Effective Dose and Adverse Effects of Maintenance *Bacillus Calmette-Gue´Rin* in Intermediate and High Risk Non-muscle Invasive Bladder Cancer: a Meta-analysis of Randomized Clinical Trial

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ABSTRAK

Tujuan: *mengevaluasi dosis efektif dan efek samping pemberian BCG.* ***Metode:*** *dilakukan pencarian publikasi uji klinis acak di Medline dan Cochrane sebelum Oktober 2013. Penelitian yang berkaitan dengan pemberian BCG setelah TUR dan pemantauannya pada pasien kanker kandung kemih non-otot invasif (KKKNIO) dengan risiko sedang dan tinggi dimasukkan sebagai kriteria inklusi. Kriteria eksklusi meliputi pasien KKKNIO risiko rendah, pemberian BCG dengan dosis lain dan kanker buli infasif otot.* ***Hasil:*** *studi meta-analisis 6 uji klinis yang meliputi 2719 pasien KKKNIO risiko sedang-tinggi menunjukkan angka kekambuhan setelah pemberian dosis penuh (81 mg), dosis rendah (27 mg) dan dosis sangat rendah (13,5 mg) berturut-turut 33,3%, 34,7%, dan 30%. Meta analisis (2175 pasien), dosis BCG 81 mg menghasilkan hasil yang lebih baik dari dosis 27 mg dalam mengurangi kekambuhan tumor (RR 0,86; 95% CI 0,77-0,96, I2 = 0% dan p=0,008). Meta-analisis (544 pasien), efektivitas dosis rendah dinilai lebih tinggi dibandingkan dengan dosis sangat rendah (RR 0,66; 95% CI 0,49-0,89, I2 = 8,8% dan p=0,006). Efek samping sistemik terjadi pada 25% dosis tinggi, 28,5% dosis rendah, dan 15,5% dosis sangat rendah. Dosis rendah dinilai superior terhadap dosis penuh pada efek samping sistemik (p=0,000) namun tidak terhadap efek samping lokal (p=0,137) pada 2 meta analisis (1816 pasien).* ***Kesimpulan:*** *dosis penuh BCG memiliki hasil superior dalam hal menurunkan angka kekambuhan KKKNIO dibandingkan dengan dosis rendah atau sangat rendah. Tidak ada perbedaan bermakna antara dosis terhadap efek samping lokal. Namun, dosis penuh memiliki angka efek samping sistemik yang lebih tinggi dibandingkan dengan dosis rendah dan sangat rendah.*

Kata kunci: *Bacillus Calmette-Gue´Rin, dosis dan efek samping, kanker kandung kemih non-otot invasif (KKKNIO).*

ABSTRACT

Aim: *to evaluate the effective dose and adverse effects of BCG doses.* ***Methods:*** *we searched published RCTs in Medline and Cochrane database before October 2013. Article using maintenance BCG after TUR in intermediate-high risk non-muscle invasive bladder cancer (NMIBC) and followed for effectiveness, local and systemic side effect are included. Low risk patients, other dose and MIBC were excluded.* ***Results:*** *meta-*

analysis of 6 clinical trials involving 2719 intermediate-high risk NMIBC patients showed recurrence rate in full dose (81 mg), low dose (27 mg) and very low dose (13.5 mg) were 33.3%, 34.7% and 30%, respectively. Meta-analysis of 2175 patients, 81 mg BCG was found to be superior to 27 mg in reducing tumour recurrences (RR 0.86; 95% CI 0.77-0.96, I2 = 0% and p=0.008). Meta-analysis of 544 patients, the effectiveness reducing tumour recurrences in 27 mg BCG was found to be superior to 13,5 BCG (RR 0.66; 95% CI 0.49-0.89, I2 = 8.8% and p=0.006). Systemic side effects were happened in 25%, 28.5%, and 15.5% in the doses 81.27 and 13.5 mg BCG, respectively. Low dose was superior to full dose in affecting systemic side effect (p=0,000) but no difference in affecting local side effect (p=0.137) in the meta-analysis of 1816 patients in 2 clinical trials. ***Conclusion:*** *full dose BCG had superior outcome to reduce recurrences compared to low dose and very low dose. There were no significant differences between each dose in local side effect. However full dose regimen has higher systemic side effect compared to low and very low dose.*

Key words: *Bacillus Calmette-Gue´Rin, dose and adverse effect, non-muscle invasive bladder cancer (NMIBC).*

INTRODUCTION

Non muscle invasive bladder cancer is characterized by a high risk of recurrence and progression to a muscle invasive disease.[1] The individual estimated risk of recurrence and progression can be calculated by using the risk score introduced by European organisation of Research and Treatment of cancer (EORTC) risk table or a simplified risk group classification.[2,3] Intravesical instillation of Bacilus Calmette-Guerin (BCG) is the most effective adjuvant therapy after transurethral resection of intermediate or high risk superficial bladder tumours and recommended as the first line treatment for patients with carcinoma in situ.[2,4,5] In the intermediate and high risk patients, the protective effect of long term therapy BCG are more pronounced compared with chemotherapy.[6,7] Since the introduction of BCG in the mid 1970s for the treatment and prophylaxis of superficial bladder TCC, it has become the biological response modifier of choice for tumours at high risk of recurrence and progression.[8] Several randomised trials and meta-analyses published threafter suggested that maintenance BCG instillations during 1-3 years is superior to both chemotherapy and induction BCG alone in reducing recurrences and even progression to muscle-invasive disease.[3,7,9-11] Morales et al mentioned that induction BCG instilation performed every 6 week and aditional BCG instilation reduce recurrence but optimal duration of maintenance instilation remains controversial.[9,12,13] Based on several meta-analysis, the EAU guidelines recommend at least 1 year of maintenance.

BCG can produce either local or systemic adverse effects such as bacterial or chemical cystitis, dysuria, frequency, hematuria, granuloma prostatitis, epididymitis, urethral obstruction and contracted bladder, fever, influenza like symptoms include general malaise and chills, lung infection, liver toxicity and sepsis. The occurrence of adverse effects is one of the main reasons why urologist try to avoid the use of BCG, particulary in intermediate-risk patients, for whom chemotherapeutic agents are often prescribed. BCG efficacy and toxicity are dose-dependent and the problem lies in finding a very low BCG dose that is effective and has low toxicity. A reduction in side effects might be achieved in several different ways, for example, by reducing the BCG dose, administration of the antituberculosis drug INH,[6,14] antibiotic ofloxacin,[15] or by reducing its dose. However, the optimal duration of maintenance instillation remains controversial.[4,8,16]

By the late 1980s, two groups were trying lower doses than normal in an attempt to decrease the frequency and intensity of adverse reactions but the lack of agreement among these studies induced the Spainish urological club for oncological treatment (CUETO: Club Urologico Espanol de Tratamiento Oncologico) to undertake a study to ascertain the therapeutic value and toxic effect of a three-fold lower dose of BCG compared with the standard dose.[17,18]

The aim of this study is to find effective

dose and evaluate dose related local as well as systemic side effects of BCG.

METHODS

Review Questions and Study Protocols

The proposed questions aimed to be answered by our study are what is the effective dose and what are the side effects of maintenance BCG in intermediate and high risk non-muscle invasive bladder cancer? This meta-analysis are conducted under guidance of Quality of reporting of Meta-analysis (QUOROM) statements.

Literatures Search

We searched literatures in Medline and Cochrane database before October 2013 using systematic searching strategy with keywords "dose and side effect", "intermediate and high", "non-muscle invasive bladder cancer", "Bacillus Calmette-Guerin". Only English language papers were included in this study.

Eligibility Criteria

This meta-analysis is performed based on published randomized controlled trials. Inclusion criterias were: a). publication which use single BCG instilation with full dose (81 mg), low dose (27 mg) and very low dose (13.5 mg) after transurethral resection, b). patient with moderate and high risk NMIBC, c). follow up for local side effects (bacterial or chemical cystitis, frequency, hematuria, granulomatous prostatitis, epididimytis, ureteral obstruction and scar tissue in bladder) and systemic side effects (fever more than 39ºC, influenza like symptoms such as chill and malaise, BCG induced lung infection, liver toxicity and sepsis induced BCG).

Exclusion criterias were: a). low risk NMIBC patient, b). other dose of BCG, c). invassive bladder cancer.

Data Extraction and Statistical Analysis

Data extracted from each trial consisted of sample size, mean follow up duration, BCG doses consisted of full dose (81 mg), low dose (27 mg) and very low dose (13.5 mg), regimen of BCG therapy, local and systemic side effect of each dose. Statistical analysis using Fixed effects model or random effects model with Mantzel Haenzel methods to calculate relative risk and 95% confidence interval and compared every dose given. Authors assessed the heterogeneity by calculating the I2 statistic (low (25%-50%), moderate (50%-75%) and high (>75%). All analysis performed using stata statistical software version 12.0 (StataCorp).

RESULTS

From 429 publications authors selected 20 publications. There are only 6 randomized controlled trial (RCT) which were feasible for further meta-analysis (**Figure 1**).

Meta-analysis from 6 RCT from 2719 patients with intermediate and high risk non muscle invasive bladder cancer patients, the recurrence rate for full dose (81 mg), low dose (27 mg) and very low dose (13.5 mg) was 33.3% (374/1120), 27.5% (365/1323) and 30% (83/276) (**Table 1**).

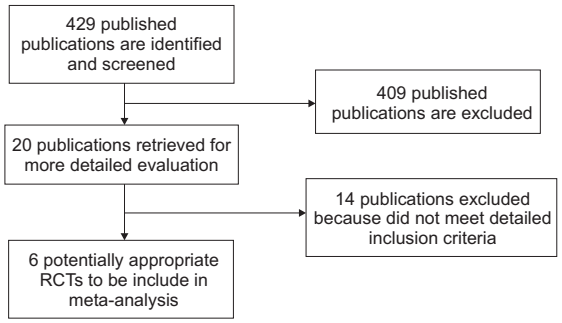

Figure 1. Literature searching

Meta-analysis from 4 RCT which compared full dose (81 mg) BCG (with the mean follow up 77,3 months) and low dose (27 mg) (mean follow up 70 months) in 2175 patients found that full dose of BCG was superior over low dose in reducing reccurence NMIBC 33.3% and 38.5% respectively (RR 0.86; 95% CI 0.77-0.96, I2 = 0% and p=0.008). (**Figure 2**)

The results of two RCT with 544 NMIBC patient with moderate and high risk patients, comparing effectivity of low dose BCG (268 patient with mean follow up 58.2 months) and very low dose BCG (276 patient with mean follow up 58.5 months) to reduce reccurence rates found that low dose BCG was superior than very low dose (RR 0.66; 95%CI 0.49-0.89, I2 = 8.8% and p=0.006). About 20.1% patients with low dose

Table 1. Recurrence rate in clinical trial compared full dose BCG with low dose BCG as NMIBC therapy

Study	Year	Inclusion Criteria	Therapy Regimen	Dose					
				P	N total	Full dose n/N	Mean Follow-up	Low dose n/N	Mean Follow-up
Odden J et al[1]	2013	pT1G3or multipel pTa–T1, grade 1–3 Bladder urothelial carcinoma	Once a week for 6 week, After that every 3 week on 3, 6, 12, and 18 month	0.045	1355	276/677	85.2 Mo	311/678	85.2 Mo
Martinez JA et al[8]	2002	Ta, T1, dan Tis Bladder cancer	Once a week for 6 week, after that every 2 week for 6 times	0.58	499	29/252	69 Mo	33/247	69 Mo
Semper M et al[19]	2010	carcinoma insitu (CIS) bladder	every 3 week at 3, 6, 12, and 18 month	>0,05	138	34/93	76 Mo	34/93	55 Mo
Unda M et al[20]	2009	Ta-T1 GIII and or carcinoma insitu (CIS) bladder	every 3 week on 3, 6, 12, and 18 month	>0.05	183	35/98	79 Mo	35/98	71 Mo
Total					2175	374/1120	77.3 Mo	406/1055	70 Mo

Table 2. Recurrence rate in clinical trials compared low dose with very low dose BCG in NMIBC therapy

Study	Year	Inclusion Criteria	Therapy Regimen	Dose					
				P	Total N	Low dose n/N	Mean Follow-up	Very low dose n/N	Mean Follow-up
Ojea A et al[4]	2007	TaG2 and T1G1-2 bladder cancer	Once a week for 6 weeks, continue every 2 week for 12 weeks	0.517	281	38/142	53.7 mo	50/139	61.2 mo
March N et al[21]	2002	T1G1-2 bladder cancer	Once every 6 week,continue every 2 week for 12 weeks	0.58	263	16/126	62.7 mo	33/137	55.9 mo
Total					544	54/268	58.2 mo	83/276	58.5 mo

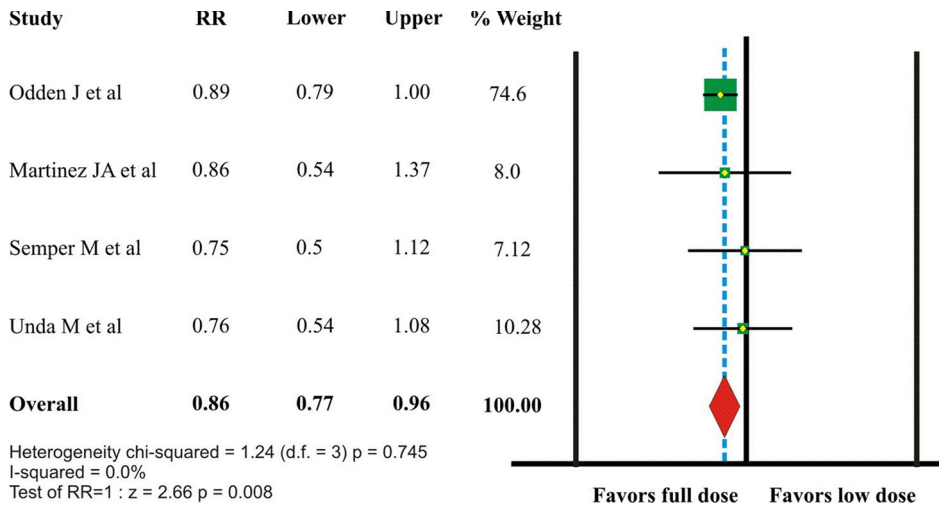

Figure 2. Forest plot reccurence rate full dose compared with low dose of BCG.

BCG experience reccurence compare with 30% patient with very low dose BCG. (**Figure 3**)

In meta-analysis from 4 RCT with total 2360 moderate-high risk NMIBC patient, incidence local side effect after full dose, low dose and very low dose BCG instilation were 59.3% (537/905), 60.0% (708/1179), and 63.7% (176/276). Systemic side effects occured in 25.4% (230/905), 28.5% (337/1179), and 15.5% (43/276) respectively.(**Table 3 and 4**)

In meta-analysis with 1816 patient, there was no significant difference in local side effect (p=0.137), but low dose was better to reduce systemic side effect (p=0.000). In meta-analysis with 544 patient given low dose and very low dose BCG also had no significant difference

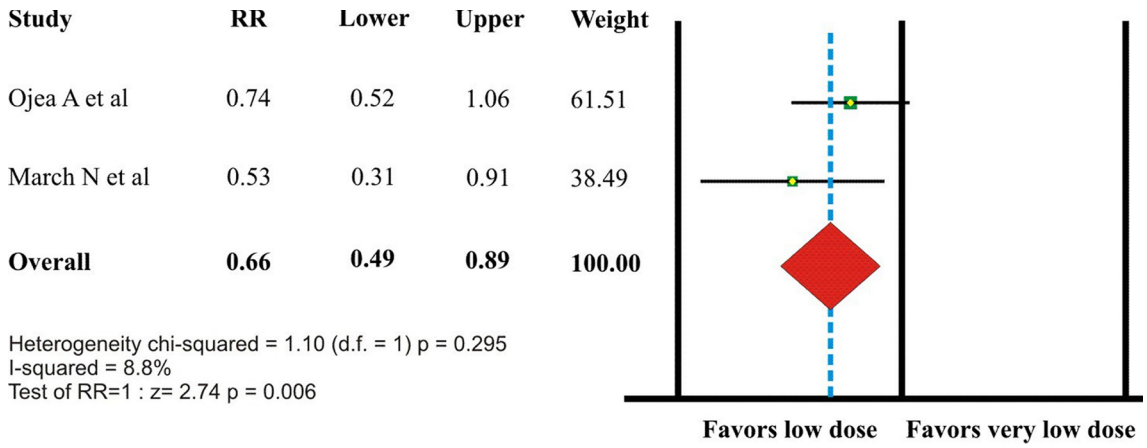

Figure 3. Forest plot reccurence rate in low dose patient compared with very low dose of BCG

Table 3. Study compared side effect full dose and low dose BCG in NMIBC therapy

Study	Year	Inclusion Criteria	Therapy Regimen	Local side effect			Systemic side effect		
				N Total	Full dose n/N	Low dose n/N	N Total	Full dose n/N	Low dose n/N
Brausi M et al[22]	2013	pT1G3 or multiple pTa–T1, grade 1–3 urothelial bladder cancer	Once a week for 6 weeks, continue every 3 weeks in 3,6,12 and 18 month	1316	412/657	414/659	1316	192/657	211/659
Martinez JA et al[8]	2002	Ta, T1, dan Tis bladder cancer	Once a week for 6 weeks, continue every 2 weeks for 6 times	500	125/248	168/252	500	38/248	89/252
Total				1816	537/905	528/911	1816	230/905	300/911

Table 4. Study compared side effect low dose and very low dose BCG in NMIBC therapy

Study	Year	Inclusion Criteria	Therapy Regimen	Local side effect			Systemic side effect		
				N Total	Low dose n/N	Very low dose n/N	N Total	Low dose n/N	Very low dose n/N
Ojea A et al[4]	2007	TaG2 dan T1G1-2 Bladder cancer	Once every 6 week, continue every 2 weeks for 12 weeks	281	93/142	89/139	281	16/142	15/139
March N et al[21]	2002	T1G1-2 Bladder cancer	Once a weeks for 6 weekss, continue every 2 weeks for 12 weeks	263	87/126	87/137	263	21/126	28/137
Total				544	180/268	176/276	544	37/268	43/276

(p=0.400) and (p=0.600) (**Figure 4 and 5**).

DISCUSSION

Over 35 years ago, Morales et al published the first study on the use of intravesical BCG immunotherapy for NMIBC.[22] Efficacy of BCG instillation does not seem to be increased significantly when combined with intradermal BCG vaccination simultaneously.[21] Since then, several meta-analysis have shown that adjuvant intravesical treatment reduces NMIBC recurrency. The choice between adjuvant intravesical tratments, namely chemotherapy or BCG immunotherapy, depends on the risk that needs to be reduced : recurrence or progressive.

Intravesical instillation of BCG reduces the risk of recurrence and delays the time to reccurence compared with transurethral alone or other drugs given intravesically. However the mechanism is not completely understood. The Japanese groups suggest that cytokines play an important role in the effector mechanism of BCG, especially interleukin-2 (IL-2) that can be used to monitor the reaction of a patient to BCG.[23] This can be used to classify responders and non responders to BCG and tailored BCG schedule and doses.[24] Based on meta-analysis, maintenance BCG schedule was found to be essential in preventing progression.[25] Despite this advantages, BCG is not free from complications such as bacterial or chemical cystitis, dysuria, frequency, hematuria, granuloma prostatitis, epididymitis, urethral obstruction and contracted bladder, fever, influenza like symptoms include general malaise and chills, lung infection, liver toxicity and sepsis.

A clinical trial by Ojea et al. and March et al., on 544 moderate-high risk NMIBC patients found that low dose BCG was more effective and significantly reduce recurrence compared to very low dose. Oden et al., Martinez et al., Semper et al., and Unda et al., who compare full dose with low dose in 2175 patient found that full dose seems better in reducing the reccurence of tumor.

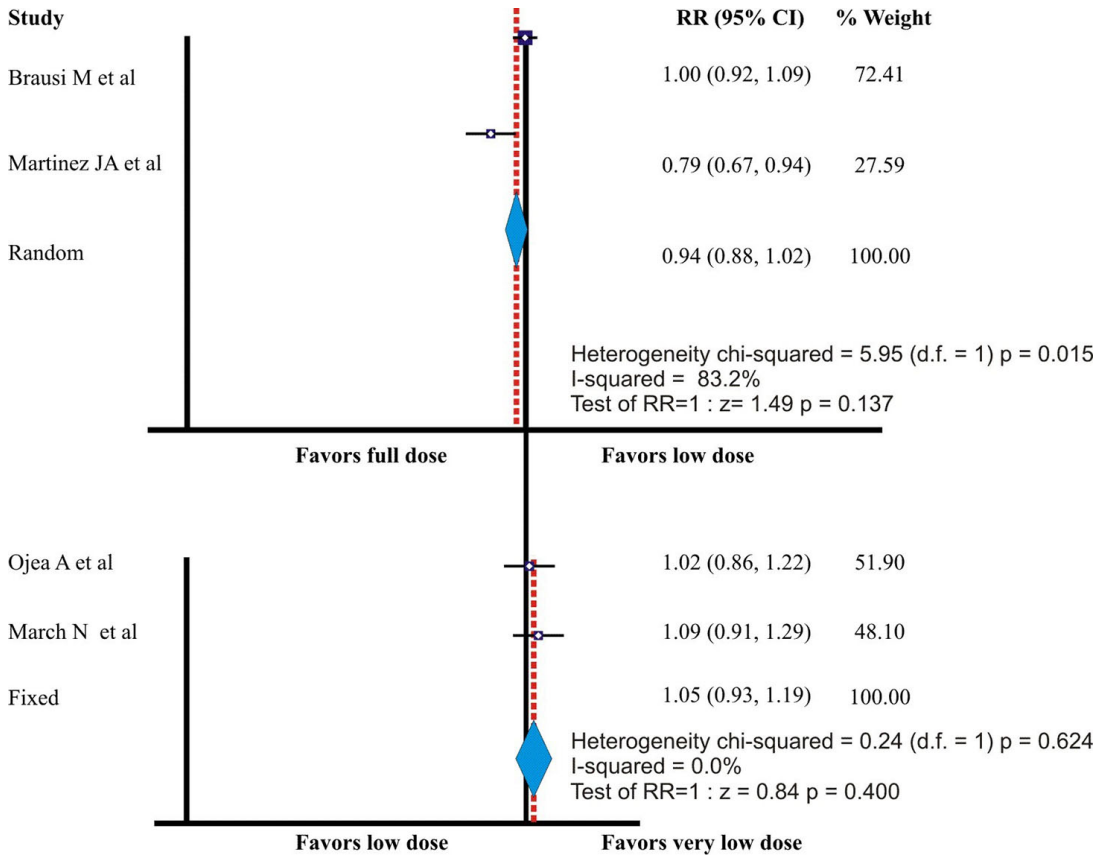

Figure 4. Forest plot local side effect of full dose, low dose and very low dose BCG

The mechanisms by which BCG leads to the development of infectious complications is not fully understood. One explanation is its action as an immunotherapeutic agent on helper T cell cytokine profile known as the "Th1 response".[26] Considerable debate exists about whether infectious complications due to BCG represent a hypersensitivity reaction or ongoing active infection. The hypersensitivity hypothesis gained early attention based upon the presence of granulomas and the absence of recoverable organisms. In a number of case reports, acid-fast bacilli have not been demonstrated and organisms have not grown despite a high clinical suspicion of BCG infection.[27,28] A response to glucocorticoids, administered along with antituberculous drugs, has also supported the notion of a hypersensitivity response.

The fastidious growth nature of BCG in culture and a doubling time of 24 to 48 hours contribute to the difficulty in its isolation. It should be emphasized that >95% of patients tolerated BCG without significant morbidity. Most of symptoms associated with BCG immunotherapy are a result of immune stimulation that is required to effectively eradicate cancer cells. These symptoms include urinary frequency and burning, mild malaise and low grade fever.[29]

Local side effect includes bacterial or chemical cystitis, dysuria, frequency, haematuria, granulomatous prostatitis, epididymitis, urethral obstruction and contracted bladder. The most common local side effect was drug induced cystitis, manifested as iritative voiding with negative urine culture and hematuria that resolves in 48 hours without the need to stop BCG instilation.[30-32] Systemic side effects include fever (>39°C), influenza like symptoms, including general malaise and chills, BCG induced lung infection, liver toxicity, and sepsis.

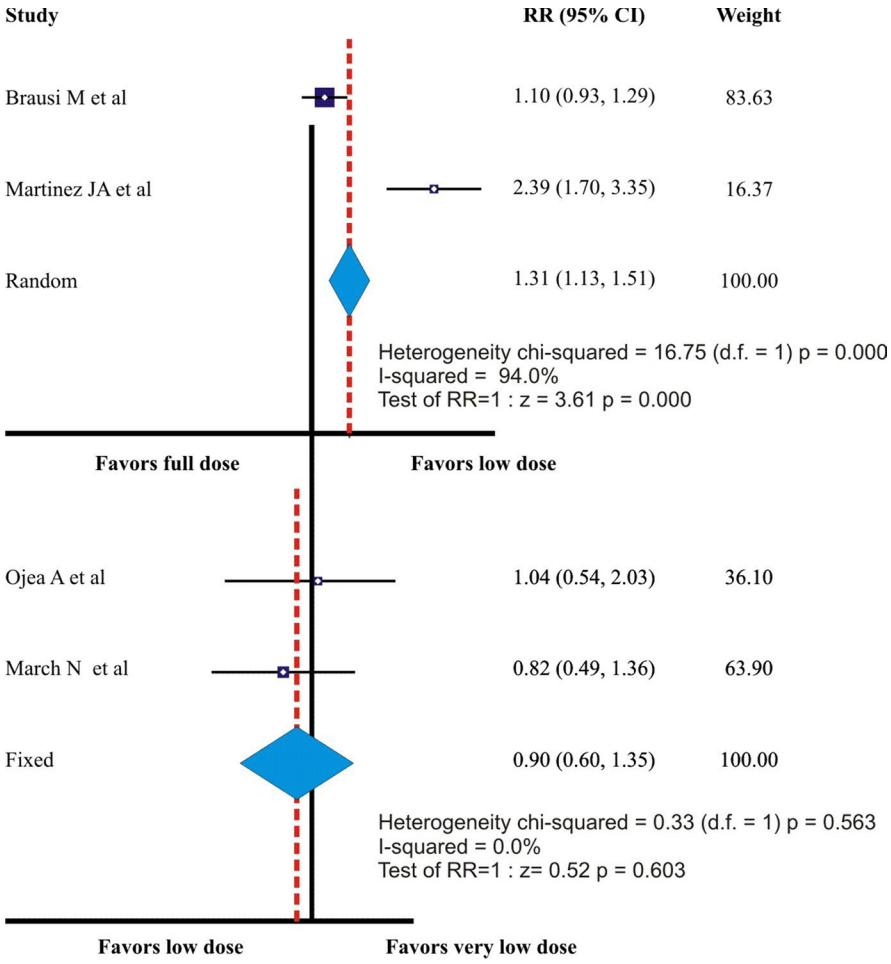

Figure 5. Forest plot systemic side effect of full dose, low dose and very low dose BCG

Even, rare severe systemic reaction of BCG can be found due to active infection with immune response, such as systemic granulomatous disease with high fever that can progressed into multi organ failure. Onset of the symptoms can be months until years after last instilation. This phenomenon may be due to the prescence of BCG for long time in body. Skin rash, atralgia and arthritis were classified as possible allergic reactions. Fever, which occurred predominantly in BCG-sensitised patients, was the only factor in a multivariate analysis significantly related to a decreased recurrence rate and increased toxicity. Drug related life threatening side effect such as septic BCG could be occurred due to systemic BCG absorption.[30]

Maintenance BCG has been suggested by many authors as the treatment of choice for patients with high risk superficial bladder cancer or carcinoma insitu.[25,28] This is reflected in various guidelines on non muscle invassive bladder cancer that include BCG as first line adjuvant therapy after transurethral resection in high risk patient.[2,5] The widely accepted maintenance schedule is based on southwest oncology group regimen, starting with series of six weekly induction followed by three weekly instilation at 3 months and then every 6 months for 3 year.[9] European Association of Urology Guidelines recommend at least 1 year of BCG maintenance therapy.[2] However, the side effects make urologists reluctant to administer BCG to their patient when the disease is not high risk. Thus, it is important to decrease BCG toxicity while maintaining its efficacy. There are some ways to overcome the BCG side effects such as administration of isoniazid 300 mg daily or dose reduction. Patient with evidence of BCG infection such as epididimytis, hepatitis or symptomatic prostatitis are treated with isoniazid plus rifampin 600 mg daily. In EORTC trial in which intravesical epirubicin, BCG and BCG plus isoniazid were compared in 957 patients. Isoniazid does not seem to reduce the side effects of BCG. The most dangerous complication of BCG is systemic septic and/or hypersensitivity reaction, characterized by chills, fever, hypotension, and progressive multi organ failure but the incidence of this event is very low 0.4%.[29]

In 2012, Brausi[21] compared side effects of low dose (27 mg) with full dose (81 mg) of maintenance BCG and concluded no significant difference in toxicity was detected according to dose (one-third dose vs full dose) or duration of treatment. A randomized prospective trial comparing a standard full dose (81 mg) of intravesical BCG with a reduced dose (27 mg) in superficial bladder cancer showed the proportion of patient with no toxicity, either local or systemic, was significantly higher in the reduced dose than in stnadard dose.[8] The difference in severe systemic toxicity were not significant, indeed 4.4% of patient in the reduce dose group and 3.6% in the standard dose. Neither life – threatening episodes nor sepsis were reported for either group. There is a report of granulomatous epididimytis and simultanoeus polyneuropathy in reduced dose patient, but whether it was caused by BCG is unclear.

A randomized prospective trial comparing adjuvant therapy for intermediate risk superficial bladder cancer between one-third dose, full dose BCG and mitomycin C concludes the disease free interval was significantly longer after treatment with BCG 27 mg and the number of recurrence was lower in BCG 27 mg than in 30 mg mitomycin C group. This study suggests that the minimum effective dose of BCG is one third of the standard dose. One sixth of standard dose is not indicated as adjuvant treatment for superficial bladder cancer of intermediate risk because it has the same efficacy as mitomycin C 30 mg but is more toxic. In fact, the toxicity level of one sixth of the standard dose is similar to that observed with one third of the standard dose.[4]

March[21] in his study compared 30 mg MMC with 27 mg and 13.5 mg BCG as adjuvant therapy in medium and low risk superficial bladder cancer. The recurrent rate was lower in 27 mg BCG group but the time to recurrence also higher in this group. No significant difference between other groups, and there were no significant difference in adverse effect between the two BCG treatment groups.

CONCLUSION

Full dose (81 mg) of BCG showed slightly superior effect in reducing recurrences compared to low and very low dose in moderate–high risk non muscle invasive bladder cancer following transurethral resection. Low dose BCG had less systemic side effect compared to full dose, however it had no difference in all doses regimen for local side effects. BCG instilation in moderate-high risk NMIBC patient should be considered as primary therapy in Indonesia.

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