patients. Gemcitabine is active in patients with NPC but not as active in other HNC patients. The three drugs combination of TPF, GPF (Gemcitabine, Taxan, 5FU) and others combination(s) seem more active than the standard PF in phase II studies in these patients. For all the above reasons our "standard" total treatment for locally advanced NPC not on protocol(s) is induction CT with TPF or its modification of TCF in which the 5FU given as 24 hour infusion day and weekly for three cycles. This followed by concurrent CT+RT with chemotherapy a single agent platinol, and our choice is the weekly carboplatin.

Meta-analyses

Many meta-analyses appeared in the literature since the use of CT with RT and as part of combined modality therapy for patients with locally advanced and previously untreated HNC [47-50]. These meta-analyses included most of the randomized phase III trials and some of the phase II studies. They included all investigation with CT single agent(s), and all combinations that were published before these meta-analyses. All the published meta-analyses reported significant improvement of overall survival when CT was added to RT over RT only in these patients. But all these analyses except one reported no advantage of induction CT followed by over RT alone, and the only significant improvement in overall survival was for the concurrent CT+RT vs. RT only. When the authors of the single meta-analysis separated the type of induction CT given before RT of PF vs. all the others, there was significant improvement in overall survival for the induction CT of PF followed by RT as compared to RT only [Table 8] [47].

This is an important point that we always have to use the most effective CT we have in our future clinical trials if we expecting improvement in our overall survival results. Since the three drugs combination of TPF followed by the best local treatment(s) is even superior to PF followed by the same best local treatment(s), there are no doubt that three drugs combination followed by RT will be superior to RT alone in any study or meta-analysis [51].

Randomized Trials and Future Directions

There are urgent needs for proper prospective phase III randomized studies to answer the role of induction CT in patients with locally advanced HNC. These are to include the role of induction CT before concurrent CT+RT for patients with laryngeal preservation, for those with unresectable/inoperable disease and patients with locally advanced previously untreated NPC. The only randomized trials active at the present

time (2008) are those for unresectable/inoperable patients excluding NPC patients. As we mentioned above that in the early investigation of induction CT in patients for laryngeal preservation, that three cycles of PF may be equal to surgical resection in these patients. Since the three drugs combination of TPF is even superior to the same number of courses of PF, there are definite needs to investigate induction CT in patients with resectable/operable HNC. These patients may be randomized to receive induction CT with TPF or its modification followed by concurrent CT+RT vs. the "standard" treatment of surgery followed by RT alone or concurrent CT+RT depend on the final stage after the operation, surgical margins, and other risk criteria.

Summary and Conclusions

Induction CT have evolved since its introduction in the mid of 1970s for patients with previously untreated locally advanced HNC. We went from single agent cisplatin to cisplatin bleomycin combinations, to PF and now to the three drugs combination of TPF or its safer modification. We started with single cycle of induction CT, to two courses and now the best to give is the three cycles of CT. We not only improved on the effectiveness of the induction CT, but also reduced the possible side effects and improved the quality of life for those receiving such treatment. Induction CT followed by RT alone is superior to RT only in patients with previously untreated unresectable/inoperable HNC. Although, the "standard" of care of these patients today is concurrent CT+RT. Induction TPF followed by the best local treatment(s) usually concurrent CT+RT was superior to PF followed by the best local therapy in these patients. Will this mean that in patients with locally advanced unresectable/inoperable HNC induction TPF followed by concurrent CT+RT is the treatment of choice, in our opinion is yes, but this is not acceptable by the majority of investigators. This is why we do have more than four prospective randomized phase III trials trying to answer such an important question.

In our opinion and strong believe that all patients with locally advanced HNC including patients with NPC not on active protocol(s) may be offered induction three drugs combination followed by concurrent CT+RT as their primary planned treatment. In those patients who are resectable/operable before any such therapy and did not respond (CR or PR) to such induction CT may offer surgical resection followed by post-operative concurrent CT + RT. Table 5 summarize the rational of the continue use of the total treatment of induction CT followed by concurrent CT+RT in patients with previously untreated and locally advanced HNC.

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